International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 1; January 2018; Page No. 35-40

Arecanut (*Areca catechu* L.) is not carcinogenic but cures cancer: A bibliography

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Abstract
Arecanut is the fruit / seed / endosperm of an oriental palm *Areca catechu* L. growing in most of the South and Southeast Asian countries. This nut is generally used for mastication by millions of people in different parts of the world as it is believed to have many medicinal properties. It is chewed mainly along with several other ingredients such as the leaf or inflorescence of *Piper betle*, calcium hydroxide, catechu, etc. Such combination of chewing product is commonly called as betel quid or *pan*. In India, chewing of arecanut or betel quid, is a good old practice, the tradition of which goes back to 650 BC. Arecanut has very important place in religious functions in many Asian and Oceanic countries. This nut has also exhibited ample medicinal properties and most of them are now authenticated by proper Scientific evidences. In China, there are already more than 30 medicines formulated and marketed using areca nut as one of the ingredients. In spite of such medicinal properties of areca nut, it is also tagged as carcinogenic by several researchers. It is equally true that there are several other contradictory research results which said that arecanut is not carcinogenic in normal dose but even cures cancer. Such reports are collected and highlighted in this paper.

Keywords: arecanut, betel nut, *Areca catechu*, betel quid, anti-carcinogenic, medicinal uses

1. Introduction
Areca palm, *Areca catechu* L. (Palmaceae family) is an important commercial crop of several South Asian and Southeast Asian countries such as India, Indonesia, Myanmar, China, Bangladesh Thailand, Malaysia, Vietnam, Philippines, etc [1]. The fruit or seed (endosperm) of this palm is called arecanut [2]. In some parts of the world arecanut is misnamed as 'betel nut' as it is commonly chewed along with the leaf of *Piper betle*, a tropical, evergreen, perennial vine of Piperaceae family. Since time immemorial, arecanut is being used for chewing or mastication throughout the world, especially in Indian sub-continent and other parts of Southeast Asia as it is believed to have lots of medicinal properties [3]. In India, the use of areca nut has been noticed as early as 1300 BC as cited by Sisu Mayana in 'Anjana Chaitra' [4] and the practice of its chewing from 650 BC as mentioned by Magha in 'Shishupala Vadha'[5]. In other countries such as Vietnam, the antiquity of areca nut even goes back to Bronze Age [6]. In India, areca nut and betel leaf are considered as sacred and no ceremonial function is complete without them [7].
Arecanut has an important place in the ancient system of medicines in several countries such as India [8-10], China [11, 12], Bangladesh [13], Philippines [14], etc. The World Health Organization [15] has listed out as many as 25 beneficial effects of *A. catechu* and included areca palm in the list of medicinal plants of Papua New Guinea. Most of the folklore medicinal properties of arecanut are now validated with proper scientific data [16, 17]. It has antioxidant, anti-inflammatory and analgesic [18-21] anti-diabetic [22-24], hypolipidemic [25-28], antibacterial [29-31] anti-fungal [32,33] anti- malerial [34], anti-viral [35], anti-HIV [36], treatment for AIDS [37] anti-aging [38], treatment for Alzeimer's [39-41] and Schizophrenic patients [42], wound healing [43-45], anti-ulcer [46,47], anti-migraine [48], antihypertensive [49], antidepressant [50], anti-allergic [51], anthelmintic [52-54], aphrodisiac [55], anti-venom [56, 57], hepatoprotective [58], cytoprotective [59], etc. In China as many as 30 medicines prepared using arecanut as one of the ingredients are already in the market for the treatment of several disorders of man [11, 12]. In India, two to three ayurvedic preparations containing arecanut are advocated by doctors for the management of diabetes [60].
Though arecanut has got all these beneficial properties, several researchers highlighted that arecanut chewing might cause cancer [61, 62]. The adverse effects reported in association with arecanut chewing might be due to several other factors such as small sample size, the role of other ingredients used in the preparation of betel quid, the quality of arecanuts (including contaminations and adulterations) used for making different preparations of chewing products, etc [63-65]. Ironically, these factors were not taken into consideration or discussed at all in most of the publications which said that arecanut chewing was dangerous, but simply blamed arecanut for all the ill effects. There are several other contradictory reports which said that arecanut as such was not cancerous but cures cancer. Such reports are collected by searching text books, old journals, PubMed, Google Scholar, Science Direct, etc. and presented in this bibliography. This gives an insight for further detailed research in this field.

2. Studies carried out on laboratory animals
2.1 Using arecanut
Certain studies carried out on laboratory mice (A/Iisc strain) confirmed that the extracts of arecanut (prepared from 100g of arecanut powder) and betel quid without tobacco (extract of

the mixture containing 100g of betel leaves + 50g of arecanut powder + 4g of lime) were not carcinogenic [66]. The authors arrived at this conclusion by applying these extracts to both normal as well as immune suppressed mice for two years. The extracts did not induce any tumor in both the conditions. The irony is that this paper was not discussed in most of the review papers on the carcinogenicity of Arecanut [61, 62].

Non carcinogenic activity of arecanut was also reported by Ranadive *et al*. [67]. The authors experimented on both mice and hamsters by painting arecanut extract on their inter-scapular region and cheek pouch, respectively throughout the life of these animals. Arecanut extract was found safe up to 0.1ml to a mouse weighing around 30g. This is equal to 200ml of arecanut extract per day for an adult human being weighing around 60kg. The same dose was found safe for hamsters as well.

The effects of feeding of the common types of arecanut available in the market were studied on Swiss albino mice and found that the Ripe Unprocessed and Sundried (R-UP-SD); Ripe Processed and Sundried (R-P-SD) and Unripe Processed and Sundried (UR-P-SD) were found safe and did not induce any tumor in mice at 1.0g/kg bw/day [68]. These types of arecanut are commonly called as Chali, Red whole and Red split, respectively.

In a study conducted on rats (ACI strain) for 480 days to find out the effects of consuming individual components of betel quid (20% arecanut powder, 20% betel leaf powder, and 20% arecanut powder mixed with 1% calcium hydroxide) it was reported that none of the animals fed with such diet mixed food showed any carcinogenic effects [69]. However, epidermal thickening was frequently observed in the tongue, esophagus or fore-stomach of rats when fed with the diet of betel nut mixed with calcium hydroxide and the betel leaves diet. Such epidermal changes in the upper digestive tracts were scarcely seen in rats given either betel nut alone or normal diet. This confirms that even in such high doses (20%), arecanut as such is not harmful or carcinogenic.

2.2 Using pan masala

Ramchandani *et al*. [70] did not notice any tumor development on the skin of mice (ICRC strain) when it was pasted with 50mg of pan masala (without tobacco) extract continuasly for 40 weeks. Similarly, administration of 50mg pan masala extract by gavage did not develop any tumor in any of the internal organs of the treated mice. This dose comes to about 1.7g of pan masala/kg body weight of the animal.

2.3 Using betel quid without tobacco

In Taiwan, the betel quid generally consists of a bisected fresh green arecanut (including the husk) sandwiched with a spike of betel vine and a brown paste containing slaked lime and catechu. The effect of such betel quid on the cheek pouch of hamster was studied by inserting 1.5g of such betel quid into the cheek pouch for 52 weeks [71]. Treatment with the chemical carcinogen, DMBA (7,12-dimethylbenz (a) anthracene) for 6 weeks developed 11-70% carcinoma whereas, treatment of such betel quid alone during the entire period of experiment (52 weeks) or further followed by 10 weeks treatment with that chemical carcinogen did not lead to any tumor. This proved that Taiwan betel quid is neither a carcinogen nor promotes carcinogenic activity. Similarly, non-carcinogenic effect of Taiwanese betel quid which contained more than 70% of arecanut available in their market was also reported on hamsters [72]. It was also reported that the betel quid ingredients from several other Asian countries also did not induce any carcinogenic activity [73].

3. Toxicity of arecanut

The toxicity of arecanut was studied on two strains of albino rats. In both the studies it was reported that arecanut was not at all toxic to these animals. In a study conducted on Sprague-Dawley rat by administering a single dose of powdered arecanut at different concentrations by gavage it was found that the LD50 of arecanut was more than 15,000mg/kg body weight for these animals [74]. The authors even suggested to label arecanut as unclassified, non-toxic commodity. Similarly, in another study, the LD50 value of arecanut aqueous extract to Wistar albino rats was calculated to be more than 2,000mg/kg bw [75]. In another study, consuming arecoline, the main active principle of arecanut, at a dose of 100mg/kg body weight per day was reported to be safe to Wistar albino rat [76]. In the latter two experiments, instead of using arecanut as such, either its extract or the active principle was used. This might be the reason for the lower values reported in such experiments.

4. Studies on human population

4.1 Pan chewing without tobacco is not a risk factor for cancer

In a study conducted on the etiological factors in oral squamous cell carcinoma in Madras, India, it was reported that 85% of cheek carcinoma patients were chewing betel quid with tobacco as against 12.5% in the control group. On the other hand, only 8.7% of cheek cancer patients were pure betel and arecanut chewers as against 51.8% in the control group [77]. The lacuna is that, no data for non-chewers were given in this study.

In a study conducted at Bangalore, India on the occurrence of cancers of oral cavity in pan chewing people in that region, Nandakumar *et al*. [78] did not notice any increase in oral cancer in those people who chewed pan masala 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 for males and females, respectively) whereas it was significantly more ($p=0.001$) with pan chewing with tobacco. Similar results were reported in Assam also. In a study conducted at this region, it was noticed that there is no significant difference in the adjusted risks for the incidence of oral cancers between chewers (green or red arecanut with betel leaf but without tobacco) and non chewers of pan [79].

In Papua New Guinea, the betel quid generally does not contain any forms of tobacco. In a case control study conducted using 143 cases in that country, 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[80]. 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.

4.2 Pan chewing without tobacco is not a risk factor for OSF

In a hospital based cross-sectional study conducted at Nagpur, India with 1000 Oral Submucous Fibrosis (OSF) patients (830 males and 170 females) patients it was noticed that in males only 18% people showed exclusive habit of chewing arecanut, the rest (82%) chewed either kharra, gutkha or tobacco. The incidence of OSF in such people was reported to be 83%, almost to those who chewed either kharra, gutkha or tobacco. On the other hand, 82% women showed exclusive arecanut chewing habit, the rest (18%) chewed either kharra, gutkha or tobacco. Accordingly, the incidence of OSF in such people was reported to be only 17% [81]. This clearly shows that the incidence of OSF was directly related to chewing of kharra, gutkha or tobacco but not to arecanut.

4.3 Pan chewing without tobacco is not a risk factor for mortality

In Taiwan, people generally chew betel quid without tobacco. In a cohort study conducted on 6,503 participants no significant variation in cancer deaths was noticed between chewers and non-chewers of betel quid. The overall adjusted hazard ratio for cancer deaths was 1.0:1.03 between non chewers and chewers of betel quid [82]. For cancers in oral cavity and oesophagus 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.

5. Anticancer effects of arecanut

The extract of arecanut even inhibited the growth of tumors in mice [68]. The arecanut extract was reported to retard or inhibit the development and growth of tumors induced by the known chemical carcinogen 3:4, benzpyrene (BP). The acetone and DMSO extracts of arecanut, painted thrice a week with BP at 5µg level, exhibited a reduction in the tumor incidence, a delay in the day of appearance of tumors and a lessening in the number and size of the tumors as compared to the controls.
In human beings also, arecanut was found to be effective against the growth and development of certain cancers. Both arecanut extract (100-800 µg/ml) and arecoline (20-120µM), were found to markedly suppress the proliferation of oral KB cells in a dose dependent manner by 36-90% [83]. MCP-7 breast cancer cells [84] (Anajwala *et al*. 2010) and gastric and liver cancer cells [85]. The 50% inhibition concentration (IC50) value of the aqueous extract of arecanut against these cell lines was calculated to be 775.1, 5.1 and 9.3µg/ml, respectively.
The antioxidant activity of arecanut might play active role in repairing DNA damage in cancer cells. While investigating the effect of aqueous and various organic extracts from different parts of *Areca catechu* on oxidative DNA damage in human hepatocarcinoma HepG2 cells it was noticed that the methanol extract of eight month old arecanut husk showed a dose dependent inhibition of comet formation while other solvent extracts did not [86]. Significant protection of hydrogen peroxide (H2O2) induced DNA damage was observed at 0.1% w/v concentration, almost same level of protection obtained with 1µM butylated hydroxytoluene (BHT).
In a recent study at the Winship Cancer Institute of Emory University, Atlanta, USA, the arecoline hydrobromide, the major active principle of arecanut was found to arrest the growth of cancer cells. It was reported that the arecoline hydrobromide inhibited the activity of the enzyme ACAT1 (acetyl-C0A acetyltransferase) which lead to attenuation of cancer cell proliferation and tumor growth in mice [87].

6. Indirect evidences

6.1 Anti - ulcerogenic property of arecanut

In a study carried out on Wistar albino rats, the anti-ulcerogenic activity of arecanut in ethanol induced gastric ulcers was reported [46]. The authors found that the ethanol induced gastric mucosal injury in such rats was significantly reduced when they were pretreated with arecanut extract 30 min before ethanol administration. Induction of ethanol showed a significant reduction of gastric mucosal glutathione, sialic acid and DNA levels. Pretreatment with arecanut extract at 250mg/kg maintained their levels similar to normal control.
Similar results were also observed on Sprague Dawley rats. Pretreatment with the aqueous extract of arecanut at 2g/kg body weight 30 min before the induction of gastric ulceration by absolute alcohol showed potential anti-ulcerogenic effect almost comparable to the effect of Ranitidin, the standard gastric anti-secretory drug at a concentration of 50mg/kg body weight [47].
Investigations were also carried out on the protective effect of arecanut leaf extract on gastric ulcers. In a study carried out by Lee *et al*. [88] it was reported that the arecanut leaf extract protected the mucosal epithelium as well as the vascular supply in the gastric tract of treated mice. Further, such extract significantly reduced the expression of tumor necrosis factors.

6.2 Wound healing property of arecanut

Topical application of arecanut extract was reported to increase the wound healing process significantly in treated animals. In a study conducted on Wistar albino rats it was reported that 2% arecanut extract significantly increased the wound contraction rate compared to that of control and was found to be similar to that observed in test drug treated animals [44]. Further, the arecanut extract was also found to overcome the wound healing suppressive property of dexamethasone
Even oral administration of arecanut extract was reported to increase the wound healing process. In a study conducted on Wistar albino rats it was reported that oral feeding of arecanut extract at a dose of 100mg/kg significantly enhanced the wound contraction rate in all the days compared to control [45]. Further, it was also found that the dexamethasone suppressed wound contraction rate and epithelialization period were reversed significantly by oral feeding of arecanut extract at that dose.

7. Conclusion

All these reports confirm that arecanut in its pure form is not dangerous but has got a plethora of medicinal properties including curing ulcers, wounds and even cancer. Most of its folklore medicinal properties are now validated by scientific evidences. Detailed studies on the nature of active principle(s) responsible for all these properties and clinical trials on them are warranted to utilize such plant products effectively and

profitably as these palms are available in plenty in most of the South and Southeast Asian Countries. Care should be taken not to combine arecanut with any of the harmful materials and blame arecanut for the ill effects of such combinations.

8. Conflict of Interest Statement

We declare that we have no conflict of interest.

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