REVIEW ARTICLE

Anticancer property of arecanut (*Areca catechu* L.): A review

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ABSTRACT
Areca palm, *Areca catechu* L., is widely cultivated in several South and Southeast Asian countries. The seeds of this palm called areca nut, betel nut or supari is the common chewing substance all over the world since thousands of years as people believed that areca nut has lots of medicinal properties. Ancient systems of medicines like Ayurveda, Unani, Homeopathy, etc., considered areca nut as medicine since very long time. Recent scientific observations also support this and confirmed more than 25 different medicinal uses of this nut. Anticancer property is one among them.
Lots of scientific data are now available to substantiate the anticancer property of area nut. Original published documents are retrieved by referring old scientific journals found in Research Institutions, searching in Google scholar, Pub Med, internet and other facilities by using appropriate keywords. The articles collected were thoroughly read and reviewed to avoid any ambiguity. More than 20 original research papers on anticancer property of areca nut were cited and discussed in this paper. It is interesting to note that even arecoline, the major active component of areca nut, was reported to be anticancerous both in vitro and in vivo studies. Even observations made on chewers of unadulterated traditional forms of betel quid containing areca nut revealed that such habits are good for human health.
Key words: Areca nut toxicity, *Areca catechu*, betel nut, betel quid, chewing habits, anticancer

INTRODUCTION

Areca nut, the fruit of a slender but tall palm, botanically called *Areca catechu* L. of Arecaceae (Palmae) family, is an important commercial crop of India and several other south and south east Asian countries.[1] In several parts of the world areca nut 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. In Hindi arecanut is commonly called as 'supari'. This nut is mainly used for mastication.[2] The history of its chewing goes back to few thousands of years. The remains of human skeletons dated back to about 3000 BC showing the evidence of areca nut chewing was reported from Duyong Caves in the Philippines.[3] Similar proof was collected from Vietnam, where the fossil remains of human being of Bronze Age (1200-3300 BC) with stains of areca nut in their teeth were detected.[4]

Areca nut has an important place in the ancient system of medicine in several countries such as India, China, Bangladesh, the Philippines, etc.[5-8] World Health Organization has included areca palm in the list of medicinal plants and mentioned as many as 25 different medicinal properties of this palm.[9]Authentic scientific evidences are now available to substantiate them. To name some of them, areca nut has the medicinal properties such as antibacterial, antifungal, antiviral, antimalarial, anti-HIV, antidiabetic, antilipidemic, antiulcer, antitumor, analgesic, anti-inflammatory, wound healing, anti-migraine, antihypertensive, antidepressant, anthelmintic, anti-allergic, anti-venom, aphrodisiac, anti-aging, treatment for AIDS, Alzeimer's and Schizophrenia.[10] Considering all these medicinal properties of areca nut, China has developed as many as 30 medicines using areca nut as one of the ingredients.[6]

Apart from the above, areca nut extract is reported to suppress the growth and development of several types

of human cancer cells. In the present report an attempt has been made to collect and review the available original scientific reports on the anticancer properties of areca nut by searching text books, old journals, PubMed, Google Scholar, Science Direct, etc. This gives an insight for further research in the field of cancer therapy using areca nut as the ingredient.

STUDIES ON CANCER CELL LINES

In several in vitro studies conducted, areca nut extract was reported to be toxic to and arrest the growth and proliferation of several types of cancer cells.

In a study to evaluate the cytotoxic effects of the areca nut extract on human breast cancer MCF-7 cells by MTT assay it was revealed that the ethanolic extract of areca nut caused a growth inhibition of 84% when exposed to 100 µg/ml concentration for 48 h with IC_{50} value of 77 µg/ml.[11] The extract also inhibited cell proliferation and induced apoptosis. However, the IC_{50}value of the aqueous extract of areca nut by SRB essay was reported to be 775. 1 µg / ml against such cancer cells.[12]

Arecanut extract also showed strong synergistic effect on Doxorubicin, one of the chemotherapy agents often used in breast cancer therapy. In a study carried out on MCF -7 cell lines, the apoptotic effect of doxorubicin was increased from 7.76% to 23.29% when it was combined with ethanolic extract of areca nut.[13] The apoptotic effect of areca nut extract alone was reported to be 10.24%. In another study, the combination of 0.25 µg/ ml of doxorubicin with ethanolic extract of areca nut at 9.375 µg/ml concentration increased the toxicity of doxorubicin on MCF-7 cells significantly ($p<0,05$).[14]

Almost similar synergistic anticancer effects of arecanut were observed in the studies conducted on human colon cancer WiDr cell lines as well. The addition of the ethanolic extract of areca nut at 60 µg / ml concentration to doxorubicin at 500nM concentration increased the apoptotic effect of the latter from 20% to 25% on such cancer cells.[15]

It was also reported that areca nut induced apoptosis in human oral squamous cell carcinoma (OSCC) HSC- 2 and HSC-3 cell lines but not on normal cells. Both these cancer cell lines when exposed to the ethanol extract of areca nut for 24 and 48 hours significantly increased apoptosis in them.[16] Further, the extract exhibited higher toxicity on HSC-3 cells than on HSC-2 cells with the IC_{50} value of 164.06 µg/ml for HSC - 3 and 629.50 µg/ml for HSC - 2 cells. Interestingly, the authors did not notice any cytotoxic effect of areca nut extract on HaCat cells.

In another study to find out the ability of areca nut extract to induce apoptosis and caspacse-3 activity on HSC-2 and HSC-3 cells it was noticed that the ethanol extract of areca nut induced a significant increase ($p \leq 0.01$) in the percentage of cells in early apoptosis after 24 hours of exposure and late apoptosis after 48 hours of exposure in HSC-3 cells, whereas in HSC-2 cells there was a significant increase ($p \leq 0.01$) in late apoptosis at 48 hours.[17] Caspase-3 activity increased after 24 and 48 hours of exposure to areca nut extract in both these cancer cells compared to those cancer cells without the exposure of areca nut extract.

It was reported that exposure of areca nut extract for 24 hours caused a decrease in the percentage of HSC-2 cell population in G1 phase.[18] The population of such cells was found to be 11-fold lower ($p \leq 0.01$) in areca nut extract treated group when compared to untreated group. There was significant reduction in Ki-67 expression after 24 hours of areca nut extract treatment in both HSC-2 and HSC-3 cells.

A study was conducted to find out the exact component contributing to the cytotoxic effect of areca nut by MTT method.[19] Among the 11 phenolic compounds isolated from areca nut extract, the compound 11 ‘jacareubin’ was found 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_{50} value of 5.1 and 9.3 µg/mL, respectively while other compounds were found inactive.

Arecoline, the most important alkaloid of areca nut was also reported to be anticancerous. Exposure of arecoline at0.2- 0.8 mM concentrations for 24 hours inhibited the growth of KB cancer cells in a dose- and time-dependent manner with a reduction in cell number by 37 and 58%, respectively.[20] Further, arecoline induced p21 protein levels in primary human gingival keratinocyes (GK cells), whereas it declined p21 protein expression in KB cancer cells. Arecoline also induced both cell necrosis and apoptosis of KB cells but not of GK cells.

Arecoline caused cytoskeletal changes in human hepatoma HA22T/VGH cells, but not in hepatocytes at a low concentration of ≤ 100 µg/ml.[21] This was accompanied by decreased β1-integrin expression followed by apoptosis, indicating that HA22T/VGH cells undergo anoikis after arecoline treatment. Further, IL-6 expression and phosphorylation of STAT3, which provides protection against anoikis, were inhibited in such treatment. After 72h of arecoline treatment, the viability of normal hepatocytes was not changed significantly, whereas that of HA22T/VGH cells decreased in a dose-dependent manner.

Since IL-6 over expression contributes to the tumorigenic potency of cancer cells, a study was made to investigate whether arecoline altered IL-6 expression in cultured basal cell carcinoma BCC-1/KMC cells.[22] BothBCC-1/KMC cells and a human keratinocyte, HaCaT cells were exposed to arecoline at concentrations ranging from 10 to 100µg/ml and IL-6 production, expression of apoptosis and cell cycle progress-related factors were examined. Exposure of arecoline at concentrations ranging from 10 to 100µg/m inhibited BCC-1/KMC cell growth and

decreased IL-6 production in terms of mRNA expression and protein secretion, but had no effect on HaCaT cells. In another study arecoline was reported to induce cell death in K562 leukaemia cells as well.[23]

The selective toxicity of arecoline to cancer cells was further confirmed by another work wherein it was reported that arecoline effectively inhibited proliferation of diverse human leukemia and cancer cells compared with normal cells when exposed to arecoline hydrobromide in dose dependent manner.[24]

In a comparative study to find out the cytotoxic effects of arecoline and the ethanolic extract of areca nut by MTT assay on human breast cancer MCF-7 cells it was observed that areca nut extract was more toxic than arecoline on such cancer cells.[11] The arecoline caused a growth inhibition of 8-73% in such cancer cells at 10-500 µg/ml concentration with an IC_{50} value of 180 µg/ml whereas the ethanolic extract of areca nut caused a growth inhibition of 13-84% on similar cells at much lower concentration of 25-100 µg/ml itself with IC_{50} value of 77 µg/ml.

STUDIES ON ANIMALS

Several in vivo studies conducted on various laboratory animals also revealed the cytotoxic effect of areca nut extract on various cancer cells.

In a study conducted on mice, it was reported that all 10 animals treated with 5 µg of 3-4, Benzpyrene (BP), a chemical carcinogen, developed skin tumours within 39 weeks of treatment, whereas those mice treated with 5 µg of BP along with areca nut extract at 0.1ml of 2% solution were free of tumours during that period.[25]

In another study conducted on mice with more than 20 animals in each group with an experimental period of 40 weeks it was reported that the diet of saccharin coated areca nut reduced the carcinogenic potential of 1,4-dinitrosopiperazine.[26] The tumors were more common in the group treated with dinitrosopiperazine than in group treated with dinitrosopiperazine along with the extract of saccharin coated areca nut.

It was also reported that the arecanut extracts reduced cell viability, increased cell apoptosis and suppressed tumour progression in hepatocellular carcinoma (HCC) xenograft mice.[27] The IC_{50} value of areca nut extract against hepatocellular carcinoma cells was around 20-30 µg/ml after 48 h of treatment.

While studying the chemotherapeutic effect of areca nut extract on OSCC it was reported that the incidence of OSCC at the end of 23 weeks of observation in animals treated with 30ppm of cancer inducing chemical 4-nutriquinoline-1- oxide (4NQO) in drinking water for 12 weeks was 71.43%, whereas it was 0% when areca nut aqueous extract was given in drinking water at doses of 500 and 1000 mg/kg BW for 22 weeks after a gap of one week of treatment of 4NQO for 12 weeks.[28] Further, in rats treated with 4NQO alone 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 areca nut extract following 4NQO treatment.

In a study on the antitumor activity of biosynthesized silver nanoparticles (AgNPs) of areca nut extract on Dalton's Ascites Lymphoma (DAL) induced mice models it was reported that in AgNPs of arecanut extract treated mice there was significant decrease in tumor volume and significant increase in life span when compared to non-treated animals.[29] Further, there was significant increase in apoptosis of DAL tumor cells treated with AgNPs when compared to control and aqueous treated groups. Acridine Orange staining and DNA fragmentation studies on harvested tumor cells showed higher level of cytotoxicity by AgNPs when compared to aqueous extract of areca nut.

Even arecoline was found to arrest the growth of cancer cells in animals. In a study conducted on mice, it was reported that intraperitoneal administration of arecoline hydrobromide showed very clear dose dependent reduction in the size and weight of tumors developed in both H1299 and K5612 xenograft animals with complete inhibition of tumor growth at the maximum tolerated dose of 50mg/kg/day of arecoline without off-target effects.[24]

STUDIES ON HUMAN POPULATION

Traditionally, areca nut is chewed along with betel leaf (the leaf of *Piper betle*vine) and lime. This mixture is called as betel quid (BQ). Some people also add a piece of tobacco leaf with this chewing mixture (BQT). In a survey conducted on 917 people (292 chewers of traditional BQ, 393 chewers of traditional BQT and 232 non chewers of BQ or BQT) in certain major areca nut growing districts of Karnataka and Kerala it was found that chewing traditional forms of BQ or BQT was not harmful but beneficial to humans.[30] There were not much health variations reported between traditional chewers and non-chewers except for tooth problems which were much less in both BQ and BQT chewers when compared to non-chewers. Overall health problems were less in traditional BQ and BQT chewers when compared to non-chewers. In non-chewers 31.03% people reported certain health problems whereas in chewers of BQ only 13.70% and in chewers of BQT 18.07% reported such problems. The reported cases of cancer in BQ chewers were nil, whereas in those who chewed BQT there was one cancer patient but in non- chewers there were two such patients. This shows that chewing traditional forms of BQ or BQT is beneficial. Almost similar observations were reported by other researchers as well.[31,32]

DISCUSSION

All the above scientific evidences confirm that areca nut is good for health and could be considered as a potential anticancer agent. In vitro studies carried out on different cell lines clearly showed that areca nut

extract successfully inhibited the growth of several cancer cells, including those causing oral carcinoma, without any adverse effect on normal cells.[16] Further, areca nut extract showed a synergistic effect and increased the toxicity of doxorubicin against such cancer cells.[13-15] Arecoline, the important chemical compound of areca nut, was also reported to arrest the growth of cancer cells but not normal cells.[20-22,24] However, it was also reported that arecanut is more toxic than arecoline on cancer cells.[11] By this it is understood that there is some other compound in areca nut which increases its toxicity on cancer cells. In fact, polyphenols are the major chemical compounds in areca nut, contributing up to 29.8% of the total volume of the nut.[33] It was reported that the phenolic compound 'jacareubin' was also found cytotoxic against several cancer cells.[19]Hence, it is possible that both arecoline and jacareubin increased the anticancer property of arecanut.

Studies carried out on laboratory animals also confirmed the anticancer property of areca nut. The striking observation was that of Kumari et al wherein mice treated with benzpyrene developed tumors whereas the mice treated with benzpyrene along with areca nut extract did not.[25] In another study areca nut extract showed its anticancer property against OSCC as well, wherein the rats received chemical carcinogen in drinking water developed OSCC whereas those rats received areca nut extract in drinking water following chemical carcinogen treatment did not develop any OSCC.[28] Further, the nanoparticles of areca nut extract were found to be more effective than its normal extracts as anticancer agents suggesting that areca nut derived AgNPs are a novel cost effective, potent antitumor agents.[29] Again arecoline was also reported to be anticancerous in animal studies.[24] Observations on chewers of traditional forms of fresh BQ and BQT also confirmed the beneficial effects of such chewing habits.[30-32] In spite of all these facts, areca nut is labelled as cancerous by several researchers.[2,34,35] However, on close observation of the cited research papers in such reviews it is seen that in most of them there are several lacunae in the methodology.[36] Number one and foremost is that the researchers did not authenticate the chewing material as areca nut by any experts in plant science.[37,38] Instead, the authors treated all the chewing mixtures such as pan masala, gutkha, zarda, khaini, naswar, mava, etc, as areca nut and blamed areca nut for the entire ill effects developed after chewing suchmixtures. In certain other studies the researchers either exposed laboratory animals to a very high dose of areca nut or injected areca nut extract to animals and concluded that areca nut chewing is injurious.[39] In several others, the quality of the chewing product was not tested at all though there are reports to show that some of the areca nut samples or chewing products contained aflatoxins or adulterated with certain harmful heavy metals or even pesticides.[40]

CONCLUSION

The foregoing literatures clearly show that areca nut is not cancerous but anticancerous. If areca nut is really cancerous why it is not reflected in these studies is the real question to be answered. Hence, it is high time to look into this aspect more scientifically and in real perspective. No doubt, any medicine if consumed in higher dose is dangerous. Even the food material if consumed in contaminated form or in unnatural way is also dangerous.

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