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ARECANUT (*Areca catechu* L): A STORE HOUSE OF MEDICINES

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The arecanut available in the market is the endosperm of the fruit of *Areca catechu* L., a palm commonly grown in South and Southeast Asian countries such as India, China, Bangladesh, Indonesia, Myanmar, Thailand, Malaysia, Vietnam, Philippines etc. It is the common stimulatory mastication throughout the world, especially in Indian sub continent and other parts of South East Asia. Arecanut is misnamed as 'betel nut' in several parts of the world as it is usually chewed along with the leaf of *Piper betle*, a vine of Piperaceae family.

Plants have been used for their medicinal properties since the beginning of human civilization. The descriptions of such medicinal plants are well documented in the literature (Kirtikar *et al.*, 1918). Areca palm is one such medicinal plants whose medicinal properties are not much highlighted. There are lots of scattered scientific evidences which show that arecanut is very rich in medicinal values which could be exploited further for the benefit of mankind. Such reports are collected and presented in this paper.

Medicinal properties of arecanut:

Antioxidant activity: Arecanut extract showed strong antioxidant activity similar to Vitamin E and more than Vitamin C (Kim *et al.*, 1997). The methanolic extract of this nut exhibited more antioxidant activity than other types of

its extracts (Hannan *et al.*, 2012). Oral administration of arecanut aqueous extract at 100 mg/kg bw for one month significantly increased the antioxidant enzymes such as superoxide dismutase, glutathione and glutathione reductase levels in the blood of mice (Sharafudheen *et al.*, 2015).

Anti bacterial: Almost all types of arecanut extracts showed good antibacterial properties. In a study conducted using the aqueous extract of arecanut there was complete inhibition of growth of *Klebsiella* sp. and *Proteus* sp. at a concentration of 10 µg/ml, *Pseudomonas* sp., *K. pneumonia* and *Salmonella typhimurium* at a concentration of 20 µg/ml and *Streptococcus mutans*, *S. viridians* and *Escherichia coli* at a concentration of 50 µg/ml (Anthikat and Michael, 2009). The acetone extract of arecanut was antibacterial against *E. coli*, *Proteus mirabilis* and *Staphylococcus epidermidis* (Hazarika and Sood, 2015). The hydroalcoholic extract of this nut was very effective against *Staphylococcus aureus* at a concentration of 100 mg/ml and against *E. coli* at a concentration of 200 mg/ml (Pahadia *et al.*, 2013).

The 'chogaru' obtained while boiling tender arecanuts was also reported to be very effective against *Enterobacter aerogenes* (Nethravathi *et al.*, 2010). It was identified that the polyphenol content in arecanut was the

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active principle for the antibacterial efficacy of this nut (Hada *et al.*, 1989). It was further reported that the tannic acid fraction of arecanut was more potent in the growth inhibition property against the common gastrointestinal bacteria such as *Bacteroides fragillus*, *Clostridium clostridiiforme*, *C. perfringens*, *C. paraputrificum*, *E. coli*, *Enterobacter cloacae* and two strains of *S. typhimurium* (Chung *et al.*, 1998).

Anti fungal: Arecanut was also reported to be anti fungal. Anthikat *et al.* (2014a) reported growth inhibition of *Mucor sp.*, *Cladosporium sp.*, *Aspergillus niger* and *Candida albicans* at 16.67 µg/ml concentration of the aqueous extract of arecanut. Salutan and Billacura (2015) reported that ketoconazole, ethyl acetate and aqueous extracts of arecanut significantly inhibited the growth of *C. albicans* while hexane extract did not. In their study they found that the ethyl acetate and aqueous extracts of arecanut contained alkaloids, flavonoids, tannins and polyphenols whereas the hexane extract of arecanut did not contain any alkaloids and flavonoids.

Anti viral: Vermani and Garg (2002) reported that the arecanut extract had inhibitory effects against the viral pathogens responsible for HIV and herpes simplex virus (HSV-1). Kusumoto, *et al.* (1995) reported a 70% inhibition on the growth of HIV-1PR virus at a concentration of 0.2 mg/ml. The arecanut extract was also observed to inhibit the growth of the New Castle Disease Virus and Egg Drop Syndrome Virus grown in embryo cultures (Anthikat *et al.*, 2014a).

Antimalarial: It was reported that treatment of butanol extract of arecanut at a dose of 150 mg/kg/day for 4 days increased the survival rate

in malaria infested mice by 60% over control (Jiang *et al.*, 2009). Boniface, *et al.* (2014) reported remarkable mortality in *Plasmodium falciparum* when treated with arecanut extract. They further found that the butanol fraction of arecanut extract was most potent with an LC 50 of 18 µg/ml against this malarial parasite.

Anti-diabetic: The arecanut extract was reported to suppress the action of the intestinal glycosidase enzymes, primarily responsible for the metabolism and absorption of dietary carbohydrates in albino rats. The IC 50 values of the ethanolic extract of arecanut on the inhibitory activity of glycosidase enzymes such as maltase and sucrase were found to be 12 µg/ml and 30 µg/ml, respectively (Amudhan and Begum, 2008b). They also reported that oral administration of arecanut extract at 250 mg/kg body weight after feeding maltose did not increase the blood glucose level in rats, but those animals received only maltose showed very high level of blood glucose.

In the glucose tolerance test conducted on Wister albino rats it was noticed that the arecanut aqueous extract fed rats at doses of 250 and 500 mg/kg bw showed the maximum improvement in glucose tolerance when compared to that of the synthetic antidiabetic drug glibenclamide at 60 min and the decline reached its maximum at 120 min (Anthikat *et al.*, 2014b). They also reported that when such extract was administered at a dose of 250 mg/kg bw for 21 days to diabetic induced rats there was a significant reduction in blood glucose level when compared to that of diabetic rats. The insulin levels in the blood of arecanut extract treated rats increased significantly when compared to those of diabetic induced control

groups. Arecanut powder when fed to Sprague dawley rats in water suspension at a dose of 20 mg and 30 mg/rat/day for 15 days reduced the serum glucose level from 92.7 to 85.7 and 82.6, respectively (Iqbal *et al.*, 2012).

The arecoline content of arecanut was also reported to be anti-diabetic in normal dose (0.20 to 0.25 mg/kg bw) in rabbits, but neither the lower dose nor the higher dose (<0.20 mg and >0.25 mg/kg bw) of arecoline showed anti-diabetic activity in these animals (Chempakam, 1993). This clearly shows that it is the dose which matters most.

Cholesterol lowering activity: The arecanut extract supplemented food was reported to decrease the concentrations of plasma cholesterol and triglycerides significantly in rats (Jeon *et al.*, 2000). Feeding rats for six days with food containing cholesteryl oleate (0.5 g/100 g bw) increased the plasma cholesterol and triglyceride concentrations by 13.6% and 15.9%, respectively, but when such food was supplemented with arecanut extract, these figures were reduced by 13.4% and 36.9%, respectively. It was also reported that the supplementation of water soluble arecanut extract significantly lowered the absorption of triglyceride and plasma lipid concentration in rats fed with high cholesterol diet (Byun *et al.*, 2001). In another study it was also noticed that the water soluble arecanut extract (0.5%,w/w) significantly reduced the absorption of intestinal free cholesterol compared to control (Park *et al.*, 2002).

Zhou *et al.*, (2011) reported that feeding of a low dose of arecanut oil (0.335 g/kg) along with arecoline (3 mg/kg) significantly reduced the level of total cholesterol and increased the

level of high density lipoprotein cholesterol in rats compared to control groups. The arecanut also contains good amount of fibers which may also contribute in lowering cholesterol levels as plant fibers are already reported to reduce cholesterol levels in human being (Brown *et al.*, 1999).

Controls tooth decay: It was reported that arecanut chewing gave substantial protection against dental caries (Howden, 1984). He reported that the stain caused due to arecanut chewing acted as protective varnish on tooth surface. The ethanolic extract of this nut was found to be effective against several oral pathogens including *E. coli*, *K. pneumonia*, *Proteus vulgaris*, *P. aeruginosa*, *Salmonella non-typhi*, *S. typhi*, *S. flexneri* and *Vibrio cholera* (Chin *et al.*, 2013). The aqueous extract of arecanut effectively inhibited the growth of the primary cariogenic bacterium, *Streptococcus mutans* (Anthikat and Michael, 2009). The procyanidines of arecanut were the actual antibacterial principles against this cariogenic bacteria (Hada *et al.*, 1989). It was also reported that the aqueous extract of arecanut was better than even chlorhexidine, the chemical disinfectant presently used during root canal treatment against *Enterococcus faecalis*, the most common and dominant anaerobic bacteria responsible for human endodontic infections (Arathi *et al.*, 2015). The authors further suggested that arecanut could be developed as an antibacterial agent during root canal treatment.

As anti-venom: It was reported that the aqueous extract of arecanut inhibited the action of the venom of the monocellate cobra, *Naja naja kaouthia*. The medium effective dose of

this nut was reported to be 62.0 µg/mouse and the necrotizing activity caused by the venom was successfully inhibited by injecting arecanut extract at a dose of 30.0 µg/mouse (Pithayanukul *et al.*, 2005). The 'api' or 'chikni' type of red arecanut is reported to absorb the venom from the wounds of poison bites caused by scorpion, lizard and even snake (Guptha and Guptha, 2013). They reported that these nuts were found to stick on to the wounds caused by the poisonous animals when the nut is placed on the injured place and absorb the poison. After the absorption, the colour of the nut changed according to the type of poison and fell by its own. The time taken for this ranged from half an hour to 12 hours depending on the type of poison.

Eliminates worm infestations: It was reported that the decoction of arecanut was very effective against roundworm (*Toxocara canis*) and tapeworm (*Dipylidium caninum*) infestations in dogs. Two to four month old puppies when administered with the decoction of arecanut at the rate of 2 cc/kg bw provided fair control against these parasitic worms (Valenciano, 1980). Cargill *et al.* (2008) reported complete elimination of two gastrointestinal nematode parasites such as *Trichuris* and *Ascaris* in pigs by feeding with a diet supplemented with dried arecanut powder at the rate of 4 g/10kg bw once a week for 4 consecutive weeks. The body weight of pigs fed with a supplement of arecanut in their feed was increased by 82 g/day whereas in the control group the body weight was decreased by 27 g/day. In sheep, the group treated with areca crude extract at 6 mg/kg bw at 14 days intervals for six months showed a significant decrease in egg counts of gastrointestinal nematodes in the faecal matter

from the second month of the treatment and body weight significantly increased from the fifth month onwards when compared to that of the control group (Rajapakse *et al.*, 2009).

While evaluating the anthelmintic property of the arecanut aqueous extract against the liverfluke (*Fasciola gigantica*) infestations in livestock it was noticed that the arecanut extract had 100% lethal effect at a concentration of 1% and above and it was found even better than Oxytoclozanide in the treatment against this liverfluke. At 1% concentration of arecanut aqueous extract, the flukes died after 2 min of exposure, whereas at the same concentration of Oxytoclozanide the flukes died only after 4 min of exposure (Jeyathilakan *et al.*, 2010). It was also reported that in chickens, goat and sheep both the adults and eggs of roundworms and tapeworms were expelled successfully with a dose of 1g of processed arecanut/kg bw, whereas the commercial dewormers such as Albendazole and Valbazen expelled only the adults of roundworms (Tangalin, 2011).

Anti cancer effects: Arecanut as such was also reported to be anti cancerous. In mice, the acetone as well as the dimethylsulphoxide extracts of arecanut exhibited a retarding and/or inhibitory effects on the development and growth of tumors induced by a known carcinogen 3:4, benzpyrene (Kumari *et al.*, 1974). When BP alone at 5 µg/ml was applied on the skin of such animals, the tumors started developing from the 33rd weeks of exposure and all animals developed tumors before 39th weeks of exposure whereas in those animals which received BP along with arecanut extracts no such tumor was seen until that period. These results are substantiated in another study carried out

on mice where it was reported that the arecoline hydrobromide inhibited the activity of the enzyme ACAT1 (acetyl-CoA acetyltransferase) leading to attenuation of cancer cell proliferation and tumor growth (Fan *et al.*, 2016).

The aqueous extract of arecanut arrested the growth of human MCP-7 breast cancer cells. The IC 50 value of this extract was calculated to be 775.1 µg/ml (Anajwala *et al.*, 2010). 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 IC 50 values of 5.1 and 9.3 µg/ml, respectively (Xing *et al.*, 2010). In a more recent study, it was shown that arecanut could be useful as a potent anticancer agent as it induced significant apoptosis on oral squamous cell carcinoma with the IC 50 values of 164.06 µg/ml for HSC-3 and 629.50 µg/ml for HSC-2 cell lines (Sari *et al.*, 2018).

Analgesic activity: In rats, the aqueous extract of arecanut was reported to be more potent than that of Aspirin in reducing pain. The percentage of inhibition of acetic acid induced abdominal writhings in mice treated with the aqueous fraction of arecanut at a dose of 100 mg/kg bw during the first 30 min of treatment was 80.1% over control, where as with the same dose of Aspirin the inhibition was only 49.3% during that period (Khan *et al.*, 2011).

Anti-inflammatory action: It was also reported that the aqueous fraction of arecanut extract was more potent than that of Aspirin in its anti-inflammatory activity as well. The edema inhibition percentage in rats treated with the aqueous fraction of arecanut extract at a dose of 100 mg/kg bw after two hours of treatment

was 80.2%, where as with the same dose of Aspirin it was only 47.2% at that time (Khan *et al.*, 2011).

Wound healing property: It was reported that the crude extract of arecanut increased the wound contraction percentage in rats (Padmaja *et al.*, 1994). The ointment prepared with 2% ethanol extract of these nuts was found to be equally effective to that of the standard drug, silver sulfadiazine at 1% concentration (Verma *et al.*, 2012). When such ointment was applied on burn wounds of rats, complete epithelialization of the wounds occurred on the 16th day, whereas silver sulfadiazine also took almost similar period (15.67 days) to get complete epithelialization. The control group took much longer period (24.33 days) to reach that condition. Almost similar results were obtained by oral feeding of the ethanolic extract of arecanut at a dose of 100 mg and 300 mg/kg bw (Bharat *et al.*, 2014). The results showed that from day 5 onwards the wound contraction rate was significantly increased in arecanut extract fed groups compared to that of the control and was comparable with that of the standard drug, silver sulfadiazine treated groups.

Anti-ulcerogenic activity: It was reported that the ethanol induced gastric mucosal injury in rats was significantly reduced when they were pretreated with arecanut extract 30 min before ethanol administration. Pretreatment with defatted ethanol extract of arecanut at 250 mg/kg reduced the injury level caused by the administration of ethanol similar to normal control (Amudhan and Begum, 2008a). Pretreatment with the aqueous extract of arecanut at 2 g/kg body weight 30 min before the induction of gastric ulceration by absolute

alcohol also showed potential anti-ulcerogenic effect almost comparable to the effect of Ranitidin, the standard gastric anti-secretory drug at a concentration of 50 mg/kg body weight (Anthikat and Michael, 2011).

Decreases Alzheimer's symptoms: Amnesia or memory loss is one of the symptoms of Alzheimer's disease. In human being it was reported that injection of arecoline at 4 mg significantly enhanced serial learning (Sitaram *et al.*, 1978). Injection of arecoline enhanced the memory retention capacity in mice significantly (Flood *et al.*, 1985). Arecoline is also reported to increase the learning ability in monkeys (Ridley *et al.*, 1987). The methanol extract of arecanut when fed to rats at 500 mg/kg body weight for 7 and 21 days showed significant increase in memory and learning when compare to control (Joshi *et al.*, 2012).

Anti-depressant: In mice, i.p injection of ethanolic extract of arecanut at 80 mg/kg was found as good as the injection of Imipramine, the standard anti-depressant drug, at 10 mg/kg (Bhat *et al.*, 2016). This extract also showed significant antidepressant activity in rats at 4-80 mg/kg i.p (Dar and Khatoun, 1997) and 50 mg/kg oral (Bende *et al.*, 2016).

To treat Schizophrenia: Schizophrenia is a serious psychiatric illness. It was reported that in men, chewing betel nut scored significantly lower symptoms of schizophrenia when compared to non chewers (Sullivan *et al.*, 2000). It was also reported that high betel nut chewing had significantly milder positive symptoms of Schizophrenia than low chewing people (Sullivan *et al.*, 2007). In another study it was reported that significantly fewer betel nut chewers were taking anti-cholinergic

medication (Bales *et al.*, 2009). The protective effects of the ethanol extract of arecanut (oral feeding of 1% and 2% conc.) on cognition and social interaction deficit was also reported in animals (Adilijiang *et al.*, 2015).

Anti-aging: The anti-aging effects of arecanut extract on skin were investigated both *in vitro* and *in vivo* (Lee and Choi, 1999). The treatment with arecanut extract improved skin hydration, skin elasticity and reduced skin wrinkles.

Anti-migraine: Arecanut extract is a popular folk remedy for the treatment of migraine in Kerala and Tamil Nadu. Bhandare *et al.* (2011) gave scientific evidence for this in their study on rats in which they observed that oral feeding of hydroalcoholic extract of arecanut at 250 and 500 mg/kg significantly inhibited the expression of inducible Nitric Oxide Synthase (iNOS) leading to anti-migraine activity.

Antihypertensive: Angiotensin-converting enzyme (ACE) inhibitors help to relax blood vessels and thereby reduce hypertension. Inokuchi *et al.* (1986) reported that in hypertensive rats, oral administration of areca tannin (Areca II-5-C) at 100 and 200 mg/kg gave comparable results to that of Captopril, a synthetic antihypertensive drug, at 30 and 100 mg/kg, respectively. The authors further reported that the same tannin at an i.v dose of 15 mg/kg was about 5 times more effective than that of Captopril at the same dose.

Anti-allergic: It was reported that among the extracts of various oriental medicinal herbs, the extract of arecanut was found to be the most potent inhibitor of antigen-induced degranulation in mast cells with an IC₅₀ value of around 50 µg/ml. (Lee *et al.*, 2004). They

suggested that this nut might be useful for the treatment of various allergic diseases.

Aphrodisiac: Arecanut is also used in the management of certain male sexual disorders due to its aphrodisiac effect. It was reported that oral administration of arecanut extract at 150 mg/kg produced significant augmentation of sexual activity in male rats. It significantly increased the mounting frequency, intromission frequency, intromission latency, etc. without any adverse effects (Anthikat *et al.*, 2012).

Hepatoprotective: It was reported that in rats the liver injury induced by carbon tetrachloride was reversed successfully by treatment of the aqueous extract of arecanut (Pithayanukul *et al.*, 2009). It was presumed that the condensed or hydrolysable tannins found in arecanut are responsible for such protections against oxidative stress-induced liver injury.

Cytoprotective activity: Arecanut extract protected the oxidative damage induced by H₂O₂ in hamster lung fibroblast cells (Lee *et al.*, 2003), human gingival fibroblast cells (Sazwi *et al.*, 2013) and haemolysis of RBC in rats (Amudhan and Begum, 2006). Interesting observation was that at 50.0 µg/ml concentration the arecanut extract showed an increase of cell viability from 34.9% in the control to 89.3%, almost comparable with that of ascorbic acid with 82.4% at that concentration (Sazwi *et al.*, 2013).

Conclusion: It is clearly evident from the above scientific observations that arecanut is very rich in medicinal properties which could be exploited further for the sake of mankind. As this commodity is available in plenty, it is a

good biological source for the researchers and bio medical entrepreneurs to work in this field to identify and extract the active compounds to treat several human ailments.

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