Research Journal of

Medicinal Plant

ISSN 1819-3455

Academic
Journals Inc.

www.academicjournals.com

Research Journal of Medicinal Plant 5 (2): 145-152, 2011
ISSN 1819-3455 / DOI: 10.3923/rjmp.2011.145.152

Areca catechu L.: A Valuable Herbal Medicine Against Different Health Problems

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ABSTRACT

Areca catechu is a species of palm grown mainly in Asian countries for seed crop. The chemical constituents of *A. catechu* have been investigated for anti-nematodal/helmintic, antioxidant, anti-venom, modulation of phagocytosis, effect on sperm motility/catecholamine release, as immunosuppression, management of psychiatric disorder and Alzheimer's disease. Recent studies have revealed strong molluscicidal activity of *A. catechu* against harmful snails for the control of fascioliasis. Despite its laboratory studies on nematocidal/helmintic/molluscicidal activity of *A. catechu*. More field studies are recommended for effective control of these pests. Alkaloid arecoline is the major constituents of *A. catechu* for most of their biological effects. *A. catechu* deserves more attention by scientific community and health experts to explore its full range of benefits in welfare of mankind. Adverse effects of oral ingestion of *A. catechu*, causing Oral Submucous Fibrosis (OSF), oral submucous cell carcinoma should be taken in consideration, while their use is recommended in solving different health problems.

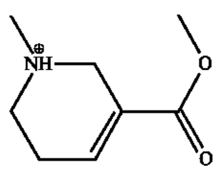
Key words: *A. catechu*, pharmacological effects, antinematodal, antibacterial, anti-venom

INTRODUCTION

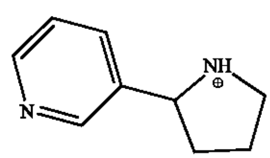
Areca catechu Linn. (Palmae, Arecaceae) commonly known as Betel palm or Betel nut tree is a species of palm. *Areca* palms are grown in India, Malaysia, Taiwan and many other Asian countries for their economically important seed crop. The seed contains alkaloids such as arecaidine and arecoline, which when chewed is intoxicating and is also slightly addictive. It is a medium-sized tree growing to 20 m tall with a trunk 20-30 cm in diameter. The leaves are 1.5-2 m long, pinnate with numerous crowded leaflets. *Areca catechu* nut is aromatic and astringent and is said to intoxicate when first taken. The natives chew these nuts all day. In India the nut has long been used as a taeniafuge for tapeworm (Grieve, 1995). *Areca catechu* nuts are extensively used as a masticatory either alone or with betel leaves. They are also employed for industrial and medicinal purposes. Powdered nuts are prescribed in diarrhea and urinary disorders (Anonymous, 1985).

Chemical composition: The main constituents of the areca nut are carbohydrate, fats, fibre, polyphenol including flavonoids and tannins, alkaloids and minerals (IARC, 2004). The fatty acid constituents of the *A. catechu* nut oil are; lauric 19.5, myristic 46.2, palmitic 12.7, stearic 1.6, decanoic 0.3, oleic 6.2, linoleic 5.4, dodecenoic 0.3, tetradecenoic 0.6 and hexadecenoic 7.2%. The chief component glycerides are 56% of fully saturated (trimyristin, dimyristins and lauromyristopalmitin); 30% monounsaturated-disaturated (mainly hexadeceno-lauromyristins) and 14% of diunsaturated-monosaturated (oleolinoleo-glycerides, mostly oleolinoleopalmitin). The amino acids present are traces of tryptophan, methionine and larger amounts of proline, tyrosine, phenylalanine and arginine. *Areca catechu* nut contains; tannin 8-18, non-tannin 7-15 and insolubles 42.44%. The tannins, commonly known as chogaru, are predominantly catechol tannins which closely resemble *Mimosa* bark tannins and are used to convert the putrefiable hides and skins into leather, for treating fishing nets and for making inks. The *A. catechu* tannins may also be used as a substitute for synthetic food colours. The polyphenols of *A. catechu* seed are mainly flavonoids and their concentration decreases with the maturity of the nut (Anonymous, 1985).

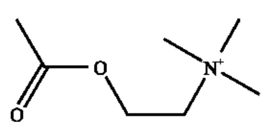
Areca catechu seed contains several alkaloids belonging to the pyridine group. Most important of them physiologically is arecoline (Chu, 2001). Other alkaloids present are arecaidine, arecolidine, guvacine, guvacoline, isoguvacine, norarecaidine and norarecoline (Anonymous, 1985; Giri *et al*., 2006). Arecoline has an effect similar to pilocarpine. It is reported to be cholinergic, exerting a sialagogue and diaphoretic action in normal dosage but in very large doses it depresses the central nervous system and paralyzes the muscles (Anonymous, 1985). It also has a stimulant effect on the occulomotor nerve causing mydriasis, followed by slight paralysis and dilation of pupil. In the liver homogenate, arecoline is decomposed to arecaidine which has no paralympathomimetic effects but only stimulating properties. Arecaidine does not affect the general activity of an animal but in higher doses exerts a sedative effect. Arecoline hydrochloride is found to be a mild antagonist of reserpine at a dose of 1 mg kg^{-1} intraperitoneally. Arecoline hydrobromide, a commercial salt, is a stronger stimulant to the salivary glands than pilocarpine and a more energetic laxative than eserine. It is used for colic in horses (Grieve, 1995). The active principle of *A. catechu* is an alkaloid, arecoline, which is considered to be the major constituent responsible for the toxicity (Anonymous, 1985). Arecoline, like nicotine, binds to certain receptors for acetylcholine.



Arecoline



Nicotine



Acetylcholine

Biological effects of *Areca catechu*: The *Areca* nut has been known for a long time for its narcotic-analgesic, sedative and antidepressant properties (Dar and Khatoon, 2000; Pichini *et al*., 2005). In rural communities and regions where there is a food deficit, it is used as an appetite suppressant (Strickland *et al*., 2003). Lopez-Vilchez *et al*. (2006) reported a case of neonatal withdrawal syndrome in an infant born to a woman who was a chronic *A. catechu* nut user. Arecoline, the principal neuroactive alkaloid in *A. catechu* seed, was found in the mother's placenta.

Oral submucous fibrosis is a chronic disease characterized by subepithelial collagen deposition with formation of bands involving the oral cavity and adjacent structures. Oral submucous fibrosis is a precancerous condition. It is caused by chewing of betel quid (*A. catechu* L., Piper betel, lime and tobacco) and ready-made products like pan masala and gutka which also contain *A. catechu* seed (Reichart and Philipsen, 2006; Ariyawardana *et al.*, 2006). The habit of chewing *A. catechu* nut independently contributes to the risk of both hyperglycaemia and type-2 diabetes in Taiwanese men. This association is dose-dependent with respect to the duration of *Areca* nut use and the quantity of *Areca* nut chewed per day (Tung *et al.*, 2004). Gilani *et al.* (2004) reported the presence of cholinomimetic and acetylcholinesterase inhibitory constituents in betel nut. Wang and Huang (2005) reported that ethanolic extract of *A. catechu* possesses low antibacterial activity against *Helicobacter pylori*. *Areca* nut extract suppresses T-cell activation and interferon-gamma production via the induction of oxidative stress (Abegunde and Adu, 2007). Arecoline is an important component of the areca. Arecoline stimulates the distal colonic spontaneous contraction in rats via M^3 receptor and M^3 receptor mediate the arecoline induced colonic contraction through extracellular Ca^{++} influx (Xie *et al.*, 2008). Due to this contraction of muscles, areca was earlier used to treat abdominal distension and constipation (Eglen, 2001; Xie *et al.*, 2002).

Anti-nematodal/helmintic activity: Alen *et al.* (2000) have evaluated the antinematodal activity of some tropical rainforest plants against the pinewood nematode, *Bursaphelenchus xylophilus*. It was found that three extracts of *Bischofia javanica*, *Knema hookeriana* and *Areca catechu* exhibited very strong activity at minimum effective dose of 0.7 mg/cotton ball.

Antioxidant activity: Methanolic extract of *Areca catechu* showed anti-aging and strong scavenging activity against super-oxide anion radical (Ohsugi *et al.*, 1999). Lee *et al.* (2003) have screened out methanolic extracts of nine medicinal plants traditionally used in Chinese medicine for antioxidant activity versus resveratrol which has been shown to protect cells from oxidative damage. The extracts of *A. catechu* strongly enhanced viability against H(2)O(2)-induced oxidative damage in Chinese hamster lung fibroblast (V79-4) cells. Relatively high levels of 1,1- diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity were detected in *A. catechu*. The activities of superoxide dismutase, catalase and glutathione peroxidase were dose dependently enhanced in V79-4 cells treated with most of the plant extracts. The extracts of *A. catechu* showed higher antioxidant activity than resveratrol in all experiments.

Modulation of phagocytosis, chemotaxis and adhesion of neutrophils: Hung *et al.* (2006) have determined the effects of *Areca* nut on phagocytosis, chemotaxis and adhesion of human neutrophils. The aqueous extracts of ripe *Areca* nut without husk (rANE) and fresh and tender *Areca* nut with husk (tANE) inhibited the phagocytic activity of neutrophils in a dose-dependent manner. The levels of internalized fluorescent bacteria in neutrophils decreased after ANE treatment (Hung *et al.*, 2005). However, exposure of neutrophils to rANE and tANE stimulated the chemotaxis activity of neutrophils to N-formyl-Met-Leu-Phe and enhanced the adhesion of neutrophils to human aortic endothelial cells in a dose-dependent manner. Moreover, treatment of neutrophils with rANE was more effective than incubation with tANE.

Effects on sperm motility and cyclooxygenase-2 expression: Er *et al.* (2006) have reported that sperm motility significantly decreases after arecoline treatment. *In vitro*, arecoline induces the cyclooxygenase-2 expression of sperm cells in a dose-dependent manner. This is the first report to demonstrate that arecoline may mediate cyclooxygenase-2 expression in human sperms, resulting in inflammation response. This situation may act on the structure responsible for the flagellar motion and cause the reduction of sperm motility.

Effects of arecoline on catecholamine release from perfused rat adrenal gland: Lim and Kim (2006) have studied the effects of arecoline, an alkaloid isolated from *A. catechu*, on the secretion of Catecholamines (CA) evoked by cholinergic agonists and the membrane depolarizer from isolated perfused rat adrenal gland. Arecoline dose-dependently inhibits CA secretion from isolated perfused rat adrenal gland evoked by activation of cholinergic receptors. At lower doses arecoline does not inhibit CA secretion through membrane depolarization, but at larger doses it does. This inhibitory effect of arecoline may be mediated by blocking the calcium influx into the rat adrenal medullary chromaffin cells without the inhibition of Ca^{2+} release from the cytoplasmic calcium store.

Areca in management of psychiatric disorders and Alzheimer's disease: Arecoline present in areca nut has been used to treat both depression and schizophrenia (Dar and Khatoon, 2000; Sulivan, 2000). Arecoline has been used to treat patients with Alzheimer's prehensile dementia (Christie *et al.*, 1981). The response is not equally effective in all persons. There are sum-populations among elderly both with and without Alzheimer's disease, who respond differently to the same drugs (Francis *et al.*, 1999).

Anti-venom activity: Tannins from plants are used as antidote of snake venom (Okuda *et al.*, 1991), which interact with snake enzyme systems (Mahanta and Mukharjee, 2001). Pithayanukul *et al.* (2005) tested plant polyphenols from the aqueous extracts of *Areca catechu* and other plants for their inhibitory activities against *Naja kaouthia* (NK) venom by *in vitro* neutralization method. *Areca catechu* extracts could completely inhibit the lethality of the venom. The ED_{50} of plant tannins in inhibiting NK venom activities varied according to condensed tannins and their content in the extracts. The anti-venom activities of these plant polyphenols by selectively blocking the nicotinic acetylcholine receptor and non-selectively by precipitation of the venom proteins were suggested.

Immunosuppression, hepatotoxicity and depression of antioxidant status: Dasgupta *et al.* (2006) have reported that arecoline arrested splenic lymphocyte cell cycle at lower concentration with induced apoptosis at higher concentration there by causing immunosuppression in arecoline recipients. Besides, it resulted in hepatotoxicity in arecoline recipient mice by disrupting the hepatocyte ultrastructure, as judged by liver ultrastructural studies that showed decreased nuclear size, RER with profusely inflated cysternae and abundance of lipid droplets and by up regulating hepatotoxic marker enzymes (SGOT and SGPT) in serum. Arecoline also caused depression of antioxidants, i.e., Superoxide Dismutase (SOD), catalase, reduced glutathione (GSH) and Glutathione-S-Transferase (GST) that are known to neutralize reactive oxygen species. Chang *et al.* (2009) reported that *Areca* nut extracts induced the complexes cytokine profile. Cytokines represent a central role in inflammatory tissue destruction and regulate the immune responses of *Areca* nut extracts increased the expression of inflammatory cytokines, tumor necrosis factor d, interleukin- 1β, 6 and 8 in peripheral blood mononuclear cells. According to Chang *et al.* (2009) oxidative stress is involved in areca nut extract- associated immune alteration.

Oral toxicity/cancer: Use of areca nut is associated with a number of important oral disorders including leukoplakia, oral submucous fibrosis (OSF), oral squamous cell carcinoma and pharyngeal carcinoma (Jeng *et al.*, 1999; Trivedi *et al.*, 2002; Lee *et al.*, 2005). The incidence of oral cancer is high in Asia, where a high proportion of the population has areca nut habits (Parkin *et al.*, 2002, 2003). Merchant *et al.* (2000) have shown that areca nut chewing cause 9.9 times more risk of developing oral cancer than no-chewers. Lin *et al.* (2006) reported that *Areca* (betel)-chewing is associated with the high prevalence of Oral Squamous Cell Carcinoma (OSCC) in Asians. NFKβ1 encodes a 105 kDa protein that can be processed to produce p50 subunit of nuclear factor-kappaβ protein complex. A insertion (ins)/deletion (del) polymorphism (-94ins/delATTG) in NFKβ1 promoter, which may drive the ins allele two-fold increase in NFKβ1 transcription relative to del allele, was recently found. This study identified that the odds ratio in OSCC carrying ins allelotype were 1.78 relative to controls (56.7 vs. 41.8%) in subjects more than 50 years old. L allelotype of heme oxygenase-1 (HO-1), accounting for a long (GT) (n) repeat in HO-1 promoter, is associated with the risks of areca-related OSCC. Subjects carried both NFKβ1 ins and HO-1 L allelotypes had significant risks for various subsets of OSCC. OSCC with lymph node metastasis or advanced stage had significantly higher frequency of NFKβ1 ins and HO-1 L allelotypes. This study suggested that the functional NFKβ1 promoter polymorphism could be valuable for assessment of cancer risk.

Molluscicidal activity: Jaiswal and Singh (2008) reported that *A. catechu* seed is a potential source of botanical molluscicides against *Lymnaea acuminata*. These snails are the intermediate host of liver fluke *Fasciola hepatica* and *F. gigantica*, which causes 94% fascioliasis in the buffalo's population of northern India (Singh and Agarwal, 1981, 1983). The active molluscicidal components of *A. catechu* seed are soluble in chloroform, ether, acetone and ethanol. The toxicity of ethanolic extract of *A. catechu* seed is higher than other extracts which indicates that the molluscicidal component present is more soluble in ethanol than other organic solvents. Jaiswal and Singh (2008) and Jaiswal *et al.* (2008) characterized that arecoline is the main molluscicidal components of *A. catechu*.

The toxicity of the active component of *A. catechu* seed, i.e., arecoline (96 h LC_{50} 0.14 mg L^{-1}) is more pronounced against *L. acuminata* than the active molluscicidal component allicin (96 h LC_{50} 3.14 mg L^{-1}) of *Allium sativum* (Singh and Singh, 1995); azadirachtin (96 h LC_{50} 0.35 mg L^{-1}) of *Azadirachta indica* (Singh *et al.*, 1996); gingerol (96 h LC_{50} 1.87 mg L^{-1}) of *Zingiber officinale* rhizome (Singh *et al.*, 1997); ferulic acid (96 h LC_{50} 1.06 mg L^{-1}) and umbelliferone of *Ferula asafoetida* (96 h LC_{50} 1.10 mg L^{-1}), eugenol (96 h LC_{50} 1.41 mg L^{-1}) of *Syzygium aromaticum*, limonene (96 h LC_{50} 1.13 mg L^{-1}) of *Carum carvi* (Kumar and Singh, 2006), papain (96 h LC_{50} 9.74 mg L^{-1}) of *Carica papaya* (Jaiswal and Singh, 2008) and trimyristin (96h LC_{50} 7.01 mg L^{-1}), myristicin (96 h LC_{50} 0.16 mg L^{-1}) of *Myristica fragrans* (Jaiswal and Singh, 2009).

A comparison of the molluscicidal activity of column purified fraction of *A. catechu* seed and active component arecoline with that of synthetic molluscicides clearly demonstrates that the purified fraction and arecoline are more potent. Thus, the 96 h LC_{50} of column purified fraction of *A. catechu* seed (3.99 mg L^{-1}) and arecoline (0.14 mg L^{-1}) against *L. acuminata* are lower than those of synthetic molluscicides- carbaryl (4.40 mg L^{-1}), phorate (15.0 mg L^{-1}), formothion (8.56 mg L^{-1}) (Singh and Agarwal, 1983) and aldicarb (11.50 mg L^{-1}) (Singh and Agarwal, 1981). Molluscicidal activity of arecoline (24 h LC_{50} 0.49 mg L^{-1}) is about 24.08 times stronger than the standard molluscicide niclosamide (24 h LC_{50} 11.8 mg L^{-1}) against *L. acuminata* (Singh and Agarwal, 1984).

CONCLUSIONS

Information from extensive literature review indicates that *A. catechu* has a broad spectrum of pharmacological effects. There are a number of studies which conclude that *A. catechu* is the main constituent responsible for oral cancer. However most of the pharmacological activities like antinematodal, antibacterial, anti-venom, antioxidant and molluscicidal activity of *A. catechu* are well accepted because of the wealth of scientific literature supporting these effects. More research should be undertaken to determine its efficacy against several diseases on man with respect to other natural products and modern drugs. Therefore, *A. catechu*, deserves more attention by scientific community and public health specialists to explore its full range of benefits in the welfare of the society.

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