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A REVIEW ON PHYTOCHEMICAL AND PHARMACOLOGICAL POTENTIAL OF *ARECA CATECHU* L. SEED

M. Senthil Amudhan*[1], V Hazeena Begum [2] and K. B. Hebbar [3]

Division of Physiology and Biochemistry, Central Plantation Crops Research Institute [1], Regional Station, Vittal-574 243, Karnataka, India

Department of Siddha Medicine, Faculty of Science, Tamil University [2], Vakaiyur, Thanjavur- 613 010, Tamil Nadu, India

Division of Physiology and biochemistry, Central Plantation Crops Research Institute [3], Kasaragod-671124, Kerala, India

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Correspondence to Author:

M. Senthil Amudhan

Division of Biochemistry, Central Plantation Crops Research Institute, Regional Station, Vittal-574 243, Karnataka, India

E-mail: senjp@yahoo.com

ABSTRACT

Arecanut seed has been used for medicinal properties more than 2000 years in South Asian countries. In fact, various pharmacological activities have been found in the arecanut seed extract or its constituents. Prevention of oxidative stress induced diseases is an urgent problem in all over the world. Traditional use of the plant for medicinal properties is to be documented for their possible use as future medicines or drugs. There is a need for identifying native natural plant sources to acquire to their recognized medicinal properties, which may widen them to use as new therapeutics for various diseases. In the present article, it has been described about usefulness of arecanut as an herbal drug and its therapeutics application prospects.

INTRODUCTION: Traditional use of medicines is recognized as a way to learn about the potential of future medicines. Plants have evolved the ability to synthesize chemical compounds that help them defend against attack from a wide variety of predators such as insects, fungi and herbivorous mammals. Many compounds are secondary metabolites generally involved in plant adaptation to environmental stress conditions.

Plants are a tremendous source for the discovery of new products of medicinal value for drug development. Today several distinct chemicals derived from plants are important drugs used in one or more countries in the world.

Many of the drugs used today are simple synthetic modifications or copies of the naturally obtained substances [1]. A vast number of natural, plant-based extracts and chemicals are purported to have beneficial effects are present in India.

Plant profile:

Arecanut: Arecanut palm (*Areca catechu* L.) is cultivated primarily for its kernel obtained from the fruit which is chewed in its tender, ripe or processed form. Arecanut belongs to the family *Palmae*.

Arecanut is the seed or endosperm (nut) of *Areca catechu* Linn. (Family: Palmaceae) Palm. *Areca catechu*, a slender, single-trunked, monoecious palm with a prominent crown shaft. In India, in the early Christian era, arecanut use was frequently referred to in Sanskrit medical literature and later also in the Hindu and Buddhist writings.

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The use of betel nut, as a masticator by humans has been known since the 4th century AD in different parts of the world.

In old Indian scripts, such as Vagbhata (4th century) and Bhavamista (13th century), betel nut has been described as a therapeutic agent for leucoderma, leprosy, anemia obesity and de-worming properties. It has been used as vermifuge. Arecanut finds place in religious, social and cultural functions of India. The presence of the betel nut is a must in the ceremonial plate, as betel nuts are believed to increase prosperity. The nut is offered to guests, along with a betel leaf, as a mark of respect. Betel quid chewing (betel leaf, arecanut and lime) in India is at least 2,000 years old. Tobacco was introduced around the sixteenth century.

Botanical name:

- Kingdom : *Plantae*
- Order : *Arecales*
- Family : *Arecaceae*
- Genus : *Areca*
- Species : *Areca catechu* L.

Local names

- Hindi, Bengali: Supari
- Tamil: Kamugu, pakku (fruit).
- Malayalam: Kavugu, Adakka
- Telugu: Pokavakka
- Kanada: Adakka
- Malay: Pinang Supari Palm.
- English: Betel nut palm, Supari palm, Pinang Palm

Arecanut palm has a slender single trunk, 30 meters tall and about 20 centimeters wide; annual rings are formed from the remains of leaf scars. Its leaves are pinnate, with a rigid, rachis and several rigid, closely packed segments. Flowers, yellow and fragrant, are unisexual, clustered in inflorescences, and enveloped by two spathes; male flowers are located at inflorescence apex, along with female flowers, present in the base. Fruits are hard, ovoid, red-orange colored; they possess a fibrous mesocarp and a thin woody endocarp enveloping one seed [2]. The palm prefers moist soil with suitable drainage and a moist tropical climate. The palm is mainly propagated from seeds.

Arecanut Phytochemistry:

1. **Polyphenol:** Arecanut contains main biochemical compounds like polyphenol (20%), fat (15%), starch (20%) and alkaloids (0.5%) [3]. The polyphenol, mostly flavonols, include about 10 percent of (+) catechin, 2.5 per cent epicatechin, 12 per cent of (+) leucocyanidin, the remaining portion being complex flavonoids in varying degrees of polymerization [4]. A series of dimeric, trimeric, and tetramertic procyanidins has been isolated from seeds of *Areca catechu* [5].

2. **Alkaloid:** The four major alkaloids isolated in arecanut are arecoline (7.5 mg/g weight), arecaidine (1.5 mg/g weight), guvacoline (2.0 mg/g weight) and guvacine (2.9 mg/g weight) [6]. All these alkaloids are chemically related; arecoline is colorless volatile resembling nicotine.

3. **Fat:** Fat consist 15-17.7% dry weight of arecanut. Arecanut fatty acid profile are 19.5% lauric acid, 46.2% myristic acid, 12.7% palmitic acid, 1.6% stearic acid, 0.3% decanoic acid, 6.2% oleic acid, 5.4% dodecenoic acid, 0.3%, tetradecenoic acid 0.6% and hexadecenoic acid 7.2% [7].

4. **Mineral content:** The mineral matter includes calcium (0.05%), phosphorus (0.13%) and iron (1.5 mg/100g). It also contains Vitamin B6 (286.9 mg) and Vitamin C (416.2 mg) [8].

Medicinal Actions and Uses:

1. **Antioxidant:** Ethanolic extract from arecanut showed potent anti-oxidative, free radical scavenging, and anti-hyaluronidase activity. Anti-oxidative effect of the extract was lower than butylated hydroxytoluene, but similar to tocopherol and higher than ascorbic acid [9]. Arecanut extract showed 1, 1 diphenyl 2-picryl (DPPH) free radical scavenging activity [10] and strong scavenging activity against superoxide anion radical ($*O_2$) evaluated by electron spin resonance (ESR) technique [11].

   Arecanut extract shwed *in vitro* inhibitory effect of on H_2O_2 induced RBC hemolysis [12].

2. **Anti-inflammatory/Anti-Melanogenisis:** Arecanut extract topical application inhibits hyaluronidase activity in vivo on delayed hypersensitivity and croton-oil induced ear edema in mice when it was. These results strongly suggest that arecanut extract may reduce immune- regulatory/ inflammatory on skin problem. Skin whitening effect of arecanut extract showed through inhibitory activity on mushroom tyrosinase activity and melanin synthesis in B16 melanoma cells. This study indicates that arecanut extract effective anti-inflammatory/ anti-melanogenesis agent and can be used as a new agent for cosmetics [13].

3. **Skin aging and Cosmetics:** The anti-aging effects of *Areca catechu* L., on the skin were investigated both *in- vitro* and *in-vivo*. The arecanut extract has a high proportion of proline (13%) of free amino acid content. The inhibitory effect of the arecanut extract on the elastase exhibited 37-90% inhibition on porcine pancreatic elastase (PPE) and human leukocyte elastase (HLE), respectively. The number of elastin fibers was increased with arecanut extract. The arecanut extract showed protection of elastic fiber against degradation by elastase enzyme *in vitro* assay. The arecanut extract increased proliferation of human fibroblast cell compared with control and standard ascorbic acid. The treatment with arecanut extract showed an increase in collagen synthesis, improvement in skin hydration, the skin elasticity, and skin wrinkles and suggested that arecanut extract can be used as a new anti-aging component for cosmetics [14].

   Arecanut extract reported to have inhibitory activity on elastase and hyaluronidase enzymes present in the skin tissues and arecanut extract purified by solvent fraction and identified to be phenolic substance which showed competitive inhibition with the substrate. These results suggest that phenolic substance purified from *A. catechu* has an anti-ageing effect by protecting connective tissue [15].

4. **Hypoglycemic activity:** Arecoline was investigated and reported to have hypoglycemic activity in an animal model of diabetes upon subcutaneous administration. Subcutaneous administration of an alkaloid fraction of *Areca catechu* to alloxanized rabbits showed a significant hypoglycemic effect lasting for 4/6 hours [16].

5. **Hypolipideamic:** Areca extracts found to exhibit a strong inhibitory activity on cholesterol absorption in high-cholesterol-fed rats. In another study, rats were fed a diet containing corn oil with areca nut extract supplement. The supplementation of the arecanut extract significantly lowered the absorption of triglyceride and the plasma lipid concentration [17].

   Arecanut extracts were found to exhibit *in vitro* strong inhibitory activities against pancreatic cholesterol esterase (pCEase) and found to lower the absorption of dietary cholesterol ester [18]. Furthermore, both absorption of intestinal free cholesterol and small intestinal pCEase activity were significantly lowered when fed a diet containing free cholesterol with areca nut extract supplement [19].

6. **α-Glucosidase inhibitory and Hypoglycemic activities:** α-Glycosidase *in-vitro* inhibitory activity and hypoglycemic effect by oral administration in rats of arecanut ethanol extracts have been investigated. Arecanut extract showed in-vitro inhibitory activity of intestinal α- glucosiadse enzymes maltase and sucrase and IC_{50} values of maltase and sucrase activity was found to be 12 µg/ml and 30µg/ml of arecanut extract respectively.

   The postprandial elevation in blood glucose level at 30 and 60 min after administration of maltose, but when administration of maltose with ethanol arecanut extracts (250 mg/kg and 500 mg/kg doses) showed significant suppression compared to control group rats in blood glucose level at 30 and 60 min. These results suggested that the arecanut extract has potent α-glucosidase inhibitors and would be effective in the suppression of elevation in blood glucose after oral administration of maltose to rats [20].

7. **Antihypertensive:** Arecanut fraction reported to have potent *in vitro* inhibitory activity on angiotensin-converting enzyme (ACE). Oral

administration of arecanut fraction spontaneous hypertensive rats (SHR) produced a lasting, dose-related antihypertensive effect, and the responses obtained with doses of 100 and 200 mg/kg were comparable to those of captopril at doses of 30 and 100 mg/kg. Intravenous administration arecanut fraction to SHR produced a rapid and marked reduction in blood pressure at doses of 10 and 15 mg/kg. The maximum antihypertensive effect of arecanut fraction at an I.V. dose of 15 mg/kg, was about 5 times as large as that of captopril at the same dose [21].

8. **Vascular-relaxation:** *Areca catechu* extract found to have relaxed aortic ring preparations of isolated rat aorta that contain endothelium and relaxation have not occurred in specimens without endothelium, while, inhibition had found during pretreatment with NG-nitro-1-arginine methyl-ester (L-NAME) [22].

   Arecoline found to have relaxed the human umbilical artery and vein rings in a concentration dependent manner; the higher the concentration of arecoline, the greater the relaxation of the rings and that relaxation was decreased after the endothelium removed or pretreated with L-NAME, a nitric oxide synthase inhibitor. Arecoline increased in a dose-dependent way the cGMP levels of human umbilical arteries and veins. Therefore, the relaxant effects of arecoline on the umbilical artery and vein rings were endothelium-dependent through the NO-cGMP systems [23].

9. **Antidepressant:** Antidepressant activity was evaluated in rodents using the forced swimming and tail suspension tests. The ethanol extract (4-80 mg/kg) caused a significant reduction in the immobility time without effecting spontaneous motor activity. This finding suggests that the ethanol extract possesses antidepressant activities [23]. Arecanut dichloromethane fraction from nut has a suppressive effect on withdrawal signs in morphine dependent mice [25]. A single intra-peritoneal injection of dichloro-methane fraction significantly delayed the onset of withdrawal jumping behavior in a concentration-dependent manner compared to saline controls. The dichloromethane fractions also significantly decreased jumping numbers and fecal and urinary excretions during the withdrawal period [25].

10. **Antimicrobial:** Arecanut fatty acids (myristic and oleic acids) and procyanidins from betel nuts (the seed of *Areca catechu* L.) were respectively revealed to be the major antibacterial principles against a primary cariogenic bacterium, *Streptococcus mutans*, and the major inhibitory activity against glucosyltransferase from *S. mutans* [26].

    Arecanut extracts inhibited the growth of the salivary organisms, which were cultured from the saliva after chewing boiled areca nut, such as *Streptococcus mutans, Streptococcus salivarius, and Fusobacterium nucleatum* and *Staphylococcus aureus*, in a concentration dependent manner, baked and boiled nuts were reported to show more potent than raw nut. It has been reported that hydrolysable tannins in the tannin fraction, which include tannic acid, could be responsible for the antibacterial properties of the nut and that prolonged intra-oral exposure to the nut can suppress bacteria in the mouth [27].

    Areca catechu reported to show inhibitory effects on the growth of *Streptococcus mutans* and *Streptococcus salivarius,* respectively and 5'-nucleotidase inhibitory activity, which may be useful dental anti-plaque preventing agents [28].

11. **Wound healing profile of *Areca catechu* extracts:** The arecoline alkaloid, polyphenol of arecanut and the combined formulation enhanced the breaking strength in the incision wound model. All the extracts increased the wound contraction on the 4th and 16th day and the period of epithelization. In the dead space model, only the areca alkaloid fraction enhanced the tensile strength of granulation tissue. This study showed that the alkaloid of arecanut and polyphenols of areca could be used to enhance the healing of burn wounds, leg ulcers and skin graft surgery [29].

12. **Protective effect of *Areca catechu* extract on ethanol induced Gastric Mucosal Lesions:** The Antiulcerogenic activity of defatted ethanol extract of *Areca catechu* was investigated. Ethanol treatment significantly increased the levels of

gastric mucosal malondialdehyde (MDA, an index of lipid peroxidation), nitric oxide (NO) and increase in the activities of myeloperoxidase (MPx, an index neutrophil infiltration) and xanthine oxidase (XO) enzymes. Pretreatment with *A. catechu* in the doses of 250mg/kg and 500mg/kg b. wt., prevented the formation of gastric mucosal MDA, NO contents and activities of MPx and XO. Ethanol induction also showed a significant reduction of the gastric mucosal glutathione (GSH), sialic acid and deoxyribonucleic acid (DNA) levels. The pretreatment with *A. catechu* maintained the above parameters levels similar to normal control level. Based on these data, the protective effects of both 250mg/kg and 500mg/kg doses of *A. catechu* on ethanol induced gastric mucosal injury may be attributed to its antioxidant effect [30].

13. **Antiradical capacity:** The methanolic extract of *A. catechu* exhibited strong antiradical activities and reducing power. In addition, the methanolic extract of *A. catechu* extract contains significant amounts of phenols and flavonoids, which play a major role in controlling oxidation. The results imply that *A. catechu* extracts may be used as an antioxidant, leading to the possibility of developing naturel antioxidant material [31].

14. **Anti-allergic:** *Arecae semen* (*Areca catechu*) reported to have most potent inhibitor of antigen-induced degranulation in mast cells. *A. semen* (*Areca catechu*) *inhibited DNP-BSA-and compound 48/80*- induced degranulation in mast cells and found to have showed inhibitory activity on compound 48/80-induced systemic anaphylaxis by 46% in mice. *A. semen* also inhibited the expression of TNF-α and the activation of mitogen activated protein kinase, ERK1/2, which is critical for the production of inflammatory cytokines in mast cells, as indicated by the suppression of the activating phosphorylation of ERK1/2.

    These results suggest that *A. semen* (*Areca catechu*) may be useful for the treatment of various immediate and delayed allergic diseases [32].

15. **Anticonvulsant activity:** Arecaidine and guvacine, constituents of the nut of *Areca catechu*, inhibited the uptake of GABA and α-alanine, but had not that of glycine, by slices of cat spinal cord. Large doses of arecadine (1g/kg subcutaneous) marginally reduced the lethal effects of bicuculline in mice but appeared to have little or no anticonvulsant activity [33].

16. **Platelet Aggregation inhibitory activity:** Arecanut crude extract inhibited platelet aggregation induced by arachidonic acid, adenosine phosphate, platelet activating factor and epinephrine and Ca^{+} ionophore. Arecanut crude extract showed more potent inhibitory activities on ADP and Ca^{+} ionophore induced aggregation. Arecanut crude extract showed significant acetylcholine esterase inhibitory activity [34].

17. **Prevention of Dental Cavities:** Previously betel nut used in toothpaste to prevent cavities. Laboratory studies suggest that betel nut may have antibacterial effects, which may reduce the development of cavities [35]. *Areca*nut made into a dentifrice on account of its astringent properties. It is considered to strengthen the gum, sweeten breath. The seed reduced to charcoal and powered, forms excellent dentifrices [36].

18. **Central Nervous System Stimulant:** Betel nut may cause stimulant and euphoric effects. As a result, it is sometimes used for relaxation [37]. Severe skin inflammatory reaction halted When transdermal device to systemically deliver arecoline, a cholinergic, for use in the managing neurological disorder in humans [37].

19. **Anti-HIV activity:** Various active constituents like procyanidins, Areca tannin B1 and extracts of the arecanut seed showed HIV protease inhibition activity [38].

20. **Proteasome inhibitors:** The proteasome hydrolyze various cell cycle regulators, transcription factors and antigenic proteins, it is a promising target for the development of drug for the treatment of a range of pathologies such as cancer, inflammation, immune diseases and others) [39]. The 26S proteasome is a multicatalytic protease complex that plays an essential role in intracellular protein

degradation. Arecoline moiety has been considered as a potential substrate for catalytic threonine which present in the peptide portion derives from the protease [40]. Proteasome the catalytic site tripeptidic sequence of both N- and C-terminal derivatives were found to bind with arecoline derivatives [41].

21. **Molluscicidal activity:** In *in vivo* and *in vitro* exposure of arecoline (the active component of *Areca catechu* seed) significantly inhibited the acetyl-cholinesterase (AChE), acid and alkaline phosphatase (ACP/ALP) activity in the nervous tissue. In other study, the increasing-effect components for molluscicides isolated from the dry nut of *Areca catechu* L. were studied. The results showed that arecoline was the most effective and it could decrease remarkably the amount of drugs when used together [42, 43].

CONCLUSION: This article provides an overview of many characteristic of arecanut seed and therapeutic effect of phytochemical effect of its biochemical on various disease conditions. Arecanut seed biochemical compounds have been recently recognized as functionally active molecules, possessing antioxidant, antidiabetic, antiallergic and other useful properties, as well as exert protective effects against cardiovascular and other diseases. As mentioned in article that further studies are required to know the underlying mechanisms and type of biochemical compounds involved in this beneficial effect and to ensure these studies, it would enable for utilization in modern medicine.

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