Arecanut and Human Health

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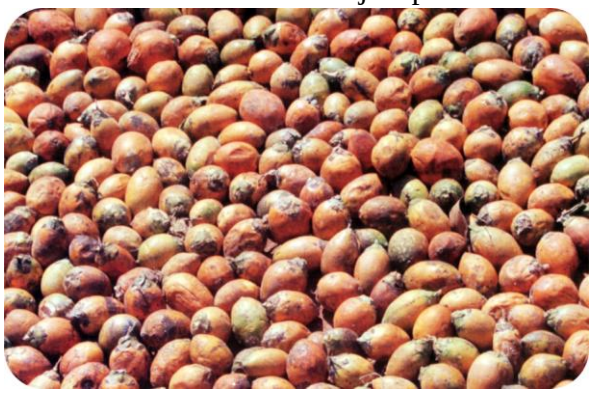
Health benefits of arecanut

1. Introduction

The arecanut (*Areca catechu* L*)* is an important commercial crop cultivated through tropical India, East Africa, Far East Asia, and South Pacific. India is the major producer and consumer of arecanut in the world. Areca nut production in India is the largest in the world, as per FAO statistics for 2016, accounting for 49.74 % of its world output, and is exported to many countries. It is estimated that nearly ten million people depend on areca nut industry for their livelihood in India. The fruits of arecanut are used in traditional herbal medicine. The nut has a characteristic astringent and slightly bitter taste. The nut may be used fresh or it may be dried and cured before use, by sun-drying, baking or roasting. 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. In India, the use of areca nut has been noticed as early as 1300 BC as cited by Sisu Mayana in 'Anjana Chaitra' and the practice of its chewing from 650 BC as mentioned by Magha in 'Shishupala Vadha'. In other countries such as Vietnam, the antiquity of areca nut even goes back to Bronze Age.



In India, areca nut and betel leaf are considered as sacred and no ceremonial function is complete without them.

2. Biochemical composition

The biochemical constituents in arecanut 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. The chemical composition of marketed arecanuts depends on the maturity of the nut since processed arecanuts are made from both green and ripe nuts. The major constituents are polyphenols, fat, polysaccharides, fibre and protein. Alkaloid is present as a minor but significant constituent. Polyphenols, which are the major components, constitute about 20 per cent of the dried arecanut. Some of the major polyphenols are (+) catechin, epicatechin, (+) leucocyanidin.

The arecanut has been shown to contain four alkaloids [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)]. Arecoline is the most important alkaloid and it is an oily liquid that is soluble in water, alcohols, and ether. Arecoline is the primary active ingredient responsible for the central nervous system effects of the areca nut. The overall pattern of chemical composition of the nut reveals that at tender stages, the total water extractives containing mainly polyphenols. Polysaccharides, fibre, fat and alkaloids are

formed rapidly in the middle stages. The hardening of the nut coincides with the drop in moisture content and formation of polysaccharides. All the major chemical constituents of arecanut, including arecoline decrease significantly while drying and storing with husk as whole nuts compared to fresh mature nuts and also while roasting, soaking and boiling.

3. Health benefits

Since time immemorial, arecanut is being used for chewing as it is believed to have lots of medicinal properties. It has an important place in the ancient Indian system of medicine such as Ayurveda, Unani and Homeopathy. WHO has listed out as many as 25 different beneficial effects of arecanut on mankind. Chewing arecanut sweetens the breath, removes bad taste from the mouth, strengthens the gums and checks perspiration. It has potent antioxidant, anti-inflammatory and analgesic, antiulcer, hypolipidemic, antidiabetic and neuroprotective properties. It is also traditionally used in a number of ailments for its laxative, digestive, carminative, antiulser, antidiarrhoeal, anthelmintic, antimalarial, antihypertension, diuretic, prohealing, antibacterial, hypoglycaemic, antiheartburn properties.

3.1 Hypoglycemic activity: Arecoline has hypoglycemic effect at low doses (0.05 - 0.25 mg per kg body weight) in an animal model of diabetes. Subcutaneous administration of an alkaloid fraction to alloxanized rabbits showed a significant hypoglycemic effect lasting for 4-6 hours. Arecanut extract also has potent -α glucosidase inhibitors and would be effective in suppression of elevation in blood glucose after oral administration of maltose to rats.

3.2 Parasympathetic action: Arecoline produces both the muscarinic and nicotinic actions of acetylcholine. As a result, bradycardia, hypotension, increase in intestinal tone, salivation and sweating are produced. Arecoline increases the tone and rhythm of the smooth muscles of alimentary canal. At presynaptic sites, arecoline appears to be useful for liberation and maintenance of neurotransmitter.

3.3 Cardiovascular Activity: All crude extracts of arecanut in different solvents - water, alcohol, acetic acid and calcium hydroxide - were found to cause capillary constriction. Cardiovascular effect of arecoline is mediated through the cholinergic system. It is effective by both subcutaneous and intravenous routes. Cardiac depression is brought about through vagal stimulation.

3.4 Vascular-relaxation: 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 nitric oxide synthase inhibitor. Arecoline increased the cGMP levels of human umbilical arteries and veins in a dose-dependent way.

3.5 Urine and electrolyte secretion: Arecoline hydrochloride (1.25 - 3.0 mg/kg subcutaneously) produced marked natriuresis and chlorouresis in hydrated dogs. This action is purely muscarinic. It has some direct effect on renal haemodynamics, as it affects the effective renal plasma flow. Arecoline increased Na, K and osmolity of urine without increasing the urine volume.

3.6 Ocular effects: Miotic effect of arecoline has been known for a long time. This effect is muscarinic in nature. It accelerate the regeneration of rhodopsin, a visual purple, by activation of the functional components other than the outer segments of the rod cells.

3.7 Antihelminthic Activity: Arecanut decoction (1 in 10 dilution) as well as arecoline and its salts have been found to be effective in taenia infections. Arecoline is reported to be useful in infections like fasciolopsian cestode, ascariasis, heterales and Rallietina sp. Areca is used in veterinary practice as a vermifuge for tapeworm and roundworm in dogs.

3.8 Antimicrobial activity: Polyphenols present in the arecanut inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Vibro cholerae* and *Salmonella typhi*strains. *E. coli* and *Pseudomonas* strains were inhibited larger extent than other bacterial strains, and is comparable with antibiotic gentamycin. Monomer catechol, epicatechol and condensed tannins or proanthocyanidins present in arecanut, collectively might be responsible for its antimicrobial activity.

3.9 Wound healing profile: Arecoline and polyphenol of arecanut and the combined formulation enhanced the breaking strength in the incision wound model. This suggest that arecanut could be used to enhance the healing of burn wounds, leg ulcers and skin graft surgery.

3.10 Antiulcer activities of arecanut: Arecanut at the dose of 250 mg/kg body weight prevent the formation ethanol induced gastric mucosal MDA, NO and there by possess antiulcerative activities. This protective action of arecanut on ethanol induced gastricmucosal injury may be attributed to its antioxidant effect.

3.11 Prevention of erythrocyte haemolysis: Ethanolic extract of arecanut inhibited H_2O_2-induced erythrocyte haemolysis in both old and young rats.

3.12 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.

3.13 Anti-inflammatory/Anti-Melanogenisis: Topical application of arecanut extract inhibits hyaluronidase activity *in vivo* on delayed hypersensitivity and croton-oil induced ear edema in mice. Skin whitening effect of arecanut extract showed through inhibitory activity on mushroom tyrosinase activity and melanin synthesis in B16 melanoma cells. Thus it is clear that arecanut extract is effective as anti-inflammatory/ anti-melanogenesis agent and can be used as a new agent for cosmetics.

3.14 Skin aging and Cosmetics: The anti-aging effects of arecanut on the skin were investigated both *in- vitro* and *in-vivo*. 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. Arecanut phenolics reported to have inhibitory activity on elastase and hyaluronidase enzymes present in the skin tissues and thus it has anti-ageing effect.

3.15 Hypolipideamic: Arecanut extracts found to exhibit a strong inhibitory activity on cholesterol absorption in high-cholesterol-fed rats. The supplementation of the arecanut extract significantly lowered the absorption of triglyceride and the plasma lipid concentration.

3.16 Antihypertension: 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.

3.17 Antidepressant: Antidepressant activity of arecanut ethanolic extract 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. Arecanut dichloromethane fraction from nut has a suppressive effect on withdrawal signs in morphine dependent mice.

3.18 Anti-allergic: Arecanut reported to have most potent inhibitor of antigen- induced degranulation in mast cells, and thus arecanut may be useful for the treatment of various immediate and delayed allergic diseases.

3.19 Anticonvulsant activity: Arecaidine and guvacine, constituents of the nut of arecanut exhibit anticonvulsant activity by inhibiting the uptake of GABA and α-alanine.

3.20 Platelet Aggregation inhibitory activity: Arecanut crude extract inhibited platelet aggregation induced by arachidonic acid, adenosine phosphate, platelet activating factor and epinephrine and Ca+ ionophore.

3.21 Prevention of Dental Cavities: Arecanut used in toothpaste to prevent cavities. Laboratory studies suggest that betel nut may have antibacterial effects, which may reduce the development of cavities. It is considered to strengthen the gum, sweeten breath. The arecanut reduced to charcoal and powered, forms excellent dentifrices.

3.22 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). Arecoline is reported to be a inhibitor of 26S proteasome, a multicatalytic protease complex that plays an essential role in intracellular protein degradation.

3.23 Antimalarial activity: Methaol extract of arecanut and its sub-fractions were evaluated for ant- malarial activities by using the SYBR-green method, and the butanol fraction of the extract showed anti-malarial activity against *Plasmodium falciparum* with an IC_{50} value of 18 µg/mL.

3.24 Psychiatric disorders and Alzheimer's disease treatment: Arecoline present in areca nut has been used to treat both depression and schizophrenia. Arecoline has been used to treat patients with Alzheimer's prehensile dementia.

3.25 Arecanut and cancer: Though arecanut has got all these beneficial properties, several researchers highlighted that arecanut chewing might cause cancer. But 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.

Arecanut was found to arrest the growth and multiplication of several human cancer cells such as MCP-7 breast cancer cells, SGC-7901 gastric cancer cells and SMMC-7721 liver cancer cells in dose dependant manner. Certain studies carried out on both normal as well as immune suppressed laboratory mice confirmed that the extracts of arecanut and betel quid without tobacco were not carcinogenic. It also reported that both riped and unripeed sundried arecanut was found safe and did not induce any tumor in mice at 1.0g/kg bw/day.

In a study conducted on the etiological factors in oral squamous cell carcinoma it was reported that 85% of cheek carcinoma patients were chewing betel quid with tobacco as against 12.5% in the control group. In another study it was found that the relative risk due to pan chewing without tobacco was found to be non-significant with both males and females whereas it was significantly more with pan chewing with tobacco. It also proved that the incidence of oral submucous fibrosis was directly related to chewing of kharra, gutkha or tobacco but not to arecanut.

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 arecanut 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 DNA damage while other solvent extracts did not.

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.

4. Conclusion

Arecanut seed possess therapeutic effect on various disease conditions. Beneficial health effects of arecanut may attract great attention for human health improvement. Studies conducted on certain rodents such as albino rats, mice and hamsters have confirmed that the arecanut was safe to these animals at a normal dose of 1.5 to 5g/kg body weight per day. This comes to 90 to 300g of arecanut for 60 kg body weight per day. Arecanut and its chewing products caused problems in experimental animals only in higher doses. 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.

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