



IJMPPO

Indian Journal of Medical and Paediatric Oncology

Official Publication of Indian Society of Medical and Paediatric Oncology



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Medknow

A review of the systemic adverse effects of areca nut or betel nut

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ABSTRACT

Areca nut is widely consumed by all ages groups in many parts of the world, especially south-east Asia. The objective of this review is to systematically review and collate all the published data that are related to the systemic effects of areca nut. The literature search was performed by an electronic search of the Pubmed and Cochrane databases using keywords and included articles published till October 2012. We selected studies that covered the effect of areca nut on metabolism, and a total of 62 studies met the criteria. There is substantial evidence for carcinogenicity of areca nut in cancers of the mouth and esophagus. Areca nut affects almost all organs of the human body, including the brain, heart, lungs, gastrointestinal tract and reproductive organs. It causes or aggravates pre-existing conditions such as neuronal injury, myocardial infarction, cardiac arrhythmias, hepatotoxicity, asthma, central obesity, type II diabetes, hyperlipidemia, metabolic syndrome, etc. Areca nut affects the endocrine system, leading to hypothyroidism, prostate hyperplasia and infertility. It affects the immune system leading to suppression of T-cell activity and decreased release of cytokines. It has harmful effects on the fetus when used during pregnancy. Thus, areca nut is not a harmless substance as often perceived and proclaimed by the manufacturers of areca nut products such as Pan Masala, Supari Mix, Betel quid, etc. There is an urgent need to recognize areca nut as a harmful food substance by the policy makers and prohibit its glamorization as a mouth freshener. Strict laws are necessary to regulate the production of commercial preparations of areca nut.

Key words: Adverse effects, areca nut, arecoline, betel nut, systemic effects

INTRODUCTION

Areca nut is the seed *Areca catechu*, and it grows in much of the tropical Pacific, Asia and parts of East Africa. It is also called as betel nut and is often chewed wrapped inside betel leaves (paan) or with tobacco (betel quid), the composition of which varies in different populations and countries.^[1,2] It is one of the most widely consumed addictive substances in the world after nicotine, ethanol and caffeine, and is consumed by approximately 10% of the world's population. Many reports suggest that chewing areca nut starts at a young age, and it is being consumed freely by children.^[3,4] The users of areca nut believe that it is helpful for the digestive system and has mild euphoric effects.^[3] Areca nut has wide-ranging effects on the human

body. It is associated with central obesity and type II diabetes.^[3] The IARC review concluded that areca nut is carcinogenic in humans and that it is linked to cancers of the oral cavity, pharynx, esophagus, liver and biliary tracts and the uterus.^[1] The effects of areca nut are diverse and can be compared with those of the other widely used addictive substances. The knowledge about areca nut and its effects is increasing very rapidly as more and more researches are being published.^[3]

MATERIALS AND METHODS

A systematic search of all the relevant literature was performed with keywords such as Non cigarette tobacco products, Carcinogens, Illegal tobacco products, Public policy, Toxicology. The literature search was performed using the Pubmed and Cochrane databases on articles published till October 2012. All the well-designed original studies published in English that covered the effect of areca nut on metabolism were selected. The literature was also enhanced by articles obtained as cross references from the bibliography of the selected articles. There have been lots of articles published on the effects of areca nut on

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DOI:
10.4103/0971-5851.133702

a single organ system or a cellular pathway, but literature showing the effect of areca nut on the human body as a whole is deficient. The aim of this article is to review and highlight the effects of areca nut on all the major organs and systems of the human body.

SYSTEMIC EFFECTS OF ARECA NUT

Metabolism of areca nut

There are four main alkaloids of areca nut, namely arecoline, arecaidine, guvacoline and guvacine [Figure 1]. The major parasympathetic and muscarinic effects of areca nut are due to arecoline. It has been presumed that both arecoline and arecaidine undergo glutathione conjugation as they form mercapturic acid in rats. The major metabolite of arecoline is arecoline 1-oxide. The main mode of arecoline metabolism appears to be hydrolysis to arecaidine and N-oxidation combined with double bond reduction of the arecaidine.^[5,6] The N-oxidation of arecoline to arecoline 1-oxidase takes place by flavin-containing monooxygenases 1, flavin containing monooxygenases 3 and not by P-450, which strongly suggests that this reaction may occur in tissues other than the liver, especially the kidneys, where flavin-containing monooxygenases 1 is found in abundance.^[6] This points to a possible role of the kidneys in the metabolism and toxicology of arecal alkaloids.^[6] The urinary metabolites of arecoline 1-oxidase are 50% arecoline 1-oxidase itself, 30% mercapturic acids

and their catabolic products and the remaining 20% are its N-oxide derivatives.^[6] A number of nitrosamines are also formed from the arecal alkaloids in the mouth, which play an important role in the causation of oral cancer, especially methylnitrosaminopropionitrile, which is the most carcinogenic among them.^[3,5,6] We hereby summarize the systemic effects of areca nut.

Effect on the nervous system

The effects of areca nut are mainly on the central and the autonomic nervous systems due to the alkaloid arecoline, which possesses parasympathomimetic properties stimulating both muscarinic and nicotinic receptors. Habitual users claim euphoria, a sense of well being, warmth, increased alertness, salivation, palpitation, anti-migraine and enhanced capability to work [Table 1].^[7] Areca nut use is associated with a dependency syndrome, which comprises increased concentration, mild euphoria, relaxation, postprandial satisfaction and a withdrawal syndrome associated with insomnia, mood swings, irritability and anxiety, the severity of which can be compared with that of amphetamine use.^[5] Areca nut leads to palpitation, increased blood pressure, increased body temperature, flushing and sweating within minutes of consumption.^[8] Significant slowing of prospective estimation of time intervals is noted with a decrease in choice reaction time, but without any effect on simple reaction time.^[9] Contrary to the popular belief, there is no significant effect on memory and concentration is actually decreased.^[9] A study comprising recording of EEG of 52 subjects before and after areca nut consumption showed that areca nut consumption caused α and β activity to increase with decreased θ activity. The changes in α activity are seen more in the occipital region, with more global changes in β and θ activity, which is consistent with a state of arousal and some degree of relaxation.^[7] There is no evidence to suggest that processing of visual information is facilitated by areca nut, but some peripheral stimulation may occur.^[10] Animal studies show that there is inhibition by areca nut of the enzyme iNOS, leading to decreased protein extravasation from the vessels, which explains its anti-migraine use by village folks in India.^[11] Arecoline, arecaidine, guvacine and guvacoline cause inhibition of neurosuppressive activity of gamma-aminobutyric acid (GABA) by blocking the receptors and inhibiting the uptake^[12] thus contributing to the euphoric effect and making a person resistant to benzodiazapines and predisposing to seizures.^[12] The schizophrenic users of areca nut show a decrease in both negative and positive symptoms and avoid other harmful recreational drugs and may have severe extrapyramidal symptoms on heavy usage due to arecoline, which has an antagonistic action to procycladine (an anti-cholinergic).^[13] Arecoline in concentrations above 50 μ M has been shown to cause

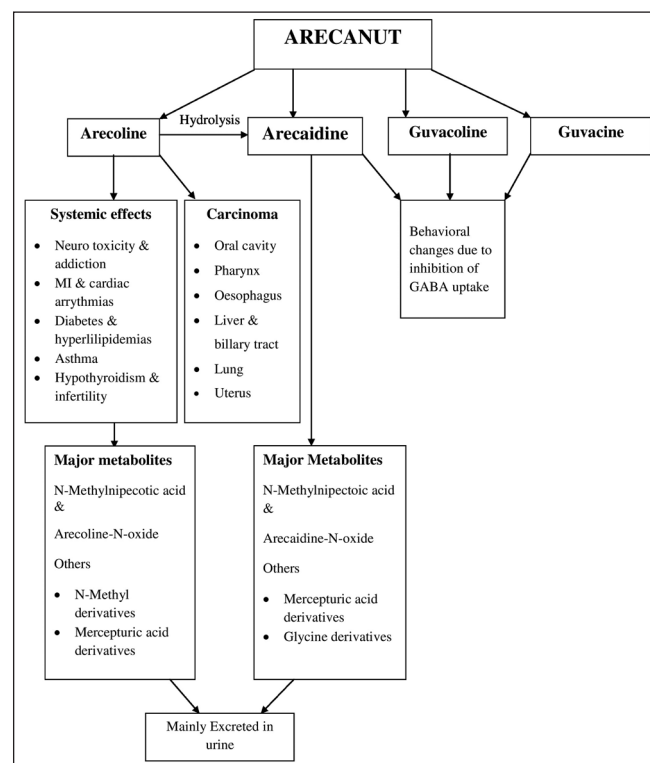


Figure 1: Major alkaloids of areca nut

Table 1: Summary of the systemic effects of areca nut

Site	Effect of areca nut	Pathway/mediators
Nervous system	Euphoria and dependency syndrome	GABA inhibition by arecoline
	Increased skin temperature	Arecoline effecting the ANS
	Salivation	
	Palpitation	
	Heightened alertness	Increased α and β activity
	Anti-migraine effect	Inhibition of iNOS
	Neurotoxicity	Suppression of anti-oxidative mechanisms
Cardiovascular system	Tachycardia and increased systolic BP	Central sympathetic response
	Decreased diastolic BP	Peripheral cholinergic effect
	Increased atherogenesis	Blocking of HDL receptors and inhibition of LDL uptake by the liver
	Coronary artery spasm	Parasympathomimetic effect of arecoline
	Increased risk of CAD	Atherogenesis and coronary artery spasm
Gastrointestinal system	Type II DM, hyperlipidemia, hypertriglyceridemia and metabolic syndrome	Arecoline inhibits adipocyte differentiation and insulin-promoted glucose uptake
	Hepatotoxicity	G ₀ -G ₁ cell cycle arrest and DNA damage
	Laxative and sialogogue effect	Action of arecoline on M ₃ receptors and AChE action
	Decreased growth in weight and BMI	Arecoline
Endocrine system and reproductive health	Thyroid	Arecoline
	Acute effect - increased T ₃ , T ₄ and decreased TSH	
	Chronic effect - hypothyroidism	
	Prostate hyperplasia	Increased expression of androgen receptors
	Infertility	Changes in sperm count, motility and morphology
	Fetus	
	Low birth weight and length, preterm labour	
	Increased exposure to teratogens and carcinogens	Arecoline
	Arrest of endothelial cell differentiation	
	Vitamin D deficiency	Increased expression of 25(OH)ase
Blood and its components	Increased fibrogenesis	Increased platelet aggregation, Ca ⁺⁺ and TXA ₂ release
	Decreased production of IL-2 and IFN- γ	Cytotoxic to splenocytes
	Suppresses T-cells and cytokine Th-1	Oxidative stress
	Cytotoxic to RBCs	Damages the RBC membrane
Leukotrienes and arachidonic pathway	Analgesic at high doses	Central and peripheral pathways
	Anti-inflammatory	Decreased release of leukotrienes, prostaglandins and histamines
	Carcinogenic and mutagenic effect	Stimulation of gingival keratinocytes
		Increased peroxy radicals
Respiratory system	Aggravation of asthma	Increased malonaldehyde
	Decreased FEV ₁	Arecoline
Acute toxicity of areca nut	Dyspnea, tachycardia, palpitations, chest tightness, vomiting, vertigo, dizziness, abdominal colic, rarely myocardial infarction and coma	Arecoline and other alkaloids

neuronal injury by causing an increase in oxidative stress and suppression of the anti-oxidant system of the nervous system, and, at higher concentrations, may cause cell death.^[14]

Effect on the cardiovascular system

Studies have confirmed that there is an increase in facial temperature by 0.5-2° C rapidly on consumption of areca nut. Areca nut consumption induces adrenal chromaffin cells to release increased catecholamines [Table 1].^[3] A study on 47 subjects showed that areca nut usage resulted in increased heart rate, irrespective of the frequency of usage, due to central sympathetic response, but the effect

on blood pressure is more varied, leading to a fall of the diastolic component due to the peripheral cholinergic effect and increase in the systolic component in nonhabitual users. Areca nut does not alter the cerebral blood flow as there is not much significant increase in blood flow of the internal carotid artery and middle cerebral artery.^[15-17] Arecoline has a blocking effect on the high-density lipoprotein receptor and inhibits the uptake of low-density lipoprotein by the liver thus leading to enhanced atherogenesis and its parasympathomimetic effect leading to spasm of the coronary arteries, both of which predispose to coronary artery diseases.^[18,19] Researchers in Taiwan have shown a

relative risk of coronary artery disease in areca nut chewers to be 3.5 in men and 1.37 in women, and the risk increases with the amount consumed.^[20,21] Studies have also linked areca nut chewing to cardiac arrhythmias like paroxysmal supraventricular tachycardia (PSVT), even causing death in a case despite exhaustive treatment.^[22]

Effect on the gastrointestinal system and food metabolism

Areca nut has diverse effects on the digestive system and metabolism of food in the human body. It leads to lowering of plasma cholesterol by up to 25% due to inhibition of intestinal acetyl co-enzyme acyltransferase (ACAT) and pancreatic cholesterol esterase (pACE), resulting in decreased cholesterol absorption [Table 1].^[23] Prevalence of type II diabetes, hyperlipidemia, hypertriglyceridemia and metabolic syndromes are more common in areca nut chewers as its metabolite, arecoline, inhibits adipogenic differentiation, induces lipolysis in 3T3-L1 adipocytes and interferes with insulin-promoted glucose uptake.^[24,25] Areca nut is hepatotoxic causing mixed type of hepatic injury, which is both cholestatic and hepatocellular, and it increases both serum transaminases and alkaline phosphatase.^[26,27] Animal studies have shown that in low doses (up to 0.5 mM), it causes G0-G1 cell cycle arrest and DNA damage and in higher doses (up to 1 mM), it causes apoptosis and necrosis, eventually leading to deranged hepatocyte growth, apoptosis, necrosis, liver cirrhosis and, finally, hepatocellular carcinoma.^[26,27] Arecoline neutralizes the effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, a toxic dye) by down-regulation of AhR on human hepatoma cells leading to attenuation of activation of CYP1A1 and thus suggesting a role of arecoline on AhR-mediated metabolism of environmental toxins by the liver.^[28] Areca nut chewers have increased gastrointestinal motility due to stimulation of colonic M3 receptors, which is dose dependent, and increased saliva secretion due to the presence of AChE inhibitors and arecoline, leading to laxative and sialogogue effects, respectively, which explains its use in the rural population.^[29,30] The increase in body weight and body mass index is slower in areca nut chewers as compared with nonchewers.^[31] A study on 458 rural subjects in the UK showed that areca nut chewers had a higher resting metabolic rate (effect seen more in males than females) by about 7% as compared with nonchewers, and this effect was due to areca nut metabolites that effect the thermoregulatory pathways, altering the thermogenic effects of the meal and also through centrally mediated effects by decreasing appetite for food.^[31-33]

Effect on the endocrine and reproductive systems

Animal studies have shown that arecoline in acute administration causes an increased release of T3, T4 and suppression of thyroid stimulating hormone (TSH); in

large doses, it activates the hypothalamic-pituitary-adrenal (HPA) axis, similar to stress response, and in regular use causes hypothyroidism [Table 1].^[34] Following regular areca nut use, the plasma concentration of melatonin decreases and that of serotonin increases. Areca nut causes an increase in testosterone concentration, but, interestingly, this effect is not seen with betel quid usage. Areca nut leads to an increased concentration of sialic acid in the seminal vesicle and fructose in the coagulating gland and increased expression of androgen receptors on prostate leading to hyperplasia and hypertrophy, causing problems of an enlarged prostate.^[35-37] Areca nut causes significantly decreased sperm motility, sperm count, sperm abnormalities and decreased activity of antioxidant enzymes, and may cause infertility with long-term usage.^[38] The salivary levels of female hormones progesterone and estradiol remain unchanged in habitual female chewers of areca nut.^[39] Areca nut users have aggravated effects of Vitamin D deficiency due to the powerful effect of increased expression of 25(OH)ase, leading to decreased serum calcitriol as areca nut has an independent effect on 25(OH)ase.^[40]

Effect on blood

Areca nut causes platelet aggregation associated with phospholipase C activation, mobilization of Ca⁺⁺, TXB₂, which leads to release of growth factors, and increased fibrogenesis that plays a crucial part in its effects on the oral mucosa and cardiovascular system [Table 1].^[41] Areca nut causes increased secretion of TNF- α and interleukin-1 β by mononuclear cells, which is time and dose dependent; interestingly, this effect is blunted by curcumin.^[42] Areca nut is cytotoxic to splenocytes and it decreases the production of IL-2 and IFN- γ ; interestingly, there is no effect on IL-4. Overall, it suppresses the activation of T-cells and production of cytokine Th-1 via increased oxidative stress thus interfering with the immune system.^[43] Destruction of important genes like p53 occurs with increased frequency when there is continuous exposure to areca nut, leading to proliferation of cells with damaged DNA and ultimately neoplastic changes.^[44] The cytotoxic effects of areca nut can be effectively countered by addition of foods rich in n-acetyl cystine or glutathione (GSH) as it increases the cellular thiol levels that prevent DNA damage.^[44] The blood of an habitual areca nut user should be used for transfusion cautiously as it is cytotoxic to RBCs, causing significant changes in morphology, loss of band 3 fraction, decreased osmotic deformability index and membrane sulfhydryl groups.^[45]

Effect on arachidonic acid and leukotrienes pathways

Areca nut has analgesic, anti-inflammatory and antioxidant properties. The analgesic effect is mediated by affecting both the central and the peripheral pathways, and the effect at a dose of 500 mg/kg is almost equivalent to pentazocine

[Table 1].^[46] The anti-inflammatory effect is mediated by reduction in release of prostaglandins, leukotrienes, histamines, IL-6, IL-1 and decreased expression of COX-2, which are pro-inflammatory, and increased release of IL-4, which is anti-inflammatory.^[46] The antioxidant properties are due to the increased concentration of total phenolic contents that help in scavenging free radicals.^[46] Areca nut induces increased production of PGE-2 and 6-keto-PGF β from gingival keratinocytes, IL-1 and decreased intracellular glutathione, which promotes inflammation and may contribute to sub-mucous fibrosis and oral cancer.^[47] Prostaglandin endoperoxidase synthase, an intracellular enzyme induced by areca nut, plays an important role in carcinogenesis by increasing peroxyl radicals, increasing malonaldehyde, which is mutagenic, and activation of carcinogens in extrahepatic tissues.^[48]

Effect on the respiratory system

Various case reports from different parts of the world have shown that the areca nut metabolite arecoline causes aggravation of disease in asthmatics by increasing bronchoconstriction in a dose-dependent manner and decreasing the forced expiratory volume in 1 second (FEV $_1$) by 30%; also, the rate of hospitalization is higher in asthmatics who chew areca nut [Table 1].^[49,50]

Effect on the fetus

Expectant mothers who consume areca nut have higher incidences of low birth weight, low birth length and preterm births.^[51] Areca nut in lower doses causes dilation of the umbilical vessels via eNOS, but with increased doses causes arrest of the endothelial cell differentiation and subsequently dysfunction.^[52] Betel quid chewers have a higher concentration of heavy metals like lead, arsenic and cadmium, which when taken by pregnant women is harmful to the fetus.^[53] Perinatal exposure to areca nut exposes the fetus to the harmful effects of carcinogens as the activity of -SH enzyme, melandialdehyde level, cytochrome-450 is altered [Table 1].^[54]

Acute toxicity

Reports are available that areca nut can cause acute toxic symptoms if taken in increased quantities, leading to dyspnea, tachypnea, tachycardia, palpitations, hypotension, chest tightness, nausea, vomiting, dizziness, abdominal colic and even myocardial infarction and coma, but, in the majority of the cases, the effects are transient and the patients have timely recovery [Table 1].^[55]

POLICY ISSUES

India has one of the highest incidences of oral cancer patients in the world. The age-adjusted rate of oral cancer

in India is 20/100,000 population, which accounts for more than 30% of the total cases of cancer.^[56] Areca nut, with its carcinogenic potential, is a contributor to the disease load. Despite contributing to numerous life-threatening diseases and carcinogenic properties, it is easily available in the country and freely consumed by all age groups. Areca nut is marketed as mouth freshener under several names such as Gutka, Paan masala, Supari mix, etc. While Gutka is a combination of smokeless tobacco and areca nut, Paan Masala/Supari Mix are pure areca nut products. The market turnover of Indian Gutka and Paan masala companies is more than 100 billion rupees, and billions more are spent on marketing.^[57] The prevalence of areca nut consumption with or without tobacco is very high in India and is a part of the normal social culture in the society, and is chewed for various reasons. In rural areas, it is consumed by about 34.7% of the males as compared with 32.4% of the females.^[58] In urban areas, the consumption rate among males is about 37.8% and in females it is about 29.7%.^[59] The use of areca nut products is prevalent in adolescents, where 16.4% use it regularly and 13% use it occasionally.^[60] Even the well-educated section of the society is consuming areca nut, where 12.5% do it regularly and 27.5% do it occasionally.^[61] It is important to note that consumption is higher in lower socio economic groups who are illiterate and daily wage earners.^[62] The Paan masala companies have stepped up their surrogate advertising in the form of mouth fresheners. This is creating a new generation of areca nut chewers in the form of naïve adolescents and youngsters. The Gutka companies had long bypassed the laws and continued their business virtually unhindered for many years. Many state governments in India have taken a positive step by banning the sale and production of Gutka. This ban is now effective in 20 states and three union territories of India. The huge loss of human lives and finances due to the morbidity and mortality caused by areca nut and Paan masala addiction is putting tremendous strain on the economy, and is much more than the revenue generated by this industry. The government needs to set up an areca nut control program. It is high time that stricter laws are made to regulate areca nut consumption and stern instructions are issued to the manufactures to have pictorial warnings on the products.

CONCLUSION

Areca nut is an addictive substance consumed in many parts of the world by people of all the age groups. Apart from being carcinogenic to the oral cavity, pharynx, esophagus, liver and uterus, it has many diverse effects on the human body affecting almost all the organs. The systemic effects of areca nut are mainly due to the principle alkaloid arecoline. Areca nut causes euphoria, increase in heart rate, increased blood pressure, GABA inhibition and damage to

neurons, but has no effect on concentration and memory. Areca nut causes hyperlipidemia, vasospasm and cardiac arrhythmias leading to an increased risk of myocardial ischemia. Arecoline interferes with the fat metabolism leading to Type II diabetes, metabolic syndromes and deranged blood lipid levels. Chronic areca nut consumption causes hypothyroidism, prostate hyperplasia, infertility and Vitamin D deficiency. Areca nut interferes with the immune system by interfering with the activation of T-cells and production of cytokines. Areca nut chewers are predisposed to asthma as it causes bronchoconstriction and decreased FEV₁. Women who consume areca nut regularly have more incidences of low birth weight and preterm deliveries. Thus, it is evident that areca nut is a harmful and addictive substance that affects the whole human body, and its use must be tightly regulated for the welfare of the society.

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How to cite this article: Garg A, Chaturvedi P, Gupta PC. A review of the systemic adverse effects of areca nut or betel nut. *Indian J Med Paediatr Oncol* 2014;35:3-9.

Source of Support: Nil. **Conflict of Interest:** None declared.

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