

Betel Nut

SCIENTIFIC NAME(S): *Areca catechu* L. Family: Palmaceae (palms)

COMMON NAME(S): Betel nut, areca nut, pinlang, pinang

CLINICAL OVERVIEW – Betel Nut

Uses: Betel nut is a CNS and salivary stimulant. The leaves may act as an antitussive and as a topical counterirritant. Antihypertensive, antidepressant, and antibacterial activity has been reported in some in vitro studies.

Dosing: Classical doses of betel nut are 2 to 8 g of the seed. A dose of 5 to 20 mg of arecoline was used in a study of appetite suppression.

Contraindications: Betel nut is contraindicated in patients with known hypersensitivity reactions to any of the components in the betel nut. The use of betel nuts during pregnancy is contraindicated. Betel nut chewing has been associated with an aggravation of asthma. A dose-response relationship may exist between the use of this drug and the development of asthmatic symptoms.

Pregnancy/Lactation: Documented adverse effects, including teratogenic and fetotoxic effects. Avoid use.

Interactions: Betel nut was reported to antagonize the anticholinergic effects of procyclidine in 2 patients, resulting in the occurrence of extrapyramidal symptoms.

Adverse Reactions: Betel may exacerbate asthma and cause periodontitis. It is contraindicated in patients with known hypersensitivity reactions to any of the components in the betel nut. The use of betel nuts during pregnancy is contraindicated.

Toxicology: Oral cancer and precancerous conditions are common among users, possibly because of other components of the quid.

BOTANY: The areca tree is a feathery palm that grows to approximately 15 m in height. It is widely cultivated in tropical India, Bangladesh, Japan, Sri Lanka, south China, the East Indies, the Philippines, and parts of Africa.¹⁻³ The tropical palm trees bear the fruit all year.¹ The nut is about 2.5 cm in length⁴ and may be used fresh, dried, or cured by boiling, baking, or roasting.¹

HISTORY: The chewing of betel nut quids dates to antiquity. In the 1st century AD, Sanskrit medical writings claim “betel possesses thirteen qualities to be found in the region of heaven. It is pungent, bitter, spicy, sweet, salty and astringent. It expels wind, kills worms, removes phlegm, subdues bad odors, beautifies the mouth, induces purification and kindles passion.”⁵ It is used primarily as a mild CNS stimulant and

digestive aid. The quid generally is composed of a mixture of tobacco, powdered or sliced areca nut, and slaked lime often obtained from powdered snail shells.² This mixture is wrapped in the leaf of the betel vine (*Piper betel* L. Family: Piperaceae). Users may chew from 4 to 15 quids a day with each quid being chewed for about 15 minutes.⁶ A correlation exists between the betel quid or areca nut chewing habit and oral cancer.²

Because of its CNS stimulating effects, betel nut is used in a manner similar to the western use of tobacco or caffeine.⁷ Chewing the nut stimulates salivary flow, thereby aiding digestion. Betel nut also has been used as an appetite stimulant.² The leaves have been used externally as a counterirritant and internally as an antitussive.

CHEMISTRY: The medicinal components are primarily associated with the nut and betel quid. The nuts contain at least 9 structurally related pyridine alkaloids including arecoline, arecaidine, arecaine, arecolidine, guvacine, isoguvacine, guvacoline, and coniine.^{2,8} However, the most common is the parasympathetic stimulant alkaloid arecoline. The total alkaloid content can reach 0.45%.⁹

The methyl esters of arecoline and guvacoline are hydrolyzed in the presence of alkali to the respective acids, arecaidine and guvacine. The hydrolysis is catalyzed by lime, which is added to the quid. Arecoline most likely is present in the nut as a salt of tannic acid, and the lime facilitates the release of the base from the salt.¹⁰

Components of the betel quid, most likely from *P. betel* and not betel nuts, contain about 1% of a volatile oil, chalbetol, chavicol, cadinene, allylpyrocatechol, and safrole.^{2,11}

USES AND PHARMACOLOGY: Nearly all of the scientific data involve animal or in vitro studies. Arecoline is a parasympathetic stimulant and acts on muscarinic and nicotinic receptors.

Glaucoma – The alkaloids of betel nut cause pupil dilation, vomiting, diarrhea, and in high doses, convulsions and death. These alkaloids have a cholinergic action, and it is believed that the central stimulating activity of arecoline is greater than that of pilocarpine. Consequently, extracts of the nut have been used for the management of glaucoma in traditional medicine.¹²

Animal/Clinical data: Research reveals no animal or clinical data regarding the use of betel nuts for glaucoma.

Hypertension – Betel nuts contain a tannin (eg, Areca II-5-C) with angiotensin-converting enzyme (ACE) inhibitory activity in vitro. The activity of this tannin was comparable with that of captopril.

Animal data: Spontaneously hypertensive rats received oral doses of 100 to 200 mg/kg of the tannin extracts and the antihypertensive effects were similar to 30 to 100 mg/kg of captopril. The IV dose of the tannin was equivalent to 5 times the effect of an equivalent amount of captopril.¹³

Clinical data: Research reveals no clinical data regarding the use of betel nuts for hypertension.

Antibacterial – Antibacterial activity is associated with the extracts of betel nuts. An ethanol extract inhibited *Staphylococcus aureus*, *Salmonella* sp., *Neisseria* sp., *Yersinia enterocolitica*, and *Listeria monocytogenes*.¹⁴

Animal/Clinical data: Research reveals no animal or clinical data regarding the use of betel nuts as an antibacterial.

Other uses – Arecoline is a basic oily liquid that has been used in veterinary medicine as a cathartic for horses and a vermifuge. Betel nut chewing induces a number of physiologic changes, including an increase in salivation,¹⁵ gradual resorption of oral calcium induced by the lime, gingivitis, periodontitis, and chronic osteomyelitis.¹⁶

Arecoline is thought to be responsible for some of the claimed effects of betel quid chewing, such as alertness, increased stamina, a sense of well-being, euphoria, and salivation.^{15,17} An antidepressant effect of the betel nut may be associated with the hexane and aqueous extracts. The extracts inhibit monoamine oxidase type A isolated from the rat brain.¹⁸ The muscarinic cholinomimetic action of the alkaloids may also relieve symptoms associated with schizophrenia.¹⁹

DOSING: Classical doses of betel nut are 2 to 8 g of the seed. A dose of 5 to 20 mg of arecoline was used in a study of appetite suppression.²⁰

PREGNANCY/LACTATION: Documented adverse effects, including teratogenic and fetotoxic effects.²¹ Avoid use.

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INTERACTIONS: Two patients taking procyclidine developed severe extrapyramidal symptoms during heavy consumption of betel nut.²² After they stopped chewing betel nut, their symptoms resolved over 4 to 7 days. An active component in betel nut, arecoline, mimics acetylcholine at muscarinic and nicotinic receptors, which may antagonize the anticholinergic action of procyclidine.

ADVERSE REACTIONS: It is reported that between 10% and 25% of the world's population chews betel quid.^{3,23,24} Betel nut chewing has been associated with significant cholinergic, neurological, cardiovascular, and GI manifestations.^{10,25,26}

Betel nut chewing has been associated with an aggravation of asthma. A dose-response relationship may exist between the use of this drug and the development of asthmatic symptoms.²⁷

TOXICOLOGY: Leukoplakia, which is considered to be a precancerous lesion, and squamous cell carcinoma of the oral mucosa have been found with unusually high frequency in long-term users of betel nut. Studies in New Guinea also have shown that chewing a betel nut-slaked lime mixture has been associated with oral leukoplakia that is precancerous in up to 10% of the cases.^{24,28-31} A recent study of users of areca products compared their degree of dependence and addiction to that of cocaine users, particularly if the product contains tobacco.^{32,33}

Experimental evidence indicates that arecaidine and arecoline have the greatest carcinogenic potential. When tested by an *in vitro* cell transformation assay, both alkaloids gave a positive response, implicating both as suspected human carcinogens.³⁴ Other compounds, in particular 3-(N-nitrosomethylamino)propion aldehyde (NMPA), are also highly active in decreasing mucosal cell viability, colony-

-forming efficiency, and in causing DNA strand breaks and cross-links in buccal cells *in vitro*. These effects indicate that these compounds may contribute to the oral carcinogenicity associated with chewing betel nut quid.³⁵

To confirm the carcinogenic potential of the plant, mice were fed daily doses of aqueous extracts of betel nut or betel leaf, the polyphenolic fraction of the nut, or distilled water. Aqueous extracts of the nut induced tumors of the GI tract, liver, and lung in 58% of the treated mice. The polyphenolic fraction induced tumors in 17% of the mice. The aqueous extract of betel leaf and the water control did not induce tumors. Other studies by the same investigators indicate that betel leaf extract exerts an antineoplastic effect in mice when injected simultaneously with betel nut extract.³⁶

The clinical implications of these animal data are poorly understood. The incidence of oral cancers increases among heavy long-term chewers of betel quids; whether this is due to the alkaloids, to the associated tannin (which accounts for 15% of the nut weight), or to carcinogens in the tobacco that is often added to the quid is unknown. What "protective" value chewing betel leaf has is also unknown.

The results of 1 small study of Filipino betel chewers found that dietary supplementation with retinol (100,000 IU/week) and beta-carotene (300,000 IU/week) for 3 months was associated with a 3-fold decrease (from 4.2% to 1.4%) in the mean proportion of oral cells with nuclear alterations suggestive of precancerous lesions.⁶ Arecaine is poisonous and affects respiration and heart rate, increases intestinal peristalsis, and can cause tetanic convulsions. Although doses of the seed in the range of 8 to 10 g have been reported to be fatal, it has been suggested that doses up to 30 g may have a low toxicity potential.⁸

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