ISSN: 0974-6943

Priyanka R. Patil et al. / Journal of Pharmacy Research 2009, 2(4),683-687

Review Article

Available online through

www.jpronline.info

Pharmacological activities of *Areca catechu* Linn. – A Review

Priyanka R. Patil*, Sachin U. Rakesh, Prof. P. N. Dhabale, Prof. K. B. Burade

**Govt. College of Pharmacy,Vidyanagar, Tal. Karad- 415 124,Dist. Satara, Maharashtra, India.*

For correspondence:Priyanka R. Patil,Govt. College of Pharmacy,Vidyanagar, Tal. Karad- 415 124,Dist. Satara, Maharashtra, India.

E-mail:priyapatil5586@rediffmail.com

Received on:15-12-2008; Accepted on :16-02-2009

ABSTRACT

Areca *catechu* Linn. is a commonly used herb in Ayurvedic medicine. This review supports all updated information on its phytochemical and pharmacological activities, traditional uses and scientific approach. The plant extracts and its chemical marker or target molecule Arecoline, have been widely used for the treatment of a large number of human ailments. The chemical entities of this plant has been used as an antidiabetic, blood pressure regulating activity, antiulceogenic, antioxidant activity, anticonvulsant activity, C.N.S. stimulant activity, oxytocic activity, antifertility, anthelmintic and antiviral activity etc. Scientifically proved activities are related with traditional concept. Scientific evidence exists with respect to their major and minor constituents. *Areca catechu* Linn. is one of the most important controversial and effective natural origin that has a tremendous future for research. The novelty and applicability of *Areca catechu* Linn. are hidden. Such things should be overcome through modern scientific concept.

Key words: *Areca catechu* Linn, Arecoline, Pharmacological activities, Toxicities.

INTRODUCTION

Areca catechu Linn. is prominently used for treatment of various aliments and in the form of various preparations especially in powdered form. It is one of the crude material of Indian system of medicine. *Areca catechu* Linn. was cited for its various medicinal properties, speciously antibacterial and antiviral[1]. *Areca* nut (*Areca catechu*) is commonly used as an ingredient of betel quid, which also includes leaf of the creeping vine piper betel and lime with or without tobacco. Betel quid chewing has been popular, especially in many Southeastern Asian countries[2,3]. Mostly, it is consumed for masticatory and psychoactive purposes[4]. It has been proven that addiction can be induced following prolonged chewing[5]. *Areca* nut contents very complex and controversial chemical entities having variable properties. The plant is tall, slender, unbranched palm with a crown of leaves, stem annulate; leaves pinnate with a conspicuous sheath; flowers in spadix, male many at the upper portion, female much larger and few at the base; fruits 3.8 – 5 cm long, smooth, orange or scarlet when ripe[6]. Parts used are seed or kernel and extracts, root and tender leaves, catechu etc. It is cultivated through tropical India and flourishes in dry plateau of Mysor, Canara, Malabar, Southern India, Assam and Estern Archipelago[7].

CHEMICAL CONSTITUENTS

The major compounds of BQ are polyphenolic compounds, alkaloids, tannin, arecoline, arecaidine and fibers[8,14]. *Areca catechu* is the only one of 54 *Areca* species known to contain alkaloids[9,10]. In early work[12], arecoline and guvacoline (methyl 1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate and methyl 1,2,3,6-tetrahydropyridine-3-carboxylate, respectively) and the corresponding carboxylic acids were isolated.

The Arecaine is the active principle of the Areca nut. Watery extract yields betel-nut catechu while the "Kernels" contain catechu, tannin 15%, gallic acid, oily matter (fat 14%), gum and alkaloids, viz. Arecoline 0.07%, arecaine 1%, arecaidine and guvacoline, guvacine and choline occur in trace only. All these alkaloids are chemically related; arecoline – is colourless volatile resembling nicotine[1].

Total amounts of phenolics in areca fruit were[12] well correlated with the length and maturation, but those of alkaloids were only correlated with the maturation. Tender shoot, the upper young stem of the tree, cooked as a delicious syrup, contained a small amount of total phenolics (0.58 mg of gallic acid equiv/gm of fresh wt), condensed tannin (0.85 mg of catechin equiv/g of fresh wt), and total alkaloids (2.38 mg/g of fresh wt.).

Two procyanidin tetramers, two trimers, and a dimer which[14] is a structural isomer of procyanidin B-1, along with (+)-catechin, (–)-epicatechin, and pro-cyandins A-1, B-1, and B-2, have been isolated pure from the seed of *Areca catechu* L., and their ^{1}H and ^{13}C n.m.r spectral data, combined with degradative studies on their reaction with toluene-α-thiol, have established that they all, except for procyanidin B-2, have the C(**4**)-to-C(**8**)[or C(6)]-linked (–)-epicatechin stereochemistry [C(2), C(3):*cis*] in the upper units, and the (+)-catechin stereochemistry [C(2), C(3): *trans*] in the terminal (lower) units.

PHARMACOLOGICAL ACTIVITIES

Blood Pressure Regulating Activity

Areca tannin has been suggested as having a blood pressure regulatory effect through its ability to inhibit the pressor response to both angiotensin I and II[15]. As genetic and environmental factors determine the susceptibility and development of diseases and no report has been published concerning the genetic interaction of metabolic effects in areca nut/betel quid (BQ) chewers, it is proposed that the cardiovascular effects of chronic BQ usage can be affected by the polymorphism of the angiotensin converting enzyme

(ACE) gene[16]. In a recent report[17] by the authors, it was observed that *ACE* insertion/deletion (I/D) polymorphism is associated with the risk of oral mucosal lesions in BQ chewers, which indicates the relative contribution of genetic and environmental factors that determine the susceptibility and development of diseases.

Hypoglycemic Activity

Arecoline was investigated and reported to have hypoglycemic activity in an animal model of diabetes upon subcutaneous administration. The Subcutaneous administration of alkaloid fraction of *Areca catechu* (0.05_/0.5 mg/kg) in alloxanized rabbits (140 mg/kg) showed significant hypoglycemic effect lasting for 4/6 hours[18]. Recently, it was observed that chronic BQ use is associated with a higher risk of type 2 diabetes mellitus and metabolic syndrome, determined by a epidemiologic survey in Taiwan[19,20].

Platelet Aggregation Activity

Areca nut (AN), a Bittle Quid component, modulates arachidonic acid (AA) metabolism, which is crucial for platelet function. AN extract (1 and 2 mg/ml) stimulated rabbit platelet aggregation, with induction of thromboxane B_2 (TXB_2) production. Catalase, superoxide dismutase, and dimethylthiourea (DMT) showed little effect on AN-induced platelet aggregation, whereas catalase and DMT inhibited the AN-induced TXB_2 production. These results suggest that AN-induced platelet aggregation is associated with iron-mediated reactive oxygen species production, calcium mobilization, phospholipase C activation, and TXB_2 production[21].

Anti-HIV Activity

Various active constituents like procyanidins, arecatannin B1 and extracts of seed showed HIV protease inhibition activity[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[23,24]. The development of proteasome inhibitors into novel therapeutic agents represents a new approach and now classes of these substances are in clinical trials or used to study the role of the ubiquitin–proteasome pathway in various cellular processes. A number of tripeptidic sequences derivatized at the N- and C-terminal with arecoline derivatives that were able to efficiently interact with the catalytic subsites of the proteasome 20S was identified[25].

Molluscicidal Activity

In *in vivo* and *in vitro* exposure of arecoline (active component of *Areca catechu* seed) significantly inhibited the acetylcholinesterase (AChE), acid and alkaline phosphatase (ACP/ALP) activity in the nervous tissue of L. acuminata. The inhibition kinetics of these enzymes indicates that arecoline caused competitive inhibition of AChE, competitive–non-competitive inhibition of ACP/ALP. Thus the inhibition of AChE, ACP and ALP by arecoline may be the cause of molluscicidal activity of *Areca catechu*[26].

Antidepressant Activity

It has been previously shown that among various alkaloid constituents from areca nut, alkaloids in dichloromethane fraction were found to be biologically active both in vivo and in vitro. This fraction potently inhibits monoamine oxidase-A activity and thus restores or increases bioavailability of monoamines, 5-hydroxytryptamine or noradrenaline in the brain. Additionally, forced swimming and tail-suspension tests supported that the dichloromethane fraction has antidepressant activity[27].

Anticonvulsant Activity

Arecaidine and guvacine, constituents of the nut of *Areca catechu*, inhibited the uptake of GABA and â-alanine, but not that of glycine, by slices of cat spinal cord. Large doses of arecaidine (1 g/kg subcutaneous) marginally reduced the lethal effects of bicuculline in mice but appeared to have little or no anticonvulsant activity[28].

Central Nervous System Stimulant

Betel nut may cause stimulant and euphoric effects. As a result, it is sometimes used recreationally. However, the known toxicities of chewing betel nut likely outweigh any possible benefits[29]. A severe skin inflammatory reaction halted the development of a transdermal device to systemically deliver arecoline, a cholinergic agonist, for use in the management of a human neurological disorder[30].

Prevention of Dental cavities

Betel nut was once used in toothpaste to prevent cavities. Laboratory studies suggest that betel nut may have antibacterial effects[31], which may reduce the development of cavities. However, other therapies to prevent tooth decay are safer, and the risks associated with betel nut likely do not outweigh the possible benefits[6]. *Areca* Nut is made into a dentrifrice on account of its astringent properties[1]. It is considered to strengthen the gum, sweeten breath. The seed, reduced to charcoal and powered, forms an excellent dentrifrices.[32]

Ulcerative colitis (more information)

Although betel nut has been suggested as a therapy to prevent or protect against ulcerative colitis, it is unlikely that the benefits are worth the risks[33].

Saliva stimulant

Betel nut has been shown to produce large amounts of saliva in people who chew betel nut. However, the toxic effects associated with its use probably do not outweigh the benefits[1]. 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[1,6,29,33].

Anti-venom activity

Tannin is one snake venom antidote found[34] widely distributed in the plant kingdom. Tannins from plants have been shown [35] to interact with snake enzyme systems. Plant polyphenols from the aqueous extracts of *Areca* was tested for their inhibitory activities against *Naja kaouthia* (NK) venom by in vitro neutralization method**.** Clinical applications of this plant polyphenols should therefore be very useful for first aid treatment of snakebite victims [36].

Antioxidant Activity

The active-oxygen scavenging activity of methanolic extract of *Areca catechu* used in China and Japan as nourishing tonics was evaluated by electron spin resonance (ESR) technique, in order to evaluate its effectiveness for anti-aging and to search for new active-oxygen scavengers from natural resources. It especially showed strong scavenging activity against super- oxide anion radical[37].

Oxytocic Activity and Anti-fertility Activity

The ethanolic extract of nuts has shown remarkable oxytocic activity at a dose of 100 mg on isolated rat uterus. The oil obtained from nuts, at a dose of 500 mg / kg exerted resorption of implants. At a dose of 100 mg/ kg oil exerted 40% antifertility activity[38].

Antimicrobial Activity

The alcoholic extract of nut showed[38] antimicrobial activity against Escherichia coli, Candida albicans, C. tropicalis, and Tricophyton interdigitale. A variety of human and veterinary isolates, both Gram + ve and Gram – ve were tested against Areca nut extract by measuring growth of organisms by spectrometric method. It is found that both Gram + ve and Gram – ve organisms are susceptible to Areca nut extract. Concentration needed for 100% inhibition of growth was found in order of 3.3-7 mg/mL for Gram – ve and 16 mg/mL for Gram + ve. Extract was also inhibit aflatoxin production by Aspergillus flavus and also inhibit the viral growth of New Castle Disease Virus and egg Drop Syndrome Virus growth in embryo calture [39].

Other Pharmacological Activities

Different extracts like aqueous, alcoholic, alkaline and acid extracts resulted in the constriction of capillaries to varying degree when tested by rat hind limb perfusion technique. 50% alcoholic extracts of leaves exhibited various pharmacological properties like effects on respiration and CVS in cat/dog and antispasmodic property on isolated guinea pig ileum[39]. Hamsters chewing betel quid or areca nut directly show a decrease in body weight. These results indicate that *Areca* nut and Bittle quid components may induce alterations in proliferation and differentiation of oral epithelial cells. Animal model of chewing BQ or AN can be useful for future tumor initiation, promotion and chemoprevention experiments simulating the condition of BQ chewing in humans[40]. The action of Arecain resembles that of Muscarine and Pilocarpine externally, internally used it contracts the pupils [1,6,29,32].

Unproven Uses

Betel nut has been suggested for many other uses, based on tradition or on scientific theories. However, these uses have not been thoroughly studied in humans, and there is limited scientific evidence about safety or effectiveness, which is given in Table.1. The dry expanded petioles serve as excellent ready made splints for fractures. It acts as a good laxative antiseptic and promotes menstrual flow[18]. Some of these suggested uses are for conditions that are potentially very serious and even life-threatening [1,6,29,32].

Table.1.

Alcoholism	Gas
Fainting	Glaucoma
Aphrodisiac	Joint pain
Appetite stimulant	Leprosy
Appetite suppressant	Menstrual abnormalities
Cough	Methanol-induced blindness
Digestive aid	Parasites
Diphtheria	Respiratory stimulant
Diuretic	Skin disorders
Ear infection	Excessive thirst

DOSE

The powered nut, in doses of 10 to 15 grains every 3 to 4 hours, is useful in checking diarrhea arising from debility[32]. Liquid extract, 1 to 2 dessert spoons, in water daily. For powder, use 15 to 60 gm. For tapeworm, 1 to 2 teaspoons of powered nut with water[41].

TOXIC EFFECTS

Suppression of Immune System

The cellular level of glutathione was diminished by Areca Nut Extract (ANE) in splenic T-cells. Collectively, these results demonstrated that ANE markedly suppressed T-cell activation and Th1 cytokine production, which was mediated, at least in part, by the induction of oxidative stress[42]. However, Areca also directly affects the functional activities of immunocompetent cells, and moreover tumor cells may hypo-respond to the CMI via diverse mechanisms such as induction of apoptosis of lymphocytes, induction of production of suppressor T cells, downregulation of MHC molecules in tumor cells, etc[43].

Oxidative Stress and Genetic Damage

Long-term exposure to sublethal doses of ANE, intracellular antioxidative activity may also be enhanced in response to increased oxidative stress. These results suggest that stress caused by long-term Areca nut extract exposure enhances oxidative stress and genetic damage in human keratinocytes [44].

Hepatocarcinoma, Oropharyngeal and Esophagus Cancers

Betal quid chewing is one of the major risk factors of hepatocarcinoma, oropharyngeal and esophagus cancers. Arecoline, the main *Areca* alkaloid of the betel nut is reported to have cytotoxic, genotoxic and mutagenic effects in various cells. It shows strong

correlation to the incidence of oral submucosal fibrosis, leukoplakia and oral cancer, and has also been found to impose toxic manifestations in immune, hepatic and other defense systems of the recipient. Here we report that arecoline arrested splenic lymphocyte cell cycle at lower concentration with induced apoptosis at higher concentration thereby causing immuno-suppression in arecoline recipients. 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[45].

Clastogenic Activity

Five components of the betel quid were examined for their clastogenic activities individually and in various combinations. They included the alkaloid, arecoline, from the betel nut (*Areca catechu* L.), eugenol, from the betel vine (*Piper betle* L.), chlorogenic acid, from tobacco leaves (*Nicotiana tabacum*), quercetin, from fennel seeds (*Foeniculus vulgare* Mill.) and the ubiquitous transition metal Mn^{2+}. The combinations of arecoline, chlorogenic acid and Mn^{2+} induced frequencies of chromosome aberrations which exceeded the sum of the clastogenic activities of individually applied compounds or the sum of the clastogenic activities of 2 jointly applied compounds (arecoline plus Mn^{2+}, or chlorogenic acid plus Mn^{2+}). The clastogenic activity was estimated as the frequency of metaphase plates with at least 1 chromatid break or chromatid exchange, or the average number of chromatid breaks and exchanges per Chinese hamster ovary (CHO) cell[46].

Enhanced Type I Plasminogen Activator Inhibitor

Type I plasminogen activator inhibitor (PAI-1) is a 50 kDa glycoprotein belonging to the serine protease superfamily. PAI-1 is consistently and dramatically upregulated in a variety of fibrotic diseases. Highly elevated PAI-1 mRNA and protein expression in normal human BMFs stimulated by arecoline. Taken together, these results suggest that PAI-1 expression is significantly up regulated in OSF tissues from areca quid chewers, and arecoline may be responsible for the enhanced PAI-1 expression in vivo[47].

Fibrotic Diseases

Substantial amounts of copper released from areca products induces lysyl oxidase activity up regulating collagen synthesis by fibroblasts, facilitating its cross linking and, thereby, inhibiting its degradation The role of copper from areca products in the pathogenesis of oral submucous fibrosis merits further investigation, particularly since it is thought to be involved in other fibrotic diseases such as scleroderma and liver fibrosis[48].

OTHER TOXIC EFFECTS

Areca catechu L. may accelerate tumor migration by stimulating MMP-8 expression through MEK pathway in at least some carcinomas of the upper aerodigestive tract. Furthermore, arecoline may be one of the positive MMP-8 regulators among BQ ingredients[49]. Areca chewing has strong association with the risk of oral leukoplakia (OL), oral submucous fibrosis (OSF), and oral cancer (OC). Areca exhibit genotoxicity and may alter the structure of DNA, proteins and lipids, resulting in production of antigenicity[43]. Concurrent use of Areca may mimic, magnify, or oppose the effect of drugs. Plausible cases of Areca-drug interactions include rigidity, bradykinesia, jaw tremor, stiffness, akithesia, inadequate control of asthma etc. which proves that Areca contains arecoline, a cholinergic alkaloid. Arecoline challenge caused dose-related bronchoconstriction in six asthma patients[50].

CONCLUSION

The extensive survey of literature revealed that Areca is an important source of many pharmacologically and medicinally important chemicals such as Arecoline, arecaine, arecaidine and guvacoline, guvacine and choline. The Arecoline is the most searched chemical constituent or target molecule of *Areca* nut.

The plant has also been widely studied for their various pharmacological activities like, antidiabetic, blood pressure regulating activity, antiulcreogenic, antioxidant activity, anticonvulsant activity, C.N.S. stimulant activity, oxytocic activity, antifertility, anthelmintic and aphrodisiac activity etc. In developing countries like India and Africa where both Areca *catechu* and AIDS are ubiquitous, it could bring enormous hope to the suffering and it can be advocated as a dietary aid. Further, the use of *Areca* by both male and female persons opting for future conception should account the antifertility activity. While *Areca catechu* has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use. It is also important to recognize that *Areca catechu* extracts may be effective not only when used singly, but may actually have a modulating effect when given in combination with other herbs or drugs. This review aims to highlight the main medicinal properties of *Areca catechu* with a view to focus on future studies of this plant.

REFERENCES:

1. Dr. Nadkarni K.M., Indian material Medica, 3rd Ed, Vol. 1, Bombay Popular Prakashan, Mumbai, 1976, Page no. 130-133.
2. Chu NS, Sympathetic response to betel chewing, Journal of Psychoactive Drugs, 27, 1995, 183-186.
3. Burton-Bradley, Papua B.G., New Guinea Transcultural Psychiatry: Some Implications of Betel Chewing, Med. J. Aust., 2, 1966, 744-746.
4. Norton SA, Betel: consumption and consequences, J Am Acad Dermatol, 38, 1998, 81-88.
5. Cawte J., Psychoactive substances in the South seas: Betel, kava, and pituri., Aust. N.Z. J. Psychiat., 19, 1985, 83–87.
6. Indian Medicinal Plants. A compendium of 500 species, 1st Ed, Vol 1, Published by Orient Longman Ltd., 1994, page no. 180.
7. H. Panda, Herbs Cultivation and Medicinal Uses, Published by National Institute Of Industrial Re, 2000, Page no.148-150.
8. IARC Working Group, Tobacco habits other than smoking; betelquid and areca-nut chewing; and some related nitrosamines. Lyon, France, 23–30, 1984. IARC Monogr Eval Carcinog Risk Chem Hum, 37, 1985, 1–268.
9. Southon, I. W. and Buckingham, J., *Dictionary of Alkaloids*, Chapman & Hall, New York, 1989.
10. Evans, W. C., *Trease and Evans' Pharmacoynosy*, BalliereTindall, London, 1989.
11. Holdsworth D. K., Jones R. A., Volatile Alkaloids From *Areca Catechu*, Phytochemistry, 48 (3), 1998, 581- 582.
12. Chin-Kun Wang, Wen-Hsiu Lee, and Chin-Hui Peng, Contents of Phe-

nolics and Alkaloids In *Areca Catechu* Linn. During Maturation, J. Agric. Food Chem., *45* (4), 1997, 1185–1188.
13. Gen-ichiro Nonaka, Feng-Lin Hsu and Itsuo Nishioka, Structures of dimeric, trimeric, and tetrameric procyanidins from *Areca catechu* L., J. Chem. Soc., Chem. Commun., 1981, 781 – 783.
14. Wang CK, Su HY, Lii CK, Chemical composition and toxicity of Taiwanese betel quid extract, Food Chem Toxicol, 37, 1999, 135–44.
15. Inokuchi J, Okabe H, Yamauchi T et al, Antihypertensive substance in seeds of *Areca catechu* Linn., Life Sci, 38,1986, 1375– 1382.
16. Fu-Mei Chung, Tien-Yu Shieh, Yi-Hsin Yang et al, The Role Of Angiotensin-Converting Enzyme Gene Insertion/Deletion Polymorphism For Blood Pressure Regulation In Areca Nut Chewers, Translational Research, 150 (1), 2007, 59- 65.
17. Chung FM, Yang YH et al, Angiotensin-converting enzyme gene insertion/deletion polymorphism is associated with risk of oral precancerous lesion in betel quid chewers, Br J Cancer, 93, 2005, 602– 606.
18. Chempakam B., Hypoglycemic activity of arecoline in betel nut *Areca catechu* L., Ind. J of Exp. Biol, 31 (5), 1993, 474-475.
19. Tung TH, Chiu YH, Chen LS et al, Keelung Community-based Integrated Screening programme No. 2. A population-based study of the association between areca nut chewing and type 2 diabetes mellitus in men (Keelung Community-based Integrated Screening programme No. 2), Diabetologia, 47, 2004, 1776–1781.
20. Chung FM, Chang DM, Chen MP et al. Areca Nut Chewing is associated with metabolic syndrome. Role of tumor necrosis factor, leptin, and white blood cell count in betel nut chewing-related metabolic derangements, Diabetes Care, 29, 2006, 1714.
21. Shiao-Yun Chen, Chang-Hui Liao, Yuan-Yii Tung, Modulation of platelet aggregation by areca nut and betel leaf ingredients: roles of reactive oxygen species and cyclooxygenase, Free Radical Biology and Medicine, 32 (9), 2002, 860-871.
22. Kavita Vermani, Sanjay Garg, Herbal medicines for sexually transmitted diseases and AIDS, Journal of Ethnopharmacol, 80, 2002, 49- 66.
23. Orlowski, R. Z, The role of the ubiquitin-proteasome pathway in apoptosis, Cell Death. Differ, 6, 1999, 303.
24. Gavioli, R.; Vertuani, S.; Masucci, M. G, Proteasome inhibitors reconstitute the presentation of cytotoxic T-cell epitopes in Epstein-Barr virus-associated tumors, Int. J. Cancer, 101, 2002, 532- 538.
25. Mauro Marastoni,, John McDonald et al, Proteasome inhibitors: synthesis and activity of arecoline oxide tripeptide derivatives, Bioorganic & Medicinal Chemistry Letters. 14, 2004, 1965–1968.
26. Jaiswal Preetee, Singh V.K., Singh D.K., Enzyme inhibition by molluscicidal component of Areca catechu and Carica papaya in the nervous tissue of vector snail Lymnaea acuminata, Pesticide Biochemistry and Physiology, 92 (3), 2008, 164-168.
27. A. Dar and S. Khatoon, Behavioral and biochemical studies of dichloromethane fraction from *Areca catechu* nut, Pharmacology, Biochemistry and Behavior, 65(1), 2000, 1-6.
28. D. Lodge, Johnston G.A.R., Curtis D.R., Brand S.J., Effects of the *Areca* nut constituents arecaidine and guvacine on the action of GABA in the cat central nervous system, Brain Research, 136 (3),1977, 513-522.
29. Chopra R.N., Nayar S.L., Chopra I.C., Glossary of Indian Medicinal Plants, 1st Ed, 4th reprint, National Institute of Science Communication, New Delhi, , 1996, Page no. 23.
30. Michael Y.L. Law, Lynn K. Pershing, Lee K. Roberts, Arecoline-induced skin inflammation: irritant or allergic dermatitis?, Internat J of Pharmaceutics, 88 (1-3), 1992, 251-260.
31. S.Suresh Babu, S.Suresh Babu M. Madhavi, M. Madhavi, Green Remedies: Healing Power of Herbs, Published by Pustak Mahal, 2005, Page no. 55- 56.
32. Dr. J C Kurian, Plants That Heal, 7th Ed, Vol 1, Oriental Watchman Publishing House, Printed and Published by E.B.Mathews, Pune, 1995, Page no. 20.
33. Kirtikar K.R. and Basu B.D., Indian Medicinal Plants, 2nd Ed, Vol 4, Published by Bishen Singh Mahendra Pal Singh, 1975, Page no. 2547-2548.
34. Okuda T., Yoshida T., Hatano T., Chemistry and biological activity of tannins in medicinal plants. In: Wagner, H., Farnsworth, N.R. (Eds.), Economic and Medicinal Plant Research, Vol. 5. Acad Press, London, 1991. Page no. 129–165.
35. Mahanta, M., Mukherjee, A.K., Neutralisation of lethality, myotoxicity and toxic enzymes of *Naja kaouthia* venom by *Mimosa pudica* root extracts, J of Ethnopharmacol, 75, 2001, 55–60.
36. Pimolpan Pithayanukula, Pakatip Ruenraroengsaka, Rapepol Bavovadab et al, Inhibition of Naja kaouthia venom activities by plant polyphenols, J of Ethnopharmacol, 97, 2005, 527–533.
37. Mizue Ohsugi , Wenzhe Fan , Koji Hase, Quanbo Xiong et al, Active-oxygen scavenging activity of traditional nourishing-tonic herbal medicines and active constituents of Rhodiola sacra., J of Ethnopharmacol, 67, 1999,111–119.
38. Lalithakumari H., Sirsi M and Covindarajan V.S., Antibacterial and antifungal activities of *Araca catechu* Linn. Indian J. Exp.Biol. 9(1), 1965, 66-69.
39. Subash R.R., Kuttan R, Antibacterial, antifungal and antiviral activity of Arecanut (Areca catechu Linn). Amala Research Bulletin, 27, 2007, 244-251.
40. Chun-Pin Chianga, Mei-Chi Changb, Jang-Jaer Leea et al, Hamsters chewing betel quid or areca nut directly show a decrease in body weight and survival rates with concomitant epithelial hyperplasia of cheek pouch, Oral Oncol, 40, 2004, 720–727.
41. Colonel Heber Drur, The Useful Plants Of India, 2nd edition, Allied Book Center, Deharadhun,1991, Page no. 48-50.
42. Wang C.C., Liu T.Y., Wey S.P. et al, Areca nut extract suppresses T-cell activation and interferon-ã production via the induction of oxidative stress, Food and Chem Toxicol, 45 (8), 2007, 1410-1418.
43. Chang M.C., Chiang C.P., Lin C.L. et al, Cell-mediated immunity and head and neck cancer: With special emphasis on betel quid chewing habit, Oral Oncology, 41, 2005, 757–775.
44. Kuo- Chu Lai, Te-Chang Lee, Genetic damage in cultured human keratinocytes stressed by long-term exposure to areca nut extracts Mutation, Research/Fundamental and Molecular Mechanisms of Mutagenesis, 599 (1-2), 2006, 66-75.
45. Romi Dasgupta, Indraneel Saha et al, Maiti.Immunosuppression, hepatotoxicity and depression of antioxidant status by arecoline in albino mice, Toxicology, 227 (1-2), 2006, 94-104.
46. H. F. Stich, W. Stich, Potentiation of genotoxicity by concurrent application of compounds found in betel quid: arecoline, eugenol, quercetin, chlorogenic acid and Mn^{2+}, Mutation Research/Genetic Toxicol, 90 (4), 1981, 355-363.
47. Shun-Fa Yanga, Yih-Shou Hsieha, Chung-Hung Tsaib et al, The upregulation of type I plasminogen activator inhibitor in oral submucous fibrosis, Oral Oncology, 39, 2003, 367–372.
48. Trivedy Chetan, Baldwin Dianne, Warnakulasuriya Saman et al, Copper content in Areca catechu (betel nut) products and oral submucous fibrosis, The Lancet, 349, 1997, 1447.
49. Shyun-Yeu Liu, Young-Chau Liu et al, Up-regulation of matrix metalloproteinase-8 by betel quid extract and arecoline and its role in 2D motility, Oral Oncol, 43, 2007, 1026– 1033.
50. Taylor R. F. H., Al- Jarad N., L. John M. E. et al, Betel-nut chewing and asthma, The Lancet, 339 (8802), 1992, 1134-1136.

Source of support: Nil, Conflict of interest: None Declared