



RESEARCH ARTICLE

ETIOPATHOGENESIS OF OSMF VERSUS BENEFICIAL EFFECTS OF ARECA NUT: A REVIEW

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ABSTRACT

The habit of chewing areca nut has been reported since ancient times. It has been used as food, medicine, social and religious purposes, as described in Sanskrit manuscripts. The harmful effects of chronic chewing of areca nut have been well established, however, not much is documented regarding the advantages of chewing areca nut. The study was done to review the various possible favourable effects of chewing Areca on the oral and general health. Structured scientific review and meta-analysis of scientific publications from past 10 years was done from various books & journals in the central library & NML and various search engines like PubMed, Wiley, Google Scholar, Science Direct and EBSCO host. It was mentioned in Charaka and Sushruta Samhitas (75 AD to 300 AD), practice of chewing of betel leaves was common after meals. Areca is used as a medicine for digestive and dental health, also used in Ayurvedic medicine to facilitate bowel movements and reduce intestinal worms. Survey of literature revealed its various medicinal properties like antibacterial, antioxidant, anticarcinogenic, antimicrobial, anti-inflammatory, anti-melanogenesis, hypolipidemic, hepatoprotective etc. Extensive information from literature review indicates that Areca catechu has a broad spectrum of pharmacological effects. More research should be undertaken to determine its efficacy against several diseases on man with respect to other natural products and modern drugs.

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INTRODUCTION

Areca nut, the seed of *Areca catechu*, has been reported to be most widely consumed addictive substances in the world after nicotine, ethanol and caffeine, and approximately 10% of the world's population consume it in different forms. It has been suggested by many reports that chewing areca nut starts at a young age, and it is being consumed freely by children (Apoorva Garg et al., 2014). Majority of epidemiological and interventional studies suggested that areca nut is the main aetiological factor for OSMF. The International Agency for Research on Cancer (IARC) regarded the chewing of betel leaf and areca nut to be a known human carcinogen, which have role in multistage progression of oral cancer. Areca nut contains arecoline and 3-(methylnitrosamino) propionitrile, while lime provides reactive oxygen radicals, each of which has a role in oral carcinogenesis (WHO, 2004). Over the last 2 decades, the role of areca nut and its constituents in the pathogenesis of OSF has been studied in detail. On elucidating the aetiology and pathogenesis substantial amount of research have been focused on changes in the extracellular matrix (ECM).

It is hypothesised that in the development of the disease the possible mechanisms is increased collagen synthesis or reduced collagen degradation. There are numerous other biological pathways explaining the pathogenesis of OSF. None of the studies explaining the etiopathogenesis of OSMF are conclusive. Despite of various etiological agents, areca nut is considered to be the main etiological agent. The harmful effects of chronic chewing of areca nut have been well established in the literature. However, not much is documented regarding the advantages of chewing areca nut. It has been mentioned in the Sanskrit manuscripts and used as food, medicine, social and religious purposes. Present situation gives a complex scenario where Dental Sciences have concept of Areca nut as main etiological agent for OSMF, however, its uses since 300 BC till date motivated us to explore the various possible favourable effects of Areca nut on the oral and general health.

MATERIALS AND METHODS

Structured scientific review and analysis of scientific publications from past 10 years was done from various books & journals in the central library & NML and various search engines like PubMed, Wiley, Google Scholar, Science Direct and EBSCO host using the keywords- Oral submucous

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Areca nut

Areca catechu (areca nut) tree is a species of palm, which are grown in India, Malaysia, Taiwan and many other Asian countries for their economically important seed crop (Preeti Jaiswal, 2011). 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. In Indian scripts, such as Vagbhata (4th century) & Bhavamista (13th century), areca nut has been described as a therapeutic agent for leucoderma, leprosy, anemia & de-worming properties. Areca nut finds place in religious, social and cultural functions of India. Its presence is must in the ceremonial plate, as it is believed to increase prosperity (Senthil Amudhan et al., 2012).

Constituents of areca nut

The main constituents of the areca nut are carbohydrate, fats, fibre, polyphenol including flavonoids and tannins, alkaloids and minerals. Alkaloids present are arecoline, arecaidine, arecolidine, guvacine, guvacoline, isoguvacine, norarecaidine and norarecoline. Of all these alkaloids, arecoline is physiologically most important (Preeti Jaiswal, 2011).

Beneficial effects of areca nut

Sushruta, in the 1st century AD wrote that 'it tends to cleanse the mouth, impart a sweet aroma to it, enhances its beauty and cleanse and strengthen the voice, tongue and teeth, the jaws and the sense organs' (Ashok Lingappa, 2011). The association of dose dependent with respect to the duration of Areca nut use and the quality of areca nut chewed various studies have been done regarding the beneficial effects of Areca nut.

Antioxidant

B J Kim et al, 1997 concluded ethanolic extract from areca nut showed potent anti-oxidative, free radical scavenging, and anti-hyaluronidase activity. Antioxidative effect of the extract was lower than butylated hydroxytoluene, but similar to tocopherol and higher than ascorbic acid (Kim, 1997). Methanolic extract of Areca Catechu showed anti-ageing and strong scavenging activity against super-oxide anion radical (Oshugi et al., 1999). Lee et al; (2003) have screened out methanolic extracts of nine medicinal plants traditionally used in Chinese medicine for antioxidant activity versus resveratrol which has been shown to protect cells from oxidative damage. The extracts of Areca catechu strongly enhanced viability against H₂O₂ induced oxidative damage in Chinese hamster lung fibroblast (V79-4) cells. Relatively high levels of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity were detected in Areca catechu. The activities of superoxide dismutase, catalase and glutathione peroxidase were dose dependently enhanced in V79-4 cells treated with most of the plant extracts. The extracts of Areca catechu showed higher antioxidant activity than resveratrol in all experiments (Preeti Jaiswal, 2011).

Anti-Inflammatory and Analgesic

S.Khan et al., 2011 reported Areca catechu extract and its aqueous fraction possess anti-inflammatory and analgesic

activities mediated possibly through cyclooxygenase and lipoxygenase inhibitory pathways, and by degradation and/or inactivation of prostaglandin E₂ (PGE₂). These findings suggest that the areca extract and its aqueous fraction have good correlations with the medicinal use of Areca catechu in inflammatory disorders in the Unani (Greco-Arab) system of medicine (Shagufta Khan, 2011). Kuk Kook et al., 1999, reported Areca nut extract topical application inhibits hyaluronidase activity in vivo on delayed hypersensitivity and croton oil induced ear edema in mice when it was. These results suggested that Areca nut extract may reduce immune-regulatory/inflammatory action on skin problem (Kuk et al., 1999). The anti-inflammatory activity has been reported for Areca nut extract (Bhandare et al., 2010) and based on the well known involvement of inflammatory processes in the development of migraine (Conner and Grisham ;1996) it seems that the anti-inflammatory potential of ANE may be responsible for its anti-migraine activity. According to the vascular theory of migraine, dilatation of extracranial (temporal) arteries occur in patients suffering with migraine attacks. This theory gives the explanation for the neurogenic vasodilatation and inflammation in migraineurs. The Areca nut extract inhibited the plasma protein extravasation and development of inflammation within dura mater, gives the sufficient evidence for its anti-migraine activity via vascular theory of migraine (Amol Bhandarea, 2011).

Antimicrobial

In a study by Sumitra Hada et al., 2006, it was revealed that the fatty acids within areca nut (myristic and oleic acids) and procyanides were the major antibacterial principles against a primary cariogenic bacterium, *Streptococcus mutans*, and the major inhibitory activity was found to be against glucosyltransferase from *S.mutans* (Sumitra Hada et al., 2006). Hung et al., 2005 concluded from his study that the growth of *E. corrodens*, *Prophyromonas gingivalis*, *C. rectus* and *Fusiform nucleatum* were inhibited by Tannic acid derived from Areca nut extract, at concentrations varying from 1.8-18 mg/ml (Hung et al., 2005). CM De Miranda et al., 1996 reported Areca nut extracts inhibited the growth of the salivary organisms, such as, *Streptococcus mutans*, *Streptococcus salivarius*, and *Fusobacterium nucleatum* and *Staphylococcus aureus*, which were cultured from the saliva after chewing boiled areca nut, in a concentration dependent manner, baked and boiled nuts were reported to show more potent than raw nut. They also reported that tannic acid which is hydrolysable tannins in the tannin fraction, could be responsible for the antibacterial properties of the nut and suggested prolonged intra-oral exposure to areca nut can suppress bacteria in the mouth (De Miranda, 1996). Iwamoto et al., 1991, reported inhibitory effects of Areca catechu on the growth of *Streptococcus mutans* and *Streptococcus salivarius*, respectively and 5'-nucleotidase inhibitory activity, which may be useful anti-plaque preventing agents (Iwamoto, 1991). Lalithakumari H. et al., 1965 in their study reported that, the alcoholic extract of areca nut had antimicrobial activity against *E. coli*, *Candida albicans*, *C. tropicalis*, and *Trichophyton interdigitale*. A variety of isolates, Gram + ve and Gram - ve were tested against Areca nut extract. The growth organisms was measured by spectrometric method and was found that both Gram + ve and Gram - ve organisms were susceptible to Areca nut extract. 3.3-7 mg/mL for Gram - ve and 16 mg/mL for Gram + ve concentrations was needed for 100% inhibition of growth (Lalithakumari, 1965).

Anticariogenic

Not much is known about the cariostatic properties of areca. Literature suggested that the betel stain, which often coats the surface of the teeth, acts as a protective varnish. Also, chronic chewers have marked attrition of cusps of teeth which leads to loss of occlusal pits and fissures, and reduces the risk of pit and fissure caries by eliminating potential stagnation areas. Sclerosed dentin produced in response to attrition may confer protection against microbial invasion. Furthermore, Trivedi *et al.*, 2002 suggested in their study that the process of chewing areca nut increases salivation in the mouth and in the presence of added slaked lime the pH increases in the oral environment which act as a buffer against acid formed in plaque on teeth (Trivedy, 2002). JC Kurian, 1995 suggested that Areca nut is made into dentifrice due to its astringent properties. It strengthen the gum & sweeten breath as well. The arecanut seed forms excellent dentifrices when reduced to charcoal and powdered (Kurian *et al.*, 1995).

Wound Healing

Azeez *et al.*, 2007 reported that the alkaloid fractions of Areca catechu and polyphenols enhanced the healing of incision and excision wounds by increasing the breaking strength of granulation tissue (Shamina Azeez *et al.*, 2007). But in the study conducted by Verma *et al.*, 2012, in their study found significant increase in the rate of contraction of burn wound and period of epithelialization and concluded that *Areca catechu* kernel favoured burn wound healing and areca nut overcome the wound healing suppressive property of dexamethasone (Deepak Kumar Verma, 2012).

Antiradical

Chia-Ching *et al.*, 2010 reported from their study that the methanolic extract of *Areca catechu* exhibited strong antiradical activities and reducing power, as it contains significant amounts of phenols and flavonoids, which play a major role in controlling oxidation. Their study results showed that *Areca catechu* extracts may be used as an antioxidant, leading to the possibility of developing natural antioxidant material (Chia-Ching Li and En-Shyh Lin, 2010).

Anti- Allergic

J H Lee *et al.*, 2004 reported Areca catechuis most potent inhibitor of antigen- induced degranulation in mast cells. It inhibits DNP-BSA-and compound 48/80- induced degranulation in mast cells and showed inhibitory activity on compound 48/80-induced systemic anaphylaxis by 46% in mice. It inhibits the expression of TNF- α and activates 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 suggested that in various immediate and delayed allergic diseases, Areca catechu may be useful for the treatment (Lee *et al.*, 2004). In a study conducted by Chia-Chi Wang *et al.*, 2013, Polyphenol derived areca nut (PANE) extract administration attenuated Ovalbumin-induced allergic responses, including the occurrence of diarrhoea and the infiltration and degranulation of mast cells in the duodenum. PANE treatment suppressed the serum level of Ovalbumin - specific IgE and the expression of interleukin-4 in the duodenum. In addition, PANE administration induced Gr-1+, IL-10+ and Gr-1+ IL-10+ cells in the duodenum. These results

demonstrate that oral intake of areca-derived polyphenols attenuates food allergic responses accompanied with a decreased Th2 immunity and an enhanced induction of functional myeloid-derived suppressor cells (Chia-Chi Wang, 2013).

Anticonvulsant

D Lodge *et al.*, 1977, in their study found areca alkaloids, arecaidine and guvacine, inhibited the uptake of GABA and α -alanine, but had not that of glycine, by slices of cat spinal cord. Large doses of arecaidine (1g/kg subcutaneous) marginally reduced the lethal effects of bicuculline in mice but appeared to have little or no anticonvulsant activity (Lodge *et al.*, 1977).

Anti HIV

M Marastoni *et al.*, 2004 (Marastoni, 2004), Kavita Vermani *et al.*, 2002 stated that various constituents of Areca nut like procyanidins, areca tannin B1 and extracts of seed showed HIV protease inhibition activity (Lodge, 1977).

Central Nervous System Stimulant

Madhusudan joshi *et al.*, 2012 observed that arecoline, the alkaloid in areca catechu has effect on CNS. They demonstrated in their study on animal that both wet *Areca catechu* and dried *Areca catechu* extract show increase in learning and memory on continuous administration without much impairment of neuromuscular tone (Madhusudan Joshi *et al.*, 2012).

Anti Venom

Okuda *et al.*, 1991 found that tannins from plants are used as antidote of snake venom, which interact with snake enzyme systems (Mahanta and Mukharjee, 2001). Pithayanukul *et al.*, 2005 tested polyphenols from the aqueous extracts of Areca catechu and other plants for their inhibitory activities against Naja kaouthia (NK) venom by in vitro neutralization method. And found that Areca catechu extracts completely inhibited the lethality of the venom. They suggested that the anti-venom activities of polyphenols from areca extracts was by selectively blocking the nicotinic acetylcholine receptor and non-selectively by precipitation of the venom proteins (Preeti Jaiswal, 2011).

Anti Molluscicidal

Jaiswal and Singh, 2008 found that seed of Areca catechu (areca nut) is a potential source of botanical molluscicides against *Lymnaea acuminata*. The active molluscicidal components of Areca catechu seed are soluble in chloroform, ether, acetone and ethanol. They also found that the toxicity of ethanolic extract of Areca catechu seed is higher than other extracts which indicated that the molluscicidal component present is more soluble in ethanol than other organic solvents. They also characterized that arecoline alkaloid is the main molluscicidal components of Areca catechu (Jaiswal *et al.*, 2008).

Antihyperglycemic

In the study by Rupesh Ghate *et al.*, 2014, it was found that the ethanolic and aqueous extracts of areca catechu flowers

exhibited significant decrease in the blood glucose level in alloxan treated rats. The hypoglycemic effect was explained to be due to increased secretion of insulin from β cells of pancreas i.e. pancreatotrophic action or due to regeneration of pancreatic cells that were partially destroyed by alloxan. It is well known that flavonoids and sterols possess antidiabetic property and the phytochemical screening of Areca catechu plant shows the presence of flavonoids, steroids, tannins, saponins in ethanol and aqueous extracts (Rupesh Ghate, 2004).

Conclusion

Each individual/ phenomenon has two aspects – Good & Bad. We have dedicated ample amount of time in explaining the deleterious effects of Areca nut. Time has come to explore the other aspects of Areca nut. Areca nut 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. 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 world.

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