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S Keshava Bhat
Arecanut Research and Development Foundation®, Varanashi Towers, Mission Street, Mangaluru: 575 001, Karnataka, India

D Ashwin
Department of Pedodontics and Preventive Dentistry, Kannur Dental College, Anjarakandy, Kannur, Kerala, India

S Mythri
Department of Periodontology, Kannur Dental College, Anjarakandy, Kannur, Kerala, India

Sukesh Bhat
Department of Pharmacology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India

Correspondence
S Keshava Bhat
Arecanut Research and Development Foundation®, Varanashi Towers, Mission Street, Mangaluru: 575 001, Karnataka, India

Arecanut (*Areca catechu* L) decreases Alzheimer's disease symptoms: Compilation of research works

S Keshava Bhat, D Ashwin, S Mythri and Sukesh Bhat

Abstract
Alzheimer's disease (AD) is a common old age neurodegenerative disorder characterized mainly by memory loss and depression. Though there is no cure for this disorder, it could be treated symptomatically by proper medications. However, the chemical drugs, if taken in the long run, pose several side effects. Traditional medicines of plant origin are now increasingly popular in the treatment of several chronic diseases. Areca palm is one such medicinal plant with lots of pharmacological properties. The useful properties of this palm has been evaluated by several researchers. This nut is also found to be very effective in the treatment of AD. In this paper an attempt is made to compile the available literature on the role of arecanut in the management of AD. Several studies conducted on rodents confirmed that the arecoline, the major alkaloid of arecanut significantly increased acetylcholine by inhibiting Acetylcholine Esterase, the enzyme responsible for breaking down acetylcholine in the brain. The aqueous and crude extracts of arecanut were found more potent than chloroform, petroleum spirit, and ethyl acetate fractions in their inhibitory effects. Significant improvement in picture recognition was observed in AD patients after treatment with arecoline. The arecanut extract especially the dichloromethane fraction was reported to reduce depression in several animals.

Keywords: Alzheimer's disease, Medicinal plants, Arecanut, *Areca catechu*, Arecoline, Memory, Depression

1. Introduction
Plants have been used for their medicinal properties since the start of human civilization. The descriptions of such medicinal plants are well documented by Tavera (1901); Kirtikar, *et al* (1918); Chopra and Chopra (1955); Aman (1969) [1-4] and several of them were now validated by scientific findings by Phadke (2007); Rahmatullah, *et al* (2009); Khan, *et al* (2012); Kaushik, *et al* (2013); Peng, *et al* (2015); Rashid, *et al* (2015); Sudan, *et al* (2016) [5-11]. Medicines derived from plants are being used by about 60% of the world's population and in rural India nearly 70% of the people depend on such medications (Seth and Sharma 1976) [12]. Areca palm, *Areca catechu* L. (Family: Palmae) is one such medicinal plants whose pharmacological and medicinal properties are widely reviewed by Arjungi (1976); ShankaraBhat (2008); Patil, *et al* (2009); Jaiswal, *et al* (2011); Amudhan, *et al* (2012); Peng, *et al* (2015) [13-18]. The World Health Organization (2009) has listed out as many as 25 beneficial effects of *A. catechu* [19]. However, there are several contradictory reports on the health effects of this nut or its active principle arecoline on human being. Some reports say that it causes cancer (IARC 2004; Chaturvedi, *et al* 2014) [20, 21]. But when such reports were scrutinized it was observed that the cancer caused only in very high doses of arecanut / arecoline or when they were given in unusual ways such as by injection or by direct application to cultured cells (KeshavaBhat 2016; KeshavaBhat, *et al* 2017) [22, 23]. There are reports which say that arecanut and arecoline are not carcinogenic but they help in curing cancer (Kumari, *et al* 1974; Fan, *et al* 2016) [24, 25].
Areca palm is cultivated mainly in South and Southeast Asian countries such as India, China, Bangladesh, Indonesia, Myanmar, Thailand, Malaysia, Vietnam, the Philippines, etc. (Cheriyan and Manojkumar 2014) [26]. Areca palm has a solitary, slender (about 50cm circumference), straight trunk growing 25-30m tall, with a compact crown surrounded by 7-12 leaves at various stages of development. Its fruit is fibrous, ovoid drupe with a central ruminant endosperm or nut covered by thin pericarp (husk) which is green when unripe and orange-yellow when ripe (Ananda 2004) [27]. The endosperm of this fruit is commonly called as arecanut in open market.

It is the common stimulatory mastication throughout the world, especially in Indian sub continent and other parts of South East Asia. Arecanut is misnamed as 'betel nut' in several parts of the world as this nut is usually chewed along with the leaf of *Piper betle*, a vine of Piperaceae family.

The major constituents of arecanut (both green and ripe) are 17.3–25.7% polysaccharides, 11.1–29.8% polyphenols (including flavonoids and tannins), 8.2–15.4% fibres, 8.1–15.1% fats, 6.2–9.4% proteins, 1.1–2.5% ash and 0.11–0.24% alkaloids including arecoline (Shivashankar, *et al* 1969) [28]. Apart from arecoline, other minor alkaloid content of arecanut are arecadine, guvacine, guvacoline, isoguvacoline and arecolidine (Annamalai, *et al* 2004) [29]. Arecoline is the main alkaloid and physiologically the most active one and has a stimulating effect on the central nervous system (Bhat 2008) [30]. Arecanut also contains Vitamin B6 (286.9mg%) and Vitamin C (416.2mg%) (Annamalai, *et al* 2004) [29]. The Fatty acid compositions of arecanut are: lauric acid (19.5%), myristic acid (46.2%), palmitic acid (12.7%), oleic acid (6.2%), linoleic acid (5.4%), hexadecenoic acid (7.2%) and minor proportions of stearic acid, decanoic acid and monoethylenic acids (Pathak and Mathur 1954) [31]. Polyphenols were reported to decrease whereas polysaccharides, alkaloids, fats and fibres increase with maturity of the nut (Mathew, *et al* 1964) [32]. All the major chemical constituents of arecanut, including arecoline decrease significantly while drying and storing with husk as whole nuts (Chempakam and Saraswathy 1985) [33] and also while roasting, soaking and boiling (Awang 1988) [34].

2. Alzheimer's disease

Alzheimer's disease (AD) is a common old age irreversible neurodegenerative disorder wherein the patient generally complain about memory loss, sleeplessness, anxiety, depression, etc. and eventually the ability to carry out the simplest tasks is lost. It is one of the most common causes of dementia contributing as much as 60% of total causes among elderly people, and nearly 15 million people in the world suffer from this disease (Francis, *et al* 1999) [35]. Currently there is no proper and definite medication to cure this disease but certain treatments either prolong the progression of the disease or temporarily provide certain amount of symptomatic relief. Most of the synthetic drugs prescribed for the treatment of depression have lots of side effects such as dry mouth, fatigue, gastrointestinal and respiratory problems, drowsiness, etc (Dhingra and Sharma 2006) [36]. Because of all these, increasing interest is being developed world wide for the search and use of much safer plant based medicines in place of synthetic drugs. Lot of work has been carried work using plant extracts to reduce the symptoms of Alzheimer's disease (Perry, *et al* 1999; Howes and Houghton 2003; Houghton and Howes 2005; Jawaid, *et al* 2011; Rao, *et al* 2012; Gautham, *et al* 2013; Vyoma 2015; Kumari, *et al* 2016) [37-44]. The research carried out using arecanut to reduce Alzheimer's disease symptoms are searched using Google scholar, Pub Med, textbooks and old journals until June 2017and compiled in this paper.

3. Arecanut improves memory

3.1 Effect of Arecoline

Amnesia or memory loss is one of the primary symptoms of AD (Singhal, *et al* 2012) [45]. It is characterized by low levels of acetylcholine (ACh), a neurotransmitter responsible for the transmission of nerve impulses in the brain and is directly associated with cognitive functions, and a cholinergic deficit has been correlated with the severity of AD (Megha 2000; Howes and Houghton 2009) [46, 47]. Low level of acetylcholine is due to the action of another enzyme, acetylcholinesterase (AChE) which is responsible for breaking down acetylcholine (Jivad and Rabiei 2014) [48]. By inhibiting AChE enzyme, the activity of acetylcholine could be increased in the brain (Mohammed 1993; Obulesu and Rao 2011) [49, 50]. Natural therapy using medicinal plants having AChE inhibitors or having muscarinic agonists and cholinergic drugs which increase acetylcholine production has been used to treat such disorders like AD since a long time (Avery, *et al* 1997; Murray, *et al* 2013; Akram and Nawaz 2017) [51-53]. Arecoline, the major alkaloid of arecanut, is one such muscarinic agonist on which lot of works have been done on memory improvement on lab animals and human beings.

It is reported that in mice, injection of cholinergic drugs such as arecoline, edrophonium, oxotremorine and tacrine subcutaneously (SC), individually or in combination, enhanced the memory retention capacity significantly (Flood, *et al* 1985) [54]. It was further noticed that the combination of arecoline and tacrine was much more efficient than either of the drugs administered alone (Flood 1988) [55]. Chronic administration of arecoline for 20 days at a dose of 28.5 mg/kg or more/day increased the level of acetylcholine in the Central Nervous System of mouse (Molinengo, *et al* 1988) [56]. There are reports which say that arecoline selectively increases cerebral glucose utilization in animal models (Maiese, *et al* 1994) [57]. Glucose has been found to improve memory in animals and humans through increased acetylcholine synthesis and interacting with other neurotransmitters (Messier and Gagnon 1996) [58].

Arecoline is also reported to increase the learning ability in other animals. In monkeys such as the common marmoset (*Callithrix jacchus*) administration of arecoline increased their learning ability (Ridley, *et al* 1987) [59]. In human being also, injection of arecoline at 4 mg significantly enhanced serial learning (Sitaram, *et al* 1978) [60]. In their study it was also noticed that arecoline reversed the impaired learning behavior in human being who received scopolamine, a cholinergic antagonist. The effect of arecoline on memory improvement in Alzheimer patients was studied by administering 2 and 4mg of this compound intravenously on 11 patients with a clinical diagnosis of Alzheimer dementia (Christie, *et al* 1981) [61]. In their study, significant improvement in picture recognition was observed at 4mg of arecoline. Slight improvement was seen in majority of patients at 2mg, but it was clear and consistent only in two patients. While studying the effects of infusion of different doses of arecoline (1, 2 and 4mg/h) on AD patients, it was noticed that there were marginal improvements in word finding and picture recognition abilities at lower doses (Tariot, *et al* 1988) [62]. The infusions were well tolerated by the patients.

Continuous administration of arecoline intravenously at low doses up to 2 weeks significantly improved memory in five out of nine subjects with mild to moderate AD patients (Soncrant, *et al* 1993) [63]. No adverse drug effects were observed in them. In an attempt to improve cognitive function in AD, arecoline was given to patients showing probable AD and verbal memory function by administering escalating doses from 0.5 to 40 mg/day by intravenous infusion continuously for two weeks, it was observed that in six out of eight patients there was a significant improvement in verbal memory at a dose of 4mg/day though two patients did not respond to any of the doses used (Raffaele, *et al* 1991) [64]. The effects of five different doses of arecoline, ie., 1, 4, 16, 28 and 40mg/day were studied by administering intravenously on

nine human patients showing probable dementia of the Alzheimer type (Raffaele, *et al* 1996) [65]. They found that verbal ability tended to improve at lower doses whereas attention and visuospatial ability improved at higher doses of arecoline.

The action of arecoline as muscarinic receptor 1 agonist was very well demonstrated in Alzheimer's dementia models of rats (Chandra, *et al* 2008; Kumar, *et al* 2009) [66, 67]. Muscarinic binding activity of arecoline was reported in rat brain models *in vitro* (Yang, *et al* 2000) [68]. They also found that arecoline exerted its excitatory actions by binding to M-2-muscarinic receptors and such actions of arecoline were antagonized by the treatment of atropine, a common muscarinic antagonist.

It was reported that high dose (5mg *i.v* over 30min) of arecoline produced unpleasant side effects in AD patients whereas no such side effects were observed in chronic (0.5–40mg *i.v*/day over 2 weeks) exposure to arecoline (Asthana, *et al* 1995) [69]. The optimal dose of plasma arecoline level to enhance memory in rats was measured as 0.31+/_0.14 ng/ml (Asthana, *et al* 1996) [70].

3.2 Effect of Arecanut extract

Arecanut is chewed mainly in two different forms, one wet type and another dry type. In wet type, the ripe arecanuts are chewed as such and in dry type the ripe arecanuts are sun dried for 40 to 45 days and then chewed. The effects of both these types of arecanut on learning and memory improvement were studied separately on Wistar albino rats (Joshi, *et al* 2012) [71]. The extracts were prepared with methanol and orally fed to the experimental animals at a dose of 500mg/kg body weight for 21 days and observations were made on day one and seven and 21 days of feeding. It was observed that both the groups of animals showed significant increase in memory and learning in comparison to control groups. They also found that the extract prepared from wet type was more potent than that prepared from dry type. The period for finding the food in radial arm maze for the control group was 4.2 min in day 1 and 2.3 min in day 21, whereas the figures for the group treated with dry type were 3.9 and 0.9 and for wet type 3.7 and 0.3 for day 1 and day 21, respectively. They postulated this difference between wet and dry types for the higher amount of arecoline present in wet type (0.2%) compared to dry type (0.16%). This is in conformity with the earlier observations that all the major chemical constituents of arecanut, including arecoline, were found to decrease significantly while drying arecanuts (Chempakam and Saraswathy 1985) [33]. The hydroalcoholic extract of arecanut was also reported to be neuroprotective and increased memory in Swiss mice (Kannan, *et al* 2013) [72].

The crude extract of arecanut caused significant spasmogenic effect in rabbit jejunum similar to that caused by acetylcholine thus exhibiting cholinomimetic effect (Gilani, *et al* 2004) [73]. Similarly, good AChE inhibitory activity of arecanut crude extract was also reported by them. Among the several forms of extracts tested, they found that the aqueous and crude extracts of arecanut were more potent than chloroform, petroleum spirit, and ethyl acetate fractions in their AChE inhibitory effects. The hydroalcoholic extract of arecanut at 200 and 400mg/kg (p.o) doses also observed to decrease significantly AChE level in the brain of treated mice (Kannan, *et al* 2013) [72].

4. Arecanut as anti-depressant

Depression is another common symptom of AD. It is characterized by features such as sadness, indifference to surroundings, irritability, changes in sleep patterns, appetite, impaired concentration, fatigue, feelings of shame and guilt, thoughts of dying, etc. Though several antidepressant drugs are being prescribed nearly 30% of patients don't respond to such drugs and there are lots of side effects. Hence, efforts are underway to develop effective herbal medicines as anti-depressant agents.

Several extracts of arecanut, especially the ethanol, methanol, hexane hydroalcoholic and aqueous fractions revealed antidepressant activities on rodents (Kannan, *et al* 2013; Dar and Khatoon 1997; Dar, *et al* 1997; Ruckmani, *et al* 2014; Bhat, *et al* 2016a & 2016b; Bende, *et al* 2016) [72, 74-79]. Both aqueous (at 300mg/kg p.o) and methanolic (at 250mg/kg p.o) extracts of arecanut showed antidepressant activity in Swiss mice comparable to that of Imipramine, a standard antidepressant drug at 10mg/kg p.o concentration (Ruckmani, *et al* 2014) [76]. One lacuna in their study was that they did not try lesser doses of arecanut extracts in their experiment. In a later study using Swiss mice it was found that the ethanolic extract of arecanut at a dose of 80mg/kg i.p was equally effective with that of Imipramine at 10mg/kg i.p in reducing depression (Bhat, *et al* 2016a & 2016b) [77, 78]. The ethanolic extract of arecanut also showed significant antidepressant activity in other rodents such as albino rats at 4-80mg/kg i.p Dar and Khatoon 1997) [77] and 50mg/kg oral (Bende, *et al* 2016) [79]. The action was mainly by inhibiting monoamine oxidase (MAO), an enzyme which catalyzes the breakdown of the neurotransmitters leading to the development of depression (Dar, *et al* 1997) [75]. The inhibitors of MAO thus forms a group of antidepressant drugs (Marco 2014) [80]. Among the three different types of arecanut extracts (ethanolic, hexane and aqueous) the aqueous fraction was found to be the most effective one in inhibiting MAO and its effect was reported to be similar to that of Clorgyline, a specific MAO-A inhibitor (Dar, *et al* 1997) [75]. The hydroalcoholic extract of arecanut at 200 and 400mg/kg (p.o) doses also reported to reduce significantly the level of MAO in the brain of mice (Kannan, *et al* 2013) [72].

The dichloromethane fraction of arecanut is identified as the inhibitor of MAO-A. The forced swim and tail-suspension tests conducted on albino rats indicated that the dicloromethane fraction caused significant reduction in the immobility time similar to that of Moclobemide, a selective inhibitor of MAO-A (Dar and Khatoon 2000) [81]. They further reported that the alkaloids of arecanut such as arcoline, arecadine, etc were not inhibiting MAO. The phytochemical analysis of arecanut extract revealed that saponins (by elevation of neurotransmitters or monoamines such as serotonin and noradrenaline in the hippocampus portion of the brain) may be the active component for the antidepressant action of this nut (Abbas, *et al* 2013) [82]. It is reported that the dichloromethane fraction of arecanut also elevates serotonin and dopamine in the brain, thus reducing depression (Khan, *et al* 2014) [83].

5. Conclusion

Alzheimer's disease is an incurable disorder of the brain wherein the patient generally complain about memory loss and depression. Though several chemical drugs are being used for the symptomatic treatment of this disease, most of them pose several side effects. Medications prepared from herbs are always better than chemical drugs in the long run. Areca palm, *Areca catechu* L. is largely grown in several south and south east Asian countries. It is the reservoir of several useful phytochemicals which could be better utilized

as medicines for mankind. Its effect in ameliorating the symptoms of AD is well documented by several researchers. Clinical studies may be conducted to confirm its usefulness on Human being and proper dosage be worked out.

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