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Review Article

ARECANUT (*ARECA CATECHU* L.) POLYPHENOL AS ANTI-VENOM: COMPILATION OF LITERATURE

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ABSTRACT

Envenomation is a common public health problem in several countries, especially in rural areas. Though several synthetic anti venom drugs are available to treat poison bite patients, transportation of victims to hospitals, improper storage facilities of such drugs in rural areas are some of the hurdles in the management of such victims. Plants have rich source of phytochemicals with lots of medicinal properties. Such medicinal values are being used widely by traditional healers. Several researchers have now validated the ethnomedical properties of such plants with proper scientific data. Polyphenols of plants are known for anti-venom properties since very long time. Application of such knowledge might be very useful as first aid in the treatment of poison bites. The fruit of areca palm, *Areca catechu* L, commonly called as arecanut or betel nut is mostly chewed for its medicinal values. This medicinal plant also contain good amount of polyphenols (35 to 55%) in its nuts. However, very less research work has been done on the antivenom properties of this medicinal plant. Present review is focused on compiling such works by searching Google scholar, Pub Med, textbooks and old journals until June 2017 and urged the researchers for further detailed studies on these lines. It was reported that the aqueous extract of the seeds of arecanut was reported to inhibit the action of the venom of the monocellate cobra, *Naja naja kaouthia*. The medium effective dose of arecanut was reported to be 62.0µg/mouse. The necrotizing activity caused by the venom was also successfully inhibited by injecting arecanut extract at a dose of 30.0µg/mouse. Processed tender arecanuts, known as chikni supari were also reported to be effective in absorbing the venom from the bite wounds of scorpions, lizards and even snakes. This knowledge could be used as the basis for further detailed studies on the anti-venom properties of this plant.

INTRODUCTION

The areca palm, *Areca catechu* L. belongs to the family Arecaceae or Palmae is a tall palm tree growing up to 30m height with a solitary slender (about 50cm circumference) and erect stem. It has a compact crown surrounded by 7-12 leaves or fronds with 1.2 to 1.8m in size at various stages of their development. The leaves are pinnate with a basal leaf sheath and numerous leaflets in the distal portion. The leaf sheath which is about 54cm in length and 15cm in breadth completely encircles the stem forming a protective covering for the developing inflorescence. The leaflets which are 62.5cm in length and 7cm in breadth are partly fused with one or more midribs. The inflorescence of arecanut is a spadix and produced in the leaf axils. The stalk of the inflorescence is short having more than 60cm long branched rachis with sessile female and male flowers separately. The female flowers are confined singly to the tertiary rachis and to the distal end of the secondaries. The male flowers are produced in pairs the filiform branches which generally arise beyond the female flowers. The areca fruit is a mono-locular one seeded drupe with a thin fibrous layer of husk surrounding the

endosperm. The shape of the fruit varies from oval to round with 5.3cm in length and 4.2cm in breadth when fully matured[1].

This palm is distributed mainly in South and South East Asian Countries, especially in India, Sri Lanka, Bangladesh, Myanmar, Nepal, China, Philippines, Thailand, Indonesia, Malaysia, etc[2]. The processed endosperm is marketed as supari. In some parts of the world it is misnamed as 'betel nut' as this nut is usually masticated along with the parts of *Piper betle* a perennial and evergreen vine of Piperaceae family. India ranks first in the production of arecanut with nearly 50% of world production followed by Indonesia with 16% and China with 10%[3]. The fruit of this palm is commonly called as arecanut. The major constituents of arecanut on dry weight basis are polyphenols including flavonoids and tannins (11.1–29.8%), polysaccharides (17.3–25.7%), proteins (6.2–9.4%), fats (8.1–15.1%), fibres (8.2–15.4%), alkaloids (0.11–0.24%) and mineral (1.1–2.5%) matter[4,5].

Medicinal properties of arecanut

Arecanut is chewed mainly as 'betel quid' along with several other ingredients, especially with the leaf or inflorescence of *P. betle* and slaked lime in several countries as it is believed to have numerous medicinal values[6,7]. The World Health Organization has listed out as many as 25 beneficial properties of arecanut[8]. It has antioxidant, anti-inflammatory and analgesic[9-11], anti-diabetic[12,13], hypolipidemic[14,15], antibacterial[16,17] anti-fungal[18], anti-malerial[19-20], antiviral[21] anti-HIV[22] and AIDS[23], anti-aging by reducing wrinkles formation in skin[24], learning and memory improvement[25,26], wound healing[27,28], anti-ulcer[29,30], anti-migraine[31], antihypertensive[32], anti-depressant[33], anti-allergic[34], anthelmintic[35,36], aphrodisiac[37], hepatoprotective[38,39],cytoprotective[40], and even anti-cancer[41] properties. Several review papers have been published on these aspects[7,42,43].

In rural areas of India and several other countries, traditional herbal antidotes are being used as folk medicine by several tribal people for the treatment of various poison bites and several of them are now validated with scientific evidences[44-46]. Ample number of review papers has already been published in recent years on this subject[47-51]. It was reported that several plants possess neutralization properties against the snake venom enzymes such as hyaluronidase, acetylcholinesterase, phospho-lipase A_2 and plasma proteases[45,52]. The effectiveness of certain herbs for the treatment of scorpion bite is also reported by some researchers.[53,54]

Plant polyphenols as anti-venom

It is reported that polyphenols, especially flavonoids and tannins of plants are the key phytochemicals effective against several snake venoms, such as that of the monocellate cobra, *Naja naja kaouthia*, the carpet viper *Echis ocellatus, etc*[44,55-57]. The protective effects of polyphenols including tannic acids against the toxicity of snake (*N. kaouthia*) venom have already been established[58]. They observed that the binding ability of tannic acid with the venom led to the precipitation of the venom protein, thus inhibiting the effects of venom on target animals. Hence, it is suggested to use tannic acid and plant polyphenols as first aid for the emergency treatment of snakebites[44,59]. The factors responsible for inhibiting the venom of Russell's viper (*Daboia russellia*) and black scorpion (*Heterometrous bengalensis*) present in the root extract of Indian sarsaparilla, *Hemidesmus indicus* were isolated and designated as HI-RVIF and H.I-1, respectively[54,60].

Arecanut as antidote of venom

Arecanut is rich in polyphenols. It is reported that certain processed varieties of arecanuts, especially those obtained from tender nuts contain even up to 55.2% polyphenols, including flavonoids and tannins[4]. These phytochemicals of arecanut effectively inhibits the action of the snake venom. In a comparative study conducted in Thailand on laboratory mice using the aqueous extracts of the seeds of arecanut *A. catechu,* the leaf galls of gall oak *Quercus infectoria*, the barks of the elephant foot tree *Pentace burmanica* and the sweet tamarind *Pithecellobium dulce* on *N. kaouthia* venom injected mice it was noticed that the lethality of the venom at 4 LD_{50} concentration was completely inhibited by the extracts of *A. catechu*, *P. burmanica* and *P. dulce* with the arecanut extract faring better than others[44]. The medium effective doses of *A. catechu*, *P. burmanica*, *P. dulce* and *Q. infectoria* were reported to be 62.00, 185.78, 364.50 and 510.04 µg/mouse, respectively. While analyzing the tannin content of all these plant extracts it was noticed that the extract of *Q. infectoria* contained only hydrolysable tannin and those of *A. catechu*, *P. burmanica* and *P. dulce* contained both condensed and hydrolysable tannins. Hence, the authors postulated that the combination of condensed and hydrolysable tannins exerted better activity. Earlier reports also say that arecanut contains 8-15% condensed tannins[61]. It was also observed by them that when the tannin content in the venom–tannin mixture was increased from 0.001% to 10.0% (w/v), the venom proteins gradually disappeared in

a dose dependent manner and precipitated. This clearly shows that arecanut could be better utilized as anti venom.

The inhibitory activities of the polyphenols from the aqueous extracts of *A. catehu*, *Q. infectoria*, *P. burmanica* and *P. dulce* on the development of necrosis on rat skin caused by the injection of minimum necrotizing dose of the venom of *N. kaouthia* were studied[44]. It was noticed that by injecting the extracts of *A. catechu* at 30 µg/rat they could completely protect rats from necrotizing activity caused by the poison of *N. kaouthia*. The extracts of *A. catechu* and *P. burmanica* were able to precipitate the venom proteins completely at the tannin content of as low as 1.0%, while *P. dulce* and *Q. infectoria* produced the same effect at higher tannin contents of at least 5.0%. It could be possible that both *A. catechu* and *P. burmanica* contain higher ratio of condensed to hydrolysable tannins than that of *P. dulce*. Polyphenols from the extracts of *A. catechu* and *Q. infectoria* were also reported to inhibit the actions of phospholipase A_2, proteases, hyaluronidase and l-amino acid oxidase of the venom of monocellate cobra, *N. kaouthia* and the Malayan pit viper, *Calloselasma rhodostoma* in vitro and both the extracts inhibited the hemorrhagic activity of *C. rhodostoma* venom and the dermonecrotic activity of the *N. kaouthia* venom in vivo tests[62]. The inhibitory activity of polyphenols against local tissue necrosis induced by snake venoms was attributed to the inhibition of inflammatory reactions, hemorrhage and necrosis.

Acetylcholinesterase is an enzyme responsible for breaking down acetylcholine, a neurotransmitter responsible for the transmission of nerve impulses in the brain[63]. The venom of *N. kaouthia* was reported to inhibit the activity of acetyl-cholinesterase by 100%, thereby blocking the action of acetylcholine. The extract of *A. catechu* was observed to completely (99%) nullify the acetylcholinesterase activity of *N. kaouthia* venom at the tannin content of only 0.10% (w/v), by which the action of acetylcholine is reverted to normal level in the brain[44]. Hence, natural therapy using medicinal plants having acetylcholinesterase inhibitors such as arecanut could be better utilized in anti-venom therapy.

Arecanut is processed mainly by two methods[64,65]. In the first method, the ripe arecanuts are dried for 35-40 days in the sun and dehusked afterwards to get 'White chali'. In the other method, the unripe arecanuts are dehusked first, boiled as whole nuts or boiled after cutting the kernel into 2-3 slices, coated further with the extract of previous boiling and then dried to get 'Red variety'. One of the 'Red varieties' of arecanut is called 'api' or 'chikni' which is obtained from whole tender nuts without slicing. This type of processed arecanut is reported to absorb the venom from the wounds of poison bites caused by scorpion, lizard and even snake[66]. They found that the 'chikni' supari, commonly available in Malaysia, Maldives and India (Karnataka and Assam States) was found to stick on to the wounds caused by the poisonous animals when the nut is placed on the injured place and absorb the poison. After absorption, the color of the nut changes according to the type of poison and falls by its own. The time taken for the complete absorption of poison ranged from half an hour to 12 hours depending on the poison type, whether it is caused by scorpion, lizard or snake. The authors have suspected the alkaloid, arecolidine for anti venom property as they have isolated this chemical from the chikni supari. The major lacuna in this study is that they have not considered other chemicals present in chikni supari. In arecanut, the alkaloid content is generally very less in tender nut stage and it increases as the nut matures. Alkaloid content is calculated to be 0.06% in tender nuts, 0.14% in mature nuts and 0.22% in ripe nuts. On the other hand, it is the polyphenol content which is more in tender nut stage decreases as the nut matures. In this study, the polyphenol content is reported to be 47.9% in tender nuts, 26.4% in mature nuts and 17.8% in ripe nuts[67]. As the chikni supari is prepared from tender arecanut, the polyphenol content must be more in such nuts. Thus, it might be the polyphenol content of chikni supari which played an important role in inhibiting the activity of venom as polyphenols of plants have already been proved to be anti necrotic and anti venomous[44,55,56,58,61]. However, more detailed studies are warranted to confirm this.

CONCLUSION

Polyphenols of plants are known for their anti venomous properties. Areca palm is one such plant having good amount of polyphenol in its tender nuts. Certain reports confirm that the aqueous extract of arecanut is very potent in inhibiting the development of necrosis and lethal action of the venom of *N. kaouthia* on mice. There are other reports which say that processed tender arecanut is very good in absorbing the venom from the wounds caused by several animals including scorpion and snake. Further studies on these lines will definitely help mankind.

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