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Review Article

ANALGESIC, ANTI-INFLAMMATORY AND WOUND HEALING PROPERTIES OF ARECANUT, *ARECA CATECHU* L. : A REVIEW

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ABSTRACT

Wounds are unavoidable and most frequent injuries that occur during the daily activities of man and his livestock. Unless the wounds are cured properly in time it may lead to several other complications. In modern day medicine, antibiotic treatments are generally advocated for such injuries. But, due to several side effects and development of resistance by certain bacterial strains against such antibiotics there is a need to explore some alternative and effective therapeutics of plant origin which are cheap and relatively safe for mankind. Already several folklore medicines of plant origin are in vogue in several villages. Arecanut, *Areca catechu* L. is one such medicinal palm, the nuts of which are being used for the treatment of wounds since many years. The analgesic, anti-inflammatory and wound healing properties of arecanut are now authenticated by several scientific studies. The present paper aims at compiling such literature on this medicinal palm which is abundantly grown in several south and southeast Asian countries.

KEYWORDS: Arecanut; Betelnut; Supari; *Areca catechu*; Analgesic; Anti-inflammatory; Wound healing; Polyphenol.

INTRODUCTION

Wounds are the most frequently occurring injuries on animal skin. It is very common in the daily activity of each and every individual. The causative factors for such injury are too many. They may be either due to physical, mechanical, chemical, thermal, microbial or even parasitical in origin. Generally, wound is formed by simple tearing up of skin, resulting in injury of different dimensions. Inflammation and pain are the aftereffects of the injury. Use of several effective herbal medicines to treat such wounds is very common by different tribal people and also in ancient systems of medicine such as Ayurveda and Siddha [1-8]. It has been estimated that nearly 70% of wound healing Ayurvedic medicines are originated from plants [9]. Several plants have already been reported to have wound healing property[10-12].

Arecanut, which is commonly called as betel nut or 'supari' in several parts of the world, is the seed of a perennial palm called *Areca catechu* L. It belongs to the family Palmaceae and grows as a seed crop in several south and southeast Asian countries such as India, China, Bangladesh, Sri Lanka, Myanmar, Malaysia, Indonesia, etc[13]. Traditionally, arecanuts are used for mastication as they are believed to have lots of medicinal properties. [14,15] Arecanut is commonly chewed along with several other ingredients like betel (*Piper betle*) leaf or inflorescence, catechu (*Acasia catechu*), slaked lime, tobacco (*Nicotiana tabacum*) and certain condiments and sweeteners. [16]

The major chemical constituents of arecanut are polyphenols including flavonoids and tannins (up to 29.8%), polysaccharides (up to 25.7%), proteins (up to 9.4%), fats (up to 15.1%), fibres (up to 15.4%), alkaloids (up to 0.24%) and mineral matter (up to 2.5%).[17] The mineral matters include calcium (0.05%), phosphorus (0.13%) and iron (1.5 mg/100g)[18]. Arecanut also contains Vitamin B6 (286.9mg%) and Vitamin C (416.2mg%)[19]. Among the alkaloids present in arecanut, arecoline is the main and physiologically the most active one and has a stimulating effect on the central nervous system[20]. Other minor alkaloids are arecaidine, guvacine, guvacoline, isoguvacoline, arecolidine and homoarecoline[21]. Arecoline, arecadine and guvacoline are mainly found in the brown portion of the nut, whereas guvacine is found in the white portion[22]. Polyphenols, which constitute a large proportion of the dry weight of arecanut, are responsible for the astringent taste of the nut. However, polyphenol contents are more in tender nuts, whereas poly-saccharides, fats and fibres are more in mature nuts[23]. Most of the major chemical constituents of arecanut, including arecoline decrease significantly while drying and storing, roasting, soaking or boiling the nut[24,25].

Traditional medicines, usually of plant origin are used by about 60% of the world's population and in rural India such medications are more popular and nearly 70% of the people go for such treatment[26]. Arecanut is one of these plants[27] and it has got an important place in the ancient system of medicines in several countries such as India[14], China[28], Bangladesh[29], Philippines[30] etc. Most of the folklore medicinal properties of arecanut are now validated and proved by several scientific observations. It has antioxidant[31], anti-bacterial[32], anti-fungal[33], anti-viral[34], anti-diabetic[35], hypolipidemic[36], anti-malerial[37], anti-aging[38], learning and memory improvement[39], anti-

ulcer[40], anti-migraine[41], antihypertensive[42], anti-depressant[43], anti-allergic[44], anthelmintic[45], aphrodisiac[46], hepatoprotective[47], cytoprotective[48], anti-tumour[49], anti-HIV[50], anti-AIDS[51], etc. World Health Organization (2009) has listed out nearly 25 different medicinal properties of arecanut[52]. It was also reported that all the seven alkaloids present in arecanut possess drug like properties[21].

Inflammation and pain are two common experiences of patients with all types of wounds. Unless treated properly, these activities may delay the wound healing process. The wound healing potentials of plants are mainly due to their antioxidant, anti-inflammatory and antimicrobial activities of phytochemicals present in them[7,53]. Arecanut is also a reservoir of such phyto-chemicals[17] and hence could be used successfully in the management of wounds. In this paper an attempt has been made to compile most of the works carried out on the analgesic, anti-inflammatory and wound healing properties of arecanut.

Analgesic / antinociceptive activity of arecanut

The analgesic property of arecanut is now very well established. Among different fractions of arecanut extract, it was reported that the aqueous fraction was more potent than the crude extract, its hexane and ethyl acetate fractions in its analgesic activity[54]. It was also noticed that the aqueous fraction of arecanut extract was more potent than that of the aspirin in reducing pain. The percentage of inhibition of acetic acid induced abdominal writhings in BALB/c mice treated with crude arecanut extract and its aqueous fraction at a dose of 100mg/kg body weight during the first 30 min of treatment was 65.2 and 80.1%, respectively over control, whereas with the same dose of aspirin the inhibition was only 49.3% during that period. The analgesic activity of arecanut extract might be due to the inhibition of prostaglandin synthesis[54].

The analgesic activity of the methanolic extract of the nuts of arecanut was also evaluated in Swiss mice. At feeding doses of 500 and 1000mg/kg bw such methanolic extract of arecanut reduced the pain induced by intraperitoneal injection of acetic acid to the abdomen of Swiss mice by 35.77 and 58.81%, respectively[55]. The standard drug 'indomethacin', though gave better result (70.3% reduction) it was given by injection and not by oral feeding as did with arecanut extract. The hydroalcoholic extract of these nuts also showed analgesic activity in mice[56].

The antinociceptive activity of the water extract of arecanut were also studied on Wistar albino rats by oral feeding at two doses of 200 and 400mg/kg bw and compared with that of the conventional drug, diclofenac[57]. It was found that the writhing reflex was significantly reduced in both the doses when compared to that of the control, but not as efficient as that observed with diclofenac. In the first 15 minutes of treatment, the reduction in the number of writhing movements at a dose of 400mg of arecanut extract was 59.0%, whereas in the diclofenac treated groups it was 79.6%.

The stem and leaves of areca palm are also reported to have analgesic property. The antinociceptive activity of the methanol extract (200 and 400mg/kg bw) of both stem and leaves of *A. catechu* was studied on Swiss albino mice in laboratory and found that areca stem extract was found at par with that of aspirin in reducing pain[58]. Aspirin at 200 and 400mg/kg bw reduced the writhing pain by 42.3 and 55.8%, respectively, whereas the figures for the same dose of areca stem extract were 40.9 and 59.6%, respectively. One interesting observation was that the areca leaf extract was found much better than asperin in reducing pain. The pain reduction with areca leaf extract at 200 and 400mg/kg bw was 86.5 and 88.5%, respectively, much higher than that of aspirin. The leaf extract at a dose of 50mg/kg bw was found to be as efficient as that of aspirin at 400mg/kg bw.

Anti-inflammatory activity of arecanut

The arecanut extract could also be used as anti-inflammatory drug. Similar to analgesic activity, the aqueous fraction of this nut was found more potent than its crude extraction, its hexane and ethyl acetate fractions in reducing edema[54]. It was also reported that the aqueous fraction of arecanut extract was more potent than that of the aspirin in its anti-inflammatory activity. At a dose of 100mg/kg bw, the edema inhibition percentage with crude arecanut extract and its aqueous fraction in Sprague Dawley rats after two hours of treatment was 59.5 and 80.2%, respectively. At the same dose, aspirin gave only 47.2% reduction in the inflammation. This shows that the aqueous fraction of arecanut could be better utilized as an anti-inflammatory drug.

The methanolic extract of the nuts of arecanut was also reported to be anti-inflammatory in action. It was found that at two feeding doses, 500 and 1000mg/kg bw, the methanolic extract of arecanut inhibited 14.49 and 27.75% inflammation in treated Wister albino rats. On the other hand, the standard drug diclofenac sodium when given subcutaneously, inhibited inflammation by 35.75% during that period [55]. However, these results could not be compared as the former was given orally whereas the latter was administered by injection. The ethanolic extract of the nuts of arecanut was also reported to be anti-inflammatory in action [59]. The hydroalcoholic extract of these nuts also considerably reduced paw edema in rats in dose dependent manner compared to carrageen-induced inflammation[56].

The water extract of the nuts of arecanut was orally fed to paw edema induced Wistar albino rats at two doses, 200 and 400mg/kg bw, and the anti-inflammatory activity was compared with that of the conventional drug indomethacin at10mg/kg, i.p.[57]. It was found that in all the treatments, the volume of paw edema was significantly reduced than that of the control after 60 minutes of treatments. In the control group, the volume of paw edema was 0.85, whereas in those treated with 200 and 400mg of arecanut extract, the volume of edema was only 0.55 and 0.53, respectively and in indomethacin treated group it was 0.51. The aqueous extract of *A. catechu* was also reported to exhibit anti-inflammatory action[60]. It was reported that in arecanut the procyanidines are the active compounds responsible for anti-inflammatory activity[61].

Not only the nuts of arecanut palm but also its leaves are reported to be of anti-inflammatory in action.

Paw edema volume induced by carrageenan injections on Sprague Dawley rats was found to decrease significantly by oral feeding of rats with the ethanol extract of the leaf of areca palm at a dose of 10mg/kg[62]. At this dose the increase of paw edema was only 27.3% when compared to control.

Wound healing property of arecanut

Wounds, if not treated well in time, generally welcome several microbes to gain access to internal tissues and cause infection and such complications prolong the healing process. Microbial agents are mainly bacterial, viral or fungal origin. Among them, bacteria are more common and they include species such as *Streptococcus, Staphylococcus, Pseudomonas, Bacillus, Klebsiella, Proteus* and *Escherichia coli*[63]. Hence, disinfection of wound is the primary requirement for its successful management. In this connection the herbs which possess antimicrobial properties will be of great help in hastening wound healing process by keeping the wounds sterile. Several polyherbal gels developed from different medicinal plants have been reported to possess antimicrobial and wound healing properties[53,64,65]. Arecanut is one of the herbal folk medicines to treat the problems caused by *Helicobacter pylori*, the common bacteria responsible for gastric and duodenal ulcers in Taiwan[66]. The polyphenol of arecanut is reported to inhibit the growth of several pathogenic bacteria such as, *E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, Vibrio cholerae and Salmonella typhi*[67]. The aqueous extract of arecanut was also reported to be antibacterial against certain other species of pathogenic bacteria such as *Streptococcus mutans, S. salivarius, Fusobacterium nucleatum*[68], and the water extract against *Enterococcus faecalis*[69].

Certain tribal people in south India including Maharastra State use arecanut to cure burn wounds since many years[2,4,6,70]. Enough scientific data are now available to confirm the curative property of arecanut on such wounds. The wound healing properties of the crude extract of arecanut and its two constituents namely arecoline and polyphenols were studied in Wistar albino rats on three wound models like excision, incision and dead space wound[71]. It was found that except arecoline, both polyphenol and crude extract promoted wound healing by increasing wound breaking strength, percent wound contraction and hydroxyproline level in the granulation tissue[71]. However, in another study it was found that in arecanut the arecoline alkaloid, polyphenol and their combined formulation enhanced the breaking strength in the incision wound model of Wistar albino rats[72]. All the extracts increased the wound contraction on the 4th and 16th day. They also suggested that the alkaloid and polyphenols of arecanut could be used to enhance the healing rate of burn wounds, leg ulcers and skin graft surgery. As the above two reports not consistent in their results on the role of arecoline on wound healing, some more studies are warranted to confirm the actual role of arecoline in wound healing property.

The ointment prepared with 2% ethanolic extract of the nuts of areca palm was found to be equally efficient to that of the standard drug, silver sulfadiazine at 1% concentration. When the ointment of such arecanut extract was applied topically on burn wounds of Wistar albino rats complete epithelialization of the wounds occurred on the 16th day, whereas silver sulfadiazine also took almost similar period (15.67 days) to get complete epithelialization. The control group took much longer period (24.33 days) to reach that condition. Further, it was also observed that the arecanut extract hastened the healing process when it was delayed by the application of wound healing suppressor like dexamethasone. In dexamethasone treated group, the rats took 28.33 days to get complete epithelialization, whereas it took only 19.33 days when arecanut ointment was applied to such group.[73]

. Almost similar results were obtained by oral feeding of the ethanolic extract of the nuts of *A. catechu* at a dose of 100mg and 300mg/kg bw[74]. The results showed that the wound contraction rate was significantly increased in arecanut extract fed groups compared to that of the control group from day 5 onwards and was comparable with that of the standard drug, silver sulfadiazine treated group. The period of epithelialization was also significantly faster in arecanut treated group (16 days in 100mg and 17 days in 300mg) when compared to that of the control (23 days) and comparable with that of the standard drug (16 days). In dexamethasone delayed burn wound models also, wound contraction rate was significantly increased in arecanut extract treated group when compared to that of the control. In dexamethasone treated group the period of epithelialisation was 28 days whereas in dexamethasone + arecanut extract treated group it was reduced to 20 days.

CONCLUSION

Arecanut palm is a reservoir of many beneficial phytochemicals. The analgesic, anti-inflammatory and wound healing properties of this palm are well documented. The studies have shown that almost all parts of this plant including its nuts, leaves, roots and stem exhibit these properties. The aqueous extract of the nuts was found more effective than several other extracts and even better than aspirin in reducing pain. The ethanolic extract of the nuts was found equally effective to that of silver sulfadiazine in curing wounds. Hence, the actual chemical compound responsible for such actions may be identified for further use in pharmaceutical and medical fields as this plant is grown abundantly and available in plenty in several parts of south and south east Asian countries.

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