

Areca catechu: A phytopharmacological legwork

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Abstract

Areca catechu, commonly known as supari, consists of dried ripe nuts that came under Arecaceae family, which is cultivated in the tropical region of India and Southeast Asia. It is a prevalent traditional herbal medicine that is chewed to separate collected fluid in the alimentary canal and for killing worms. *Areca catechu* seed contains alkaloids (arecoline, arecaine, arecaidine, guvacoline, guvacine, and choline), tannin, gallic acid, gum, and various minerals such as copper, calcium, phosphorus, and iron. The chemical constituents of this plant have been used as antidiabetic, stomatitis, bleeding gums, gingivitis, conjunctivitis, glaucoma, leucorrhoea, urinary disorders, anorexia, diarrhea, blood pressure regulating activity, antiulcerogenic, antioxidant activity, anticonvulsant activity, central nervous system stimulant activity, antifertility, oxytocic activity, antiviral activity, anthelmintic, and foul breath. It showed a dose-dependent toxicity profile, and various research has been done regarding its safety analysis and it would be considered safe when administered in the prescribed dose. The purpose of the present paper is to make available an up-to-date review on the ethnic, traditional description, morphology, phytochemistry, and the pharmacological and toxicological profile of this plant. Furthermore, the possible advances, trends, and a perspective for forthcoming research of this plant have also conversed.

KEYWORDS

Analgesic, antibacterial, *Areca catechu*, pharmacology, phytochemistry, phytoconstituent

1 | BACKGROUND

Nature has been a foundation of medicinal and herbal products since ages, with many valuable drug formulations from plant sources. *Areca catechu* is rich in various chemical constituents, among which tannin content is maximum and is used in daily life in the South Asian subcontinent. It traces and outlines the various morphological, geographical,

phytochemical, pharmacological, and toxicity profile of *A. catechu*. The aim of this review was to provide a summarized data regarding various aspects of this plant and its various parts, which can be beneficial for providing preliminary data for future research and also promotes the further development of various formulations that contain the areca constituent in different dosage forms.

Abbreviations: ACE, Angiotensin-converting enzyme; BuOH, Butanol; ERK1/2, Extracellular signal-regulated kinase 1/2; MAO, Monoamine oxidase; p.o., per oral; ROS, Reactive oxygen species; SD, Sprague Dawley; SHR, Spontaneous hypertensive rats

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2 | INTRODUCTION

Herbs are natural origin products. Depending on several factors, their chemical composition varies throughout the globe, from active decoctions to the use of natural herbal extracts following Western practices of mainstream medicine. These products turn out to be one of the most significant resources for evolving new lead compounds and frameworks for drug development. Natural products are experiencing an unusual demand, meeting the imperative need to develop novel effective drugs, and are playing an important role in the discovery of drugs to cure various human diseases (Yuan et al., 2016).

Traditional medicines have been used since ages. They are used not because of their therapeutic outcome, but because of the combination of belief, rituals, and experience of times and culture (Firenzuoli & Gori, 2007). The development of novel drugs depends purely on recent technologies appearing to accomplish something quite challenging in modern drug delivery system. In discovering new drugs, the first choice of the pharmaceutical industry is the selection of new lead compounds based on synthesis and combinatorial chemistry; however, the substantial efforts made during this have not resulted in the projected drug productivity (Ahsan et al., 2018). Some prominent pharmaceutical firms are facing prodigious challenges to develop novel products. Over the past several years, growing attention has consequently been paid to molecules of natural origin during the search for new drugs in amalgamation with new technology. Among natural-origin lead compounds, the herbal-origin plants and their constituents are the first choice as they are easily available in large quantity (Ngo et al., 2013).

Areca catechu, commonly known as supari, consists of dried ripe nuts that come under the family Palmae or Arecaceae, which is cultivated in the tropical region of India, Malaysia, Sri Lanka, East Indies, Philippines Islands, South China, and part of East Africa (Rashid et al., 2015). Chewing the areca nut with betel leaves (betel quid) is a traditional habit in India and in many Asian countries (Ling et al., 2001). It is predicted that around 400 million people generally chew betel quid (which chiefly consists areca nut, lime, and the betel leaf) daily (Gilani et al., 2004; Lim & Kim, 2006). The palm or areca tree reaches up to a maximum height of 10–20 m (33–66 ft). Although it is adapted to grow in a variety of different soil types, proper drainage facility and high moisture holding capacity is required for normal growth of areca plants. The kernel yield is estimated at 2.5–8 kg per palm annually (Staples & Bevacqua, 2006).

Areca nut (seed) contains gum, gallic acid, tannin, alkaloids (namely, arecaine, arecoline, arecaidine, guvacine, guvacoline, and choline), and several minerals such as copper, calcium, phosphorus, and iron. *Areca catechu* is the only one of 54 different *Areca* species identified to contain alkaloids (Buckingham et al., 1989). The Arecaine is the chief constituent of the Areca nut (Nadkarni, 1976). Indians have fewer dental caries when compared with the Western population because of the fact that areca nut is widely chewed in the Indian subcontinent, which has been recognized to decreasing dental caries probably by inhibiting Gram-positive microorganisms that are accountable for dental caries (Gupta & Ray, 2004; Hung et al., 2002).

The chief constituent of *A. catechu* is tannins. Tannins (also termed as tannic acid) are water-soluble polyphenols that are found abundantly in many plant foods. These compounds are responsible for reductions in feed intake, feed efficiency, growth rate, net metabolic energy, and protein metabolism in experimental animals. Consequently, foods rich in tannins are thought to be of low nutritional value. Tannins containing food components act by inhibiting enzymes such as hyaluronidase and 5-lipoxygenase, which constitute the action as anti-inflammatories, keratolytic agents, and antimicrobials (Chung et al., 1998). Tannins do not function exclusively as primary antioxidants (i.e., they donate electrons or hydrogen atom), but they also function as secondary antioxidants. They tend to chelate the metal ions, Fe (II), and interfere with one of the reaction stages in the Fenton reaction; this action retards the oxidation (Karamac, 2009). The other mechanism that is postulated states that tannins inhibit lipid peroxidation, thus activating the inhibition of cyclooxygenase. These therapeutic properties are assumed to be ascribed to the ability of tannins to show properties of free radical scavengers by activating antioxidant enzymes (Zhang et al., 2004).

Areca catechu has numerous pharmacological actions including effects on digestion, antiparasitic effects, antioxidant effects, nervous and cardiovascular systems, anti-inflammatory and analgesic effects, antibacterial and antifungal effects, regulatory effects on lipids and blood glucose, anti-allergic effects, as well as effects on other diseases (Liu et al., 2013). Traditionally, *A. catechu* has frequently been utilized to promote digestion and kill parasites; the seed is the foremost part of *A. catechu* used as medicine (Jung, 2016).

3 | PLANT MORPHOLOGY

3.1 | Vernacular names

Vernacular names of this plant in different languages are as follows: English—Areca nut, Betel nut; Sanskrit—Pugah; Hindi—Supari; Bengali—Supari; Malayalam—Kamuku, Adackamaram; and Tamil—Pukkumamaram (Joy et al., 1998).

3.2 | Scientific classification

Scientific classification of this plant is as follows: kingdom, Plantae; order, Arecales; family, Arecaceae; genus, *Areca*; and species, *Areca catechu* L (Senthil Amudhan et al., 2012).

3.3 | Characteristics

3.3.1 | Height

The palm climbs or reaches up to a maximum height of 10–20 m (33–66 ft).

3.3.2 | Flowers

Flowers are unisexual, with both male (staminate) and female (pistillate) flowers borne in the same inflorescence. Few female flowers are borne at the base of each terminal branch and several male flowers spreading from there out to the tip of the branch. Flowers of both sexual characteristics have six petals; female flowers are bigger in size (1.2–2 cm [0.5–0.8 in] long), along with six minor sterile stamens and ovary having three cells carrying a triangular stigma along with three different points at the apex.

3.3.3 | Fruit

A fibrous, ovoid drupe, 5–10 × 3–5 cm (2–4 × 1.2–2 in), ranges from yellow to orange or changes to red when ripe. Seeds are generally ovoid, ellipsoidal, or globose (3–4 × 2–4 cm [1.2–1.6 × 0.8–1.6 in]); the flattened base is observed sometimes; ruminant endosperm is seen (along with rigid reddish tissue from internal integument spreading horizontally into pale brown colored endosperm); embryo are conical in shape and located at seed base (Staples & Bevacqua, 2006).

3.3.4 | Leaves

Eight to 12 leaves are present as fascicles at the top of the stems. The leaves are 1.3- to 2.7-m long (together with petiole) and are light green to green in color; the blades are multitudinous, lanceolate, and both surfaces of leaves are glabrous having a length of 30–60 cm and total widths of 2.5–4 cm. The superior blades are connate in shape with an uneven tooth-like crack found at the apex (Heatubun et al., 2012).

3.4 | Distribution

3.4.1 | Worldwide

Betel nut or Areca nut is recognized scientifically as *A. catechu*, which is a relative of the fruit coconut (*Cocos nucifera*) (Artero & Santos, 1914). *Areca catechu* is a slender, single-trunked palm that can grow up to 30 m. It is cultivated from the Arabian Peninsula and East Africa across Indonesia and tropical Asia to the New Guinea and Central Pacific.

Betel nut is a cultigen that exists only where humans grow it. The theory behind its origin states that it was first grown in the Philippines. Many other areas have been suggested as the original homeland, including South or Southeast Asia (Staples & Bevacqua, 2006).

3.4.2 | India

Today, the betel nut is grown in India, Bangladesh, Sri Lanka, Myanmar, East Africa, Arabian Peninsula, Madagascar, Thailand, Taiwan Cambo-

dia, Laos, Vietnam, Southern China, Malaysia, Indonesia, and the Philippines.

3.5 | Habitat

Betel nut requires tropical ever-wet climates with evenly distributed rainfall of 1500–5000 mm (60–200 in), and it prefers elevations of 0–900 m (0–2950 ft).

Although it is adapted to an extensive range of soil types, drainage and high moisture holding capacity are required. The growth rate is moderate, about 0.5 m/year (20 in/year) (Staples & Bevacqua, 2006). The palm tree and nuts of *A. catechu* have been shown in Figure 1.

4 | PHYTOCHEMISTRY

Areca nut comprises key biochemical complexes like fat (15%), polyphenol (20%), alkaloids (0.5%), and starch (20%). More than 59 different constituents have been identified and isolated from this plant (Shivashankar & Govindarajan, 1963).

4.1 | Polyphenols

The polyphenols, typically flavanols, comprise about 12% of (+)-leucocyanidin, 2.5% epicatechin, and 10% of (+)-catechin, and the remaining fraction comprises complex flavonoids in erratic degrees of polymerization (Mathew & Govindarajan, 1963). A diverse series of tetrameric, trimeric, and dimeric procyanidins have been separated from the seeds of *A. catechu* (Nonaka et al., 1981).

4.2 | Flavonoids

Flavonoids are common constituents of numerous plants worldwide. The flavonoids isolated from *A. catechu* include isorhamnetin, chrysoeriol, luteolin, quercetin, 4',5'-dihydroxy-3',5',7'-trimethoxyflavone, 5,7,4'-trihydroxy-3',5'-dimethoxyflavanone, liquiritigenin, and jacareubin (Yang et al., 2012; Zhang et al., 2009).

4.3 | Alkaloid

Alkaloids hold prominent biological actions and are thought to be the principal active constituents in plant-derived medications (Amirkia & Heinrich, 2014). *Areca catechu* is the only herbal-origin plant comprising alkaloids of the family Arecaceae (Qi et al., 2006). The four most important alkaloids that have been isolated from the areca nut are arecaidine (1.5 mg/g weight), arecoline (7.5 mg/g weight), guvacine (2.9 mg/g weight), and guvacoline (2.0 mg/g weight) (Chu, 2001). All these isolated alkaloids are related chemically; among them, arecoline is volatile and colorless in nature resembling chemical nicotine.



a



b

FIGURE 1 (a) The figure showing images of palm tree of *Areca catechu* and (b) the fruits of *Areca catechu*

4.4 | Fat

Areca nut consists of numerous fatty acids consisting of 46.2% myristic acid, 19.5% lauric acid, 1.6% stearic acid, 12.7% palmitic acid, 6.2% oleic acid, 0.3% decanoic acid, 5.4% dodecenoic acid, 7.2% hexadecenoic acid, and 0.3% tetradecenoic acid (Pathak & Mathur, 1954).

4.5 | Tannins

Tannins are one more distinctive constituent of *A. catechu*, and the foremost types that are found in areca are condensed tannins also termed as proanthocyanidins (Ma et al., 2014). The important types of tannins in *A. catechu* are the catechins and epicatechin. The specific tannin compounds of *A. catechu* include procyanidin B1, procyanidin A1, procyanidin B2, areca tannin B1, areca tannin A1, areca tannin A2, areca tannin C1, areca tannin B2, and areca tannin A3 (Nonaka et al., 1981; Peng et al., 2015).

4.6 | Mineral content

The mineral matter includes calcium (0.05%), phosphorus (0.13%), and iron (1.5 mg/100 g). It also contains vitamin C (416.2 mg) and vitamin B6 (286.9 mg) (Raghavan & Baruah, 1958). The list of chemical constituents found in part of the plant along with their structure has been mentioned in Table 1.

5 | PHARMACOLOGICAL ACTIVITIES

Areca catechu has a long history as a medicinal plant worldwide, based on its wide spectrum of biological and pharmacological activities. Tra-

ditionally, it has been utilized to destroy parasites and also used in the treatment of dysentery, abdominal distension, constipation, and promote digestion (Jung, 2016). Areca nut demonstrates significant analgesic and anti-inflammatory, wound healing antidepressant, and anti-HIV activities (Nur Sazwi et al., 2013).

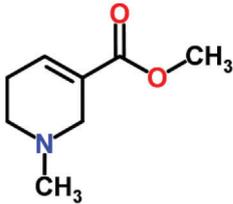
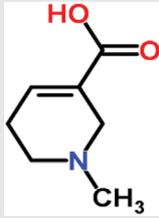
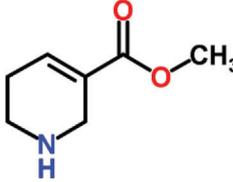
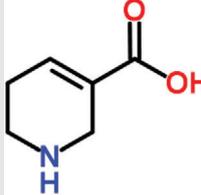
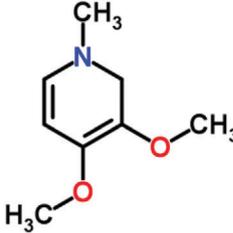
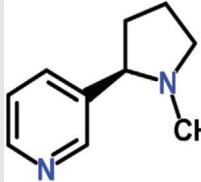
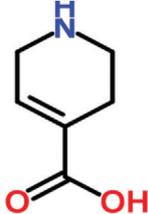
5.1 | Antioxidant

The methanol extract of *A. catechu* showed higher antioxidant actions than the other form of extract (Wetwitayaklung et al., 2006). Ethanol extract of *A. catechu* showed potent antioxidative, free radical foraging, and antihyaluronidase activity. The antioxidant properties of the extract was quite lower than butylated hydroxytoluene when compared it was similar to tocopherol and was higher than ascorbic acid (Kim et al., 1997). Also, some compounds isolated from the areca nut have been reported to possess notable DPPH radical-scavenging activities (Zhang et al., 2010). *Areca catechu* showed stronger antioxidant activity than *Salvia miltiorrhiza* and *Ulmus davidiana*, with IC_{50} of 20 and 6.0 μ g/ml, respectively (Ahn, 2009).

5.2 | Hypoglycemic activity

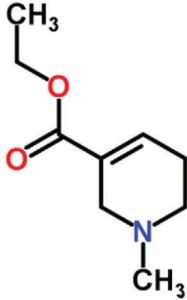
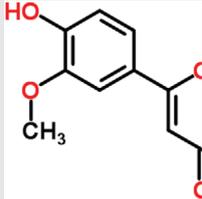
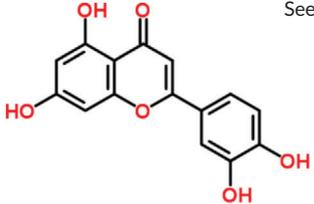
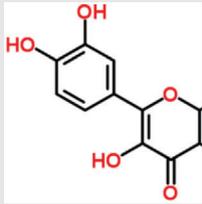
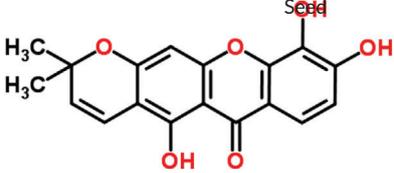
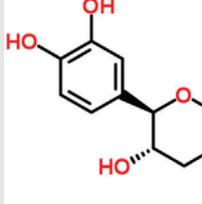
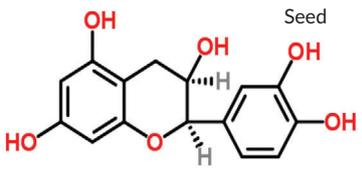
Arecoline was examined and reported to possess hypoglycemic activity in a different animal models of diabetes when administered subcutaneously. The administration of the subcutaneous alkaloid portion of *A. catechu* into alloxanized rabbits exhibited a significant hypoglycemic result that lasted for 4–6 h (Chempakam, 1993). Areca nut extract inhibited blood glucose elevation by inhibiting glucosidase activity; α -glucosidase inhibitors are used worldwide for the treatment of diabetes lowering postprandial hyperglycemia (Senthil & Begum, 2008).

TABLE 1 Chemical structures of phytoconstituents of *Areca catechu*

S. No.	Name	Formula	Structure	Part of the plant
1.	Arecoline	$C_8H_{13}NO_2$		Seed
2.	Arecaidine	$C_7H_{11}NO_2$		Seed
3.	Guvacoline	$C_7H_{11}NO_2$		Seed
4.	Guvacine	$C_6H_9NO_2$		Seed
5.	Arecolidine	$C_8H_{13}NO_2$		Seed
6.	Nicotine	$C_{10}H_{14}N_2$		Seed
7.	Isoguvacine	$C_6H_9NO_2$		Seed

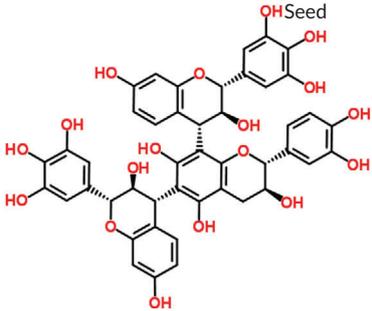
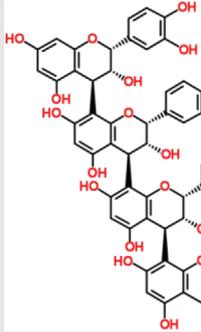
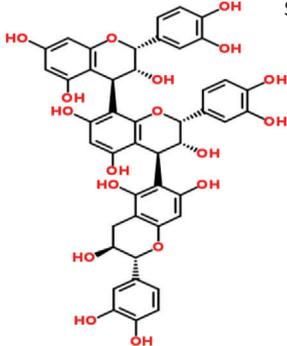
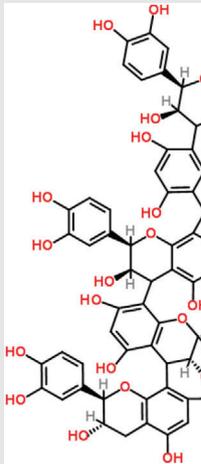
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TABLE 1 (Continued)

S. No.	Name	Formula	Structure	Part of the plant
8.	Homoareco-line	$C_9H_{15}NO_2$		Seed
9.	Chrysoeriol	$C_{16}H_{12}O_6$		Seed
10.	Luteolin	$C_{15}H_{10}O_6$		Seed
11.	Quercetin	$C_{15}H_{10}O_7$		Seed
12.	Jacareubin	$C_{18}H_{14}O_6$		Seed
13.	Catechin	$C_{15}H_{14}O_6$		Seed
14.	Epicatechin	$C_{15}H_{14}O_6$		Seed

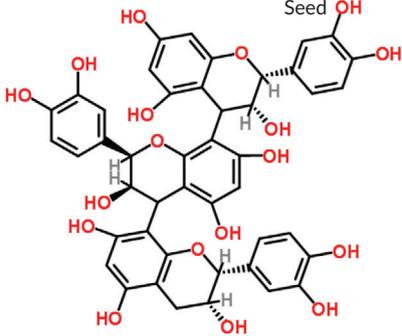
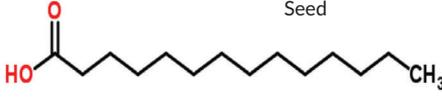
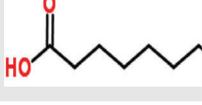
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TABLE 1 (Continued)

S. No.	Name	Formula	Structure	Part of the plant
15.	Arecatannin A1	$C_{45}H_{38}O_{18}$		Seed
16.	Arecatannin A2	$C_{60}H_{50}O_{24}$		Seed
17.	Arecatannin B1	$C_{45}H_{38}O_{18}$		Seed
18.	Arecatannin B2	$C_{75}H_{62}O_{30}$		Seed

(Continues)

TABLE 1 (Continued)

S. No.	Name	Formula	Structure	Part of the plant
19.	Arecatannin C1	$C_{45}H_{38}O_{18}$		Seed
20.	Lauric acid	$C_{12}H_{24}O_2$		Seed
21.	Myristic acid	$C_{14}H_{28}O_2$		Seed
22.	Palmitic acid	$C_{16}H_{32}O_2$		Seed
23.	Stearic acid	$C_{18}H_{36}O_2$		Seed

5.3 | Antihypertensive

The subfraction of the areca nut that contains plentiful tannins displayed a potent antihypertensive activity at a dose of 100 and 200 mg/kg (peroral [p.o.]) in instinctively hypertensive rats via angiotensin-converting enzyme (ACE) inhibition. Areca tannin has been proposed as possessing the blood pressure controlling effect through its capability to constrain the pressor response to the hormone angiotensin I and II (Chung et al., 2007). The extreme antihypertensive effect of a fraction of areca nut at a dose of 15 mg/kg intravenous was about five times as huge as that of captopril at the same dose (Inokuchi et al., 1986).

Areca II-5-C, a constituent isolated from seeds of *A. catechu* L., displayed the most effective ACE inhibitory action in vitro (Chung et al., 2007). The antihypertensive activity of *A. catechu* was therefore investigated in spontaneous hypertensive rats (SHR). At a dose of 15 mg/kg, the extreme antihypertensive effect of areca II-5-C in SHR was demonstrated when administered via intravenous route (Inokuchi et al., 1986).

5.4 | Aphrodisiac activity

The oral administration of the extract of *A. catechu* L. and *Pedaliom murex* L. at a dose of 150 mg/kg body weight displayed a significant rise

of sexual activity in male rats. *Areca catechu* group showed a significant increase in sperm count as compared to the control group. There was a continued increase in the sexual activity of normal male rats without showing any noticeable adverse effects signifying that *A. catechu* has aphrodisiac potential (Anthikat et al., 2013).

5.5 | Antidepressant

The ethanolic extract of *A. catechu* at a dose of 40–80 mg/kg instigated a significant decrease in the immobility time interval without distressing spontaneous motor activity. This result proposes that the ethanol extract of areca nut holds antidepressant activities (Kuo et al., 2005).

The aqueous ethanolic extract of *A. catechu* and aqueous fractions constrain monoamine oxidase (MAO) in homogenates of rat brain. The aqueous portion appears to be the most effective inhibitor of MAO and its response is quite similar to that of clorgyline (MAO inhibitor) (Dar et al., 1997).

5.6 | Antifungal activity

The Areca nut extract does not constrain the growth of mycelial fungal forms, for example, *Aspergillus niger*, *Mucor* sp., and *Cladosporium*

TABLE 2 The effect of areca nut extract on *Candida albicans*

Conc. + strain	Percentage inhibition					
	1 h	2 h	3 h	4 h	5 h	6 h
10 μg + <i>C. albicans</i>	0	0	0	0	0	0
20 μg + <i>C. albicans</i>	0	0	0	0	0	0
50 μg + <i>C. albicans</i>	100	100	100	100	100	100
100 μg + <i>C. albicans</i>	100	100	100	100	100	100

Note: Concentration is articulated as per 3 ml of medium.

TABLE 3 Effect of extract obtained from areca nut on gram-positive and gram-negative bacteria

Strains	Percentage inhibition			
	10 μg	20 μg	50 μg	100 μg
A. Gram negativeVeterinary isolates				
<i>E. coli</i>	0	50	100	100
<i>Klebsiella pneumonia</i>	80	100	100	100
<i>Salmonella typhimurium</i>	57	100	100	100
Human isolates				
<i>Pseudomonas</i>	36	100	100	100
<i>E. coli</i>	100	100	100	100
<i>Proteus</i>	100	100	100	100
<i>Klebsiella</i>	0	100	100	100
B. Gram positiveHuman isolates				
<i>Streptococcus viridans</i> (1603)	11	11	100	100
<i>Streptococcus mutans</i> MTCC 497	0	74	100	100

Note: Concentration is depicted as per 3 ml of medium.

sp., but the growth of single-cell fungus such as *Candida albicans* was reserved by utilizing the tube method, and the concentration desirable for 100% inhibition was obtained to be 16.67 $\mu\text{g}/\text{ml}$ (Anthikat et al., 2014). The effect of areca nut on *Candida albicans* has been mentioned in Table 2. The Areca nut extract was also analyzed for its inhibitory action against aflatoxin production of *Aspergillus flavus*. Areca nut extract was revealed to constrain aflatoxin production by *Aspergillus flavus* (Anthikat & Michael, 2009). Additionally, some complexes isolated from the pericarps of *A. catechu* were responsible to show notable antifungal action against *Colletotrichum gloeosporioides* (Yenjit et al., 2010).

5.7 | Antibacterial activity

A study reported that the different types of veterinary and human isolates, both Gram negative and Gram positive, were tested against *A. catechu* extract by determining the evolution of the organisms utilizing the spectrophotometric method. It was obtained that both Gram-

negative and Gram-positive microorganisms were vulnerable to the *A. catechu* extract. The detail has been depicted in Table 3. The concentration required for 100% inhibition of the development of Gram-negative bacteria was depicted to be 3.3–7 $\mu\text{g}/\text{ml}$ and for Gram-positive bacteria it was 16 $\mu\text{g}/\text{ml}$ (Anthikat & Michael, 2009). Different concentrations of *A. catechu* ethanol extract showed antimicrobial activity against 0.5 McFarland of mixed oral flora and clinical isolates of eight Gram-negative (*Escherichia coli*, *P. vulgaris*, *K. pneumonia*, *S. non-typhi*, *P. aeruginosa*, *S. typhi*, *V. cholera*, and *S. flexneri*) (Chin et al., 2013). *Areca catechu* extracts inhibit the development and growth of the organism found in saliva; they were cultured after chewing boiled areca nut from the saliva, such as *Streptococcus salivarius*, *Streptococcus mutans*, *Fusobacterium nucleatum*, and *Staphylococcus aureus* (De Miranda et al., 1996).

5.8 | Antimalarial

A study performed the antimalarial survival test in mice, which showed a 60% survival rate with *A. catechu* and butanol (BuOH)-treated group.

In this study, *A. catechu* and BuOH were investigated for antimalarial activity in vivo and in vitro and they showed potent antimalarial activity. In vivo, 4 days' suppressive and survival test showed a 39.1% inhibition effect after treating with 150 mg/kg/day on *Plasmodium berghei*-infected mice (Jiang et al., 2009).

5.9 | Anti-HIV activity

Numerous active constituents such as Areca tannin B1, procyanidins, and different extracts of the areca nut seed displayed HIV protease inhibition action (Marastoni et al., 2004).

5.10 | Anti-allergic

A study reported that the areca extract is a forceful inhibitor of 2,4-dinitrophenyl group-bovine serum albumin, and compound 48/80 tempted degranulation in RBL-2H3 mast cells and also induced systemic anaphylaxis 46% in mice with IC₅₀ values of 52 and 53 mg/ml, respectively (Lee et al., 2004).

Areca catechu also suppresses the expression of TNF- α and the stimulation of mitogen initiated extracellular signal-regulated kinase $\frac{1}{2}$ (ERK1/2), protein kinase that is perilous for the generation of inflammatory cytokines in mast cells, as specified by the repression of the activating phosphorylation of ERK1/2. These outcomes recommend that *A. catechu* may be beneficial for the treatment of several delayed and immediate allergic diseases (Rashid et al., 2015).

5.11 | Anti-inflammatory

The ethanolic extract of *A. catechu* at a dose of (1 and 10 mg/kg/day p.o.) for 5 days induced suppression of carrageenan-induced inflammatory edema and prostaglandin E2 levels. In addition, the ethanolic extract of *A. catechu* at a dose of 250, 500, and 1000 mg/kg p.o. produced dose-dependent and significant anti-inflammatory and analgesic activities (Bhandare et al., 2010). The ethanolic extract of *A. catechu* was described to be efficacious against nitroglycerin-induced delayed inflammatory responses in rats (Bhandare et al., 2011).

5.12 | Antinociceptive effect

The methanolic extract of the stem of *A. catechu* showed an antinociceptive effect at different doses by reducing the total number of constrictions. The stem extract restricted the writhing or constrictions by 30.8%, 36.6%, 40.9%, and 59.6%.

The methanolic extract of *A. catechu* leaves displayed an even more inhibition in the total number of writhing or constrictions when assessed at doses of 50, 100, 200, and 400 mg/kg of the body weight. The percent of inhibitions was dose dependent and significant. The above-mentioned four different doses of the leaf extract inhibited the

writhing or constrictions by 55.8%, 57.7%, 86.5%, and 88.5%, respectively (Rani Barman et al., 2011).

5.13 | Analgesic activity

5.13.1 | Hot plate test

Hydroalcoholic extract of *A. catechu* produced significant ($p < 0.01$) analgesic activity at the dose of (250, 500, and 1000 mg/kg orally) when compared to that of the control group. The dose of 1000 mg/kg of the extract of *A. catechu* displayed maximum antinociception (54.46%) for 1 h, which was steadily decreased at 90 min. The protection offered by *A. catechu* extract was found to be 41.86% after administration at a dose 500 mg/kg, which was practically analogous to that of pentazocine showing 43.15% (Bhandare et al., 2010).

5.13.2 | Formalin-induced pain in mice

Areca catechu extract decreased the paw edema significantly (after 24 h, 86.79% inhibition, $p < 0.01$) in dose-dependent manner when compared to carrageenan-induced rat. The analgesic effect of aspirin, pentazocine, and *A. catechu* extract on the time consumed in licking the paw pad was analyzed during the starting phase (0–5 min) and end phase (20–25 min) of the formalin-induced pain test, and the result showed that *A. catechu* extract significantly ($p < 0.01$) reduced the total time spent by each mouse in licking the hind paw throughout the end phase when compared to early phase. *Areca catechu* extract displayed 92.71% of inhibition at a dose of 500 mg/kg during the end phase (20–25 min) of the formalin-induced licking. *Areca catechu* extract inhibited (39.45%) at a dose of 500 mg/kg during the initial phase (0–5 min) of the formalin-induced licking, but this was found to be less significant ($p < 0.05$). The other two doses of *A. catechu* extract (i.e., 250 and 1000 mg/kg) repressed only the end phase of paw licking due to pain sensation but 500 mg/kg dose inhibited both the phases and displayed a greater effect than other doses. Aspirin showed no effect on the starting phase, but it reduced (88.96%) the pain and paw licking at 300 mg/kg during the end phase. Pentazocine reduced both the starting (45.31%) and end (64.90%) phase of formalin-induced paw licking (Bhandare et al., 2010).

5.14 | Prevention of dental cavities

Indians have less dental caries when compared with the Western population. In reality, areca nut has been recognized to reduce dental caries possibly by inhibiting the Gram-positive microorganisms that are responsible for dental caries (Gupta & Ray, 2004). Laboratory research studies recommended that betel nut probably has antibacterial effects, which is responsible for the development of cavities (Zhang et al., 2009). *Areca catechu* nut is vitally used in the manufacture of dentifrice

because of its astringent properties. The areca extract is considered to provide strength to the gum and remove foul breath. The seeds are converted to charcoal and then it is powdered; this powder forms an excellent dentifrice (Rashid et al., 2015).

5.15 | Burn wound healing

The burn wound healing property of *A. catechu* kernel was evaluated in normal as well as dexamethasone-treated rats. On the burn wound of animals, the ointment prepared from ethanolic extract of *A. catechu* nut is applied. The contraction rate of the wound was significantly augmented in *Areca catechu*-treated group at different doses when compared to normal control. In the drug-treated group, the period of epithelialization was faster when compared to the control group. A significant interruption in wound healing progression in the dexamethasone-treated group was observed when compared to control. Areca extract exhibited a significant reversal in the epithelialization period and wound contraction rate in the dexamethasone-repressed burn wound healing model (Verma et al., 2012).

5.16 | Antimigraine activity

Areca catechu nut extract is a prevalent folk preparation for the cure of migraine in the southern part India. To demonstrate the claimed potential of the plant, a research was carried out by Bhandare et al. Conclusions of the study jointly indicate that the extract showed significant inhibition of inducible nitric oxide synthase, which may be the likely mechanism for its antimigraine action, provided the evidence, at least in part, for its folkloric use (Bhandare et al., 2011).

5.17 | Antiparasitic effects

The areca nut is a traditional remedy usually used to destroy parasites including *Lumbricus*, tapeworms, pinworms, and so forth. In recent pharmacology, the antiparasitic properties of the areca nut have been broadly examined. Earlier investigations stated that the aqueous extract of areca nut can efficiently kill tapeworms, and the mechanism behind it is related to the paralytic result of the aqueous extract of areca nut on the scolex of the tapeworms. Additionally, the antiparasitic properties of the aqueous extract of areca nut in contrast to tapeworms can be improved by combining it with the extract of *Cucurbita moschata*. In the aqueous extract of areca nut, the chief constituent is arecoline and it was supposed to be responsible against tapeworms, and the mechanism was associated with the paralytic effect of areca nut. Also, it was stated that a 1% decoction of the areca nut efficiently kills blood flukes by causing disturbances in their nervous systems (Peng et al., 2015).

5.18 | Immunosuppressant

Arecoline at lower concentration ceased the cell cycle of splenic lymphocyte with encouraged apoptosis at higher concentration in that way causing immunosuppression in betel nut chewing patient (Dasgupta et al., 2006).

5.19 | Effect on gestation

The ethanolic extract of *A. catechu* at two different doses of 100 and 300 mg/kg has abortifacient and antioviulatory effects. Thus, the habit of mastication of betel nut may become a reason of abortion or interrupt normal gestation. The result was supported by analyzing the swab of rodent's vagina that was treated with different doses of areca nut (Shrestha et al., 2010). A summary of the pharmacological activity of *A. catechu* along with its mediator/pathway has been depicted in Table 4.

6 | TOXICOLOGICAL PROFILING

6.1 | Acute oral toxicity

A study regarding acute oral toxicity of *A. catechu* Linn. aqueous extract in Sprague Dawley (SD) rats stated that the LD₅₀ (lethal dose, 50%) was obtained and it was designated to be >15.0 mg/kg body weight. The result indicated a significant increase in body weight ($p < 0.05$). No mortality was detected during the whole acute toxicity, that is, 14 days' study period. No noticeable variations were found in various activity parameters in the areca-treated group when it was compared to the control group (Sari et al., 2014).

6.2 | Acute dermal toxicity

A study regarding acute dermal toxicity of *A. catechu* Linn. extract in SD rats was performed, as per Organisation for Economic Co-operation and Development (OECD) Guidelines 402 designated for acute toxicity protocols. The change in body weight, the possibility of mortality, overall signs, and behavior activity parameters were analyzed for 14 days to establish the LD₅₀ of the areca extract.

After 14 days of observation, the LD₅₀ was obtained to be >15,000 mg/kg body weight. There was a significant increase in body weight ($p < 0.05$) in animals of the treated group when compared to the normal control group. No mortality was detected during the entire 4 days' study period. A unit dose of 15,000 mg/kg of body weight did not produce any dermal treatment-related symptoms of toxicity in any of the treated group animals.

Overall, a unit dermal dose to *A. catechu* L. aqueous extract showed no toxic symptoms related to eczema, inflammation, rashes, and gross discoveries in female rats when administered at a dose of 15,000 mg/kg of body weight (Sari et al., 2016).

TABLE 4 Various pharmacological activities of *Areca catechu*

Pharmacological effects of arecoline				
Pharmacological effects	Experimental detail	Mediators/pathways	Minimal active dose/concentration and route	Reference
Antiparasitic effects	Against <i>Fasciola hepatica</i>	The paralytic effect	-	Chuanlong, Guangyu, & Meijuan, 1990
	Against <i>Cysticercus</i>	The paralytic effect	-	Zhao, Li, & Wang, 2003
	Synergetic effect against <i>Oncomelania</i>	Regulate the contractions of smooth muscle of the feet.	6.25 µg/ml (in vitro)	Feng, Li, Yang, & Gao, 1999; Li, Feng, Yang, & Gao, 2000; Yao, W et al., 2001
	Against tapeworms	The paralytic effect	-	Zheng, 1999
Effects on endocrine system	Stimulating adrenal activity and inhibiting the activity eventually	Suppression of adrenal hormonal	10 mg/kg (intraperitoneal [i.p.])	Dasgupta et al., 2010
	Stimulating production of testosterone	Activating the calcium channels (L-type), augmenting activity of 17-hydroxysteroid dehydrogenase and further enhancing expressions of the steroidogenic acute regulatory	10 mg/kg (i.p.)	Saha et al., 2007; Wang, Hwang, Chen, & Wang, 2008
	Stimulating the hypothalamus-pituitary-adrenal (HPA) axis	Promoting the release of endogenous corticotrophin-hormone releasing hormone	0.2 mg/kg (intravenous)	Calogero et al., 1989
	Stimulating adrenomedullary activities	Obstructing the influx of calcium into the adrenal medullary chromaffin cells	3 mmol/L (in vitro)	Lim & Kim, 2006
	Increasing the immune-reactivity of β-endorphin in plasma	The increase of prolactin's contents in blood plasma	3 mg/person	Risch et al., 1982
Effects on nervous system	Augmentation of the hyperactivity and the expansion of behavioral sensitization persuaded by morphine	Central nervous system cholinergic muscarinic receptor	2.0 mg/kg (i.p.)	Soncrant, Holloway, Greig, & Rapoport, 1989; Han, Sun, Li, & Liang, 2005
	Encouraging excitability of body and improving the capability of learning and memory	Gamma-aminobutyric acid inhibition by arecaidine and arecoline	0.5 mM (intrahepatic)	Johnston, Krogsgaard-Larsen, & Stephanson, 1975
	Reversing loss of memory and impairment during learning in Alzheimer's dementia	Muscarinic receptor through muscarinic 1	469 ± 2.180 µM (in vitro)	Maiese, Holloway, Larson, & Soncrant, 1994; Ono, Minamoto, Shibata, & Watanabe, 1995; Chandra, Malviya, Sadashiva, Subhash, & Rangappa, 2008

(Continues)

TABLE 4 (Continued)

Pharmacological effects of arecoline				
Pharmacological effects	Experimental detail	Mediators/pathways	Minimal active dose/concentration and route	Reference
Causing excitatory effect	–	0.5 mg/mice (i.p.)	Xiao et al., 2013	
Treatment of depression and schizophrenia	–	–	Sullivan, Allen, Otto, Tiobech, & Nero, 2000; Bales et al., 2009	
Improvement of ethanol drunkenness	Through central muscarinic receptor	0.25 mg/kg (i.p.)	Sun, Han, Luo, Chen, & Liang, 2005; Sun et al., 2010	
Effects on digestive system	Promoting activity on smooth muscle contraction	Muscarinic receptor and extracellular Ca ²⁺ influx	1 × 10 ⁻⁶ mol/L (in vitro)	Si, Wei, & Med, 2004; Yi, Liang, Tian, Zhang, & Wei, 2006
	Promoting the contractions of gastric smooth muscle and muscle strips of duodenum, ileum, and colon	–	3.33 × 10 ⁻⁵ mol/L (in vitro)	Ni, Wang, & Wang, 2004
	Boosting effects on mice's small intestine	–	3 mg/kg (intra-gastric)	Zhou et al., 2007
	Enhancing spontaneous contraction of ileum in guinea pigs	Muscarinic receptor	95.2 mg/kg (intra-gastric)	Du, Wan, Wu, & Chen, 1999
Effects on cardiovascular system	Suppression of inflammatory factor Showing expression of macrophages	Upregulation of peroxisome proliferator-activated receptor γ	10 ⁻⁵ mol/L (in vitro)	Zhang et al., 2009
	Vasodilator response	Muscarinic receptor	3 × 10 ⁻⁷ g/ml (in vitro)	Goto et al., 1997
	Impairment of the activation of polymorphonuclear leukocytes	–	2 μ g/ml (in vitro)	Lai, Lin, Yang, Liu, & Hung, 2007
	Antithrombotic responses	Stimulating the endothelial target for the neurotransmitter acetylcholine	–	Chen, Mu, & Wang, 2002
	Improvement of vascular endothelial function	Increase of cystathionine- γ -lyase expression and activation of ATP-sensitive K ⁺ channels	5.0 mg/kg/day (i.p.)	Ling et al., 2012
Anti-atherogenic effects		Increased plasma level of eNOS protein, nitric oxide, and mRNA expression; decreased plasma level of interleukin-8; downregulation of the expression of MCP-1, intercellular adhesion molecule-1 and CXCR-2 genes	5 mg/kg (intra-gastric)	Shan, Zhang, Zhao, Cui, & Wang, 2004; Duan & Wang, 2006

(Continues)

TABLE 4 (Continued)

Pharmacological effects of arecoline				
Pharmacological effects	Experimental detail	Mediators/pathways	Minimal active dose/concentration and route	Reference
Other pharmacological effects	Improving the metabolism of glucose and lipid in type 2 diabetic rats	The inhibition of hepatic gluconeogenesis	1 mg/kg (i.p.)	Yao, Zhuqing, Wang, & Zhang, 2003
	Adipogenic differentiation inhibition, and promoting the adenylyl cyclase-mediated lipolysis, hindered with insulin-induced glucose reuptake	-	10 μ M, 300 μ M, and 100 μ M, respectively	Hsu et al., 2010
	Prevention of the dysfunction of β cells of pancreas	Upregulation of pancreas-duodenum homeobox-1	1 mg/kg (i.p.)	Qi, Wang, Zhang, Zhou, & Ling, 2010
	Against <i>Candida albicans</i> , <i>Bacillus proteus</i> , <i>Bacillus anthracis</i>	-	Minimum Inhibitory concentration (MIC) values were 0.8, 0.8, and 0.8 mg/ml, respectively	Luo, Zhang, Liu, & Zhu, 2010
	Preventing basal cell carcinoma tumorigenesis	Decreasing the levels of tumor cell survival factor specially interleukin-6, accelerating the levels of tumor suppressor factor, for example, p53, and producing cell cycle arrest	60 μ g/ml (in vitro)	Huang et al., 2012
	Induce death of human leukemia K562 cells	Upmodulation of tumor necrosis factor receptor 2 surface expression	0.1 mM (in vitro)	Chen & Chang, 2012

6.3 | Cytotoxicity

Arecoline possesses cytotoxic effect via endothelium necrosis, whereas biochemical examinations indicate no considerable cellular leakage before mortality and detachment, in addition to no clear action on the mitochondrial role in viable cells. The toxicity of arecoline may thus be responsible for reducing vascularity in oral submucosal fibrosis (Ullah et al., 2014).

Arecoline, at a concentration below 0.8 μ m/ml, amplified cell growth (all types of cell); at advanced concentrations (25–400 μ g/ml), it showed a cytotoxic effect, thus triggering carcinoma in the oral squamous cell (Yang et al., 2004). Arecoline at a dose of 50–200 μ M promotes neuronal cell demise. Catalase, nicotinamide adenine dinucleotide phosphate (NADPH), oxidase inhibitors (apocynin and diphenyleneiodonium chloride), and z-VAD-fmk, which is a caspase

inhibitor; they can inhibit arecoline-mediated cell death. Furthermore, arecoline promoted reactive oxygen species (ROS) production and augmented protein expression and level of mRNA of NADPH oxidase 2, which can be diminished by NADPH oxidase inhibitors and catalase (Shih et al., 2010).

6.4 | Embryotoxicity

Embryos treated with arecoline displayed retardation in general development in a dose-dependent manner. The underlying mechanism behind growth retardation mediated by arecoline in embryos is largely due to an overall cytotoxic effect brought by the diminution of intracellular thiols (Chang et al., 2004).

TABLE 5 Toxicological profile and side effects of *Areca catechu* chemical constituents

Toxicological profile and side effects of <i>Areca catechu</i> chemical constituents				
Toxicological and side effects	Detail	Pathway/mediators	Minimal toxic concentration/dose	Reference
Inflammatory response	Regulation of inflammatory processes in KB carcinoma cells and primary oral gingival keratinocyte	Releasing and producing cytokines including prostaglandin E2, interleukin-6, and TNF- α	0.1 mM (in vitro)	Jeng et al., 2003
Genotoxicity	On HEP-2, KB, and 293 cells	Eliciting γ -H2AX phosphorylation and suppresses DNA repair	0.3 mM (in vitro)	Tsai et al., 2008
	Genotoxic effect in bone marrow cells of mouse and human peripheral blood lymphocytes	Generation of reactive oxygen species	50 μ g/ml (in vitro)	Kumpawat et al., 2003
	On V79 cells of Chinese hamster	Persuading 8-azaguanine resistant mutation	5 μ g/ml (in vitro)	Shirname et al., 1984
	Breaking of DNA strand and unscheduled DNA synthesis	–	10 μ g/ml (ad libitum in the drinking water)	Saikia et al., 1999
	On ovary cells of Chinese hamster	Increasing aberrations of chromosomes and sister-chromatid exchanges	12.5 μ g/ml (in vitro)	Dave et al., 1992
	Mutagenicity in <i>Salmonella</i> TA100, TA1535, TA98, and TA1538	Mutagenic effects	–	Shirname et al., 1983; Wang & Peng, 1996
Atherogenic effects	Oxidative stress	Stimulation of reactive oxygen species (ROS) production and adhesion molecules intercellular adhesion molecule and vascular cell adhesion molecule-1 expression	50 μ g/ml (in vitro)	Hung et al., 2011
Cytotoxicity's	On cancer cell lines GNM, KB, and TSCCa	Cytotoxic effects	25 mg/ml (in vitro)	Yang et al., 2004
	On normal cells including hepatocytes, neuronal cell, myoblasts, and endothelial cells	Cytotoxic effects	0.1 mM, 50 μ M, 40 μ M, and 111 μ g/ml (in vitro), respectively	Chou et al., 2008; Chou et al., 2009; Chang et al., 2013; Ullah et al., 2014
Immunosuppression	Immunological functions regulation	The arecoline arrested splenic lymphocyte cell cycle at lower concentration with induced apoptosis at higher concentration	5 mg/kg, 10 mg/kg, 20 mg/kg (i.p.)	Dasgupta et al., 2006
Embryos toxicity	Retardation of growth	The general cytotoxic was induced by breakdown of intracellular thiols	0.01% (weight/volume)	Chang et al., 2004
Effects on oral cells	Oral submucous fibrosis	Epithelial–mesenchymal transition	–	Yanjia & Xinchun, 2007; Arakeri & Brennan, 2013; Chang et al., 2014; Zheng et al., 2015

(Continues)

TABLE 5 (Continued)

Toxicological profile and side effects of <i>Areca catechu</i> chemical constituents				
Toxicological and side effects	Detail	Pathway/mediators	Minimal toxic concentration/dose	Reference
Oral submucous fibrosis	It is mediated through increasing inflammatory cytokines	–	Haque et al., 2000	
Oral submucous fibrosis	Total amount of collagen was increased	20 µg/ml (in vitro)	Xia et al., 2009	
Oral submucous fibrosis	Oxidative stress and producing reactive oxygen species	50 µg/ml (in vitro)	Chang et al., 2001; Thangjam & Kondaiah, 2009	
Oral squamous cell carcinoma	This genotoxic effect are responsible for carcinoma	40 mg/kg (i.p.)	Chatterjee & Deb, 1999	
Oral submucous fibrosis	Upregulation of heme oxygenase-1 mRNA and protein expression	10 µg/ml (in vitro)	Tsai et al., 2009	
Oral squamous cell carcinoma	The ataxia telangiectasia-mutated/rad3-related p53–p21WAF1 and the phosphatidylinositol-3-kinase mammalian target of rapamycin–p53 pathways	0.5 mM (in vitro)	Chou et al., 2009	
Oral submucous fibrosis	Increasing transglutaminase-2 production	20 µg/ml (in vitro)	Thangjam et al., 2009	
Oral squamous cell carcinoma	Elevation of β-catenin expression	20 µg/ml (in vitro)	Lee et al., 2012	
	Oral submucous fibrosis	Molecular processes were interfered during degradation and/or deposition of ECMs, for example, collagen, producing imbalance in the normal procedure	–	Tilakaratne et al., 2006; Utsunomiya et al., 2005; Arakeri & Brennan, 2013
Death	Causing death of mice, dog, and horse	–	The minimum lethal doses were 100, 5, and 1.4 mg/kg (p.o.), respectively	Zou et al., 2013
Hepatotoxicity and testicular toxicity	Toxicity was analyzed on mature mice	Generating ROS	10 mg/kg (i.p.)	Zhou et al., 2014
Long-term toxicity response	Hematological parameters, change in body weight, histopathological, organ coefficients were evaluated	–	200 mg/kg/day (p.o.), 14 days	Wei et al., 2015

6.5 | Genotoxicity

Genotoxic effectiveness of a raw betel nut aqueous extract with relation to the level of endogenous glutathione in mouse bone marrow cells and also in human peripheral blood lymphocytes specifies that the production of ROS by AEBN could somewhat contribute to the initiation of chromosomal abnormalities causing genotoxicity (Kumpawat et al., 2003).

6.6 | Carcinogenicity

A study of initial molecular actions following exposure of chronic arecoline at a dose of 10 $\mu\text{m}/\text{ml}$ into Swiss albino mice confirmed that betel nut encourages arecoline-induced carcinogenesis (Saikia et al., 1999).

6.7 | Hepatotoxicity and testicular toxicity

Increased risks of hepatocellular carcinoma and cirrhosis were found in betel nut chewers that were free from hepatitis B/C infection, and these hazards were synergistically additive to those of hepatitis B/C infections (Wu et al., 2009).

But one more research work has accomplished a different outcome and it states that the outcomes of the study seem to specify that even long-term areca nut chewing may not promote hepatotoxicity. Minor modifications in liver function tests were fine inside acceptable limits, and no obvious biochemical signs of liver injury were detected. A more comprehensive study is needed with a bigger sample size to significantly arrive at a definite connection of the effect of chewing of areca nut on the liver (Singroha & Kamath, 2016). The principal constituent of areca nut is arecoline; its exposure may lead to serious testicular toxicity and hepatotoxicity as described in another report (Zhou et al., 2014). A detailed toxicological profile along with their doses has been mentioned in Table 5.

7 | CONCLUSIONS

This article provides a summary of many specific characters of areca nut and their therapeutic effect of phytochemicals on various disease conditions. Biochemical compounds of areca-nut have been recently recognized as functionally active molecules, possessing antioxidant, hypoglycemic activity, antifungal, antimigraine, anti-allergic, and additional beneficial properties, as well as they exert protective effects against cardiovascular and other diseases. As mentioned in the article that 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 facilitate utilization in modern medicine.

8 | SEARCH STRATEGY

These searches were confined only to the English language. The authors have used broad Major Exploded Subject Headings (MeSH) terms and keywords (*A. catechu*, Supari, Areca nut, Betel nut) with the following prefix and suffix (phytochemistry, pharmacological use, toxicological, morphological, and geographical). With these words, we have searched EMBASE, PubMed, PsycINFO, Medline, Google, and ScienceDirect. First of all, the papers were collected whose open-access file was available; the abstract was copied from paper that was not accessible. Later following the guideline of Systematic Reviews and Meta-Analyses (PRISMA), the data that were not relevant to the theme of this paper were discarded; the remaining data were characterized according to their heading such as morphology and phytochemical. All collected publications were reviewed manually and also checked regarding the references of interest.

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CONSENT FOR PUBLICATION

All authors and the institution have given their consent for publication of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AA collected the data. TM prepared the background for writing this manuscript. FA compiled and processed the manuscript. AS prepared the tables. SA arranged the references. PB formatted and finally checked the manuscript. All authors read and approved the final manuscript.

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