Journal of Food Measurement and Characterization (2026) 20:9676–9708
https://doi.org/10.1007/s11694-026-04393-9

REVIEW PAPER

Pharmacological and biological activities of areca nut (*Areca catechu* L.): A systematic review

Abhinab Sarma[1] · Nikhil Kumar Ramesha[1] · Manoj Kumar[1] · Srivatsa Udupa[1] · Sachin Ashok Thorat[1] · Arya Kaniyassery[1] · Manjunath Krishnappa Naik[2] · Yu-Chung Chiang[3] · Annamalai Muthusamy[1]

Received: 10 November 2025 / Accepted: 13 April 2026 / Published online: 2 May 2026
© The Author(s) 2026

Abstract

The areca nut (*Areca catechu* L.) is a widely consumed masticatory product in Southeast Asian countries such as India, Indonesia, Taiwan, Thailand, and China owing to its cultural importance and potential medicinal value. The areca nut, which is the seed of the *Areca catechu* palm, is classified as a drupe and is traditionally consumed in both its unripe and ripe forms. In addition to the seeds, the leaves, roots, and inflorescences of the plant also present medicinal properties. Chemically, areca nut comprises approximately 0.5% alkaloids, 20% starch, 20% polyphenols, and 15% fats, among other constituents. To comprehensively assess its medicinal potential, we conducted a systematic literature search using four major databases, the Cochrane Library, EMBASE, PubMed, and Web of Science, supplemented by references from other relevant studies and reviews. This process yielded 262 reports, 137 of which met the inclusion criteria and were retained for further analysis. Notably, the period from 2010 to 2019 had the greatest number of publications, with antioxidant, antimicrobial, and neuropharmacological research each accounting for 16% of the total studies analysed. The results of the present study revealed a broad spectrum of pharmacological activities associated with areca nuts, including anticancer-related, antimicrobial and antiparasitic, anthelmintic, antioxidant, antihypertensive, antidiabetic, cardiometabolic and cardioprotective-related, antiaging, wound healing and gastroprotective effects, neuropharmacological, anti-inflammatory, analgesic, and other therapeutic effects. The known mechanisms underlying different medicinal properties were also explored and discussed.

Keywords Areca nut · Arecoline · Medicinal property · Pharmacological activities · Systematic review · Narrative synthesis

Introduction

Areca nut (AN), derived from *Areca catechu* L., is a traditional masticatory product widely used in South Asian and Southeast Asian countries, including India, Indonesia, Thailand, and Taiwan [1]. Historical Indian texts such as *Vagbhata* and *Bhamavista* describe its medicinal benefits, and its use in Indian culture can be traced back to 1300 BCE, as noted in *Anjana Chaitra* [2, 3]. AN, a member of the Arecaceae family, is commonly referred to by various names, including betel nut, areca sperm, supari, and tamol. It is the seed of the areca palm and is classified as a drupe. It is consumed in both its unripe and ripe forms, typically after the husk is removed and the kernel is dried. The *Areca catechu* tree is tall and slender, growing up to 10–20 m. The plant is monoecious with unisexual flowers, where stamens are located at the base of the pistil and tip of the inflorescence. The tree typically bears 8 to 12 leaves arranged as fibrous bundles at the apex of the stem, and the leaf blades are connate in form [4]. Various regional processing methods are applied before consumption, such as *Bura Tamul* in Assam, *Parcha* in Karnataka, and *Neetadaka* in Kerala [5]. Chewing areca nuts is a cultural tradition associated with a variety of

✉ Annamalai Muthusamy
a.msamy@manipal.edu

[1] Department of Plant Sciences, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal , Karnataka 576104, India

[2] Manipal School of Life Sciences, Manipal Academy of Higher Education, Karnataka 576104 Manipal, India

[3] Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung 80424, Taiwan (R.O.C.)

purposes, including improving breath, strengthening gums, promoting dental health, and alleviating bloating. Some of these effects are supported by scientific evidence, whereas others remain anecdotal [6]. From 2020 to 2021, India had approximately 739,778 hectares under AN cultivation, yielding 1,233,693 tonnes with an average productivity of 1668 kg/ha. Karnataka was the leading producing state, with 2,033 ha under cultivation, a production volume of 4,066 tonnes, and a yield of 2000 kg/ha, followed by Kerala and Assam. As of 2019, India was the world's largest producer of areca nuts, followed by Indonesia and China [7].

The chemical composition of AN includes approximately 0.5% alkaloids, 20% starch, 20% polyphenols, and 15% fats. The key alkaloids present include arecoline (7.5 mg/g), guvacoline (1.5 mg/g), arecaidine (2.0 mg/g), and guvacine (2.9 mg/g) [2]. Among the polyphenols, catechin accounts for 10%, epicatechin for 2.5%, and leucocyanidin for 12%. Other polyphenolic constituents include quercetin, isorhamnetin, and various procyanidin oligomers [8–10]. The fatty acid profile included lauric acid (19.5%), myristic acid (46.2%), palmitic acid (12.7%), stearic acid (6.8%), oleic acid (6.2%), hexadecenoic acid (7.2%), and linoleic acid (5.4%) [11]. AN also contains phosphorus (0.13%), iron (1.5 mg/100 g), calcium (0.05%), vitamin C (416.2 mg), and vitamin B6 (286.9 mg) [12]. Upon chewing, areca nut alkaloids, especially arecoline, can be converted into nitrosamines such as N-nitrosoguvacoline (NGL), 3-methylnitrosaminopropionaldehyde (MNPA), 3-methylnitrosaminopropionitrile (MNPN), and N-nitrosoguvacine (NGC). The International Agency for Research on Cancer [13] has classified AN as a Group 1 carcinogen (carcinogenic to humans). However, arecoline alone is classified as Group 2B (possibly carcinogenic to humans), as the available evidence is limited [14]. Among nitrosamines, NGL, NGC, and MNPA fall under Group 3 (not classifiable with respect to their carcinogenicity in humans), whereas MNPN is categorized as Group 2B [13]. When mixed with betel leaves, slaked lime ($Ca(OH)_2$), catechu, and other ingredients, AN forms part of a preparation known as betel quid (BQ), excluding tobacco. A quid is a substance or mixture of substances that are chewed or held in the mouth against the mucosa [3]. Numerous studies have explored the carcinogenic potential of areca nut extract (ANE) and its components, linking it to conditions such as erythroplakia, keratosis in smokers, oral lichen planus, sclerosing stomatitis, and oral cancer [15, 16]. Conversely, other studies suggest that AN, when consumed in typical doses, may not be carcinogenic and may even offer therapeutic benefits, including anticancer effects. However, current evidence from human trials is insufficient to definitively classify AN or its components as carcinogenic. Some studies also lack control for confounding variables such as dietary habits, oral hygiene, and the latency of submucosal changes. Additionally, inconsistent terminology may contribute to misconceptions regarding its safety [3, 17–19].

Despite the growing literature on Areca catechu, the reported beneficial biological effects of areca nut remain scattered across highly heterogeneous study designs, extract types, biological models, and outcome measures. In many cases, the active constituents responsible for the observed effects are incompletely characterized, and mechanistic claims are often based on crude extracts rather than direct compound-specific validation. In addition, interpretation of these findings is complicated by important toxicological and carcinogenic concerns associated with areca exposure. Therefore, the present study was undertaken as a systematic review with narrative synthesis to examine the reported medicinal and biological effects of areca nut, summarize the major extract types and bioactive constituents investigated, and critically assess the experimental evidence and proposed mechanisms across different therapeutic areas. This review also highlights recurring methodological limitations and identifies key gaps that should guide future research.

Methodology

Collection, screening, and review process

A systematic review was conducted following the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. Online searches were performed in four major databases: the Cochrane Library, Embase, PubMed, and Web of Science. The search strategy was based on a set of keywords relevant to the scope of this review. The search queries used are presented in Tables S1–S4. Additionally, studies were also collected through cross-referencing original and review articles and by hand searching. All duplicates were manually removed by one of the investigators via the online tool rayyan.ai. After removing duplicates, the number of records was manageable. The titles and abstracts were screened, and the full texts were examined when required against the predefined inclusion criteria. The screening process was performed independently by two investigators. Disagreements were resolved by discussion and, when necessary, by consultation with a third investigator. The full texts of the screened studies were reviewed. The relevant data were extracted and organized according to the medicinal properties of areca nuts. The overall selection and filtering process is illustrated in Fig. 1.

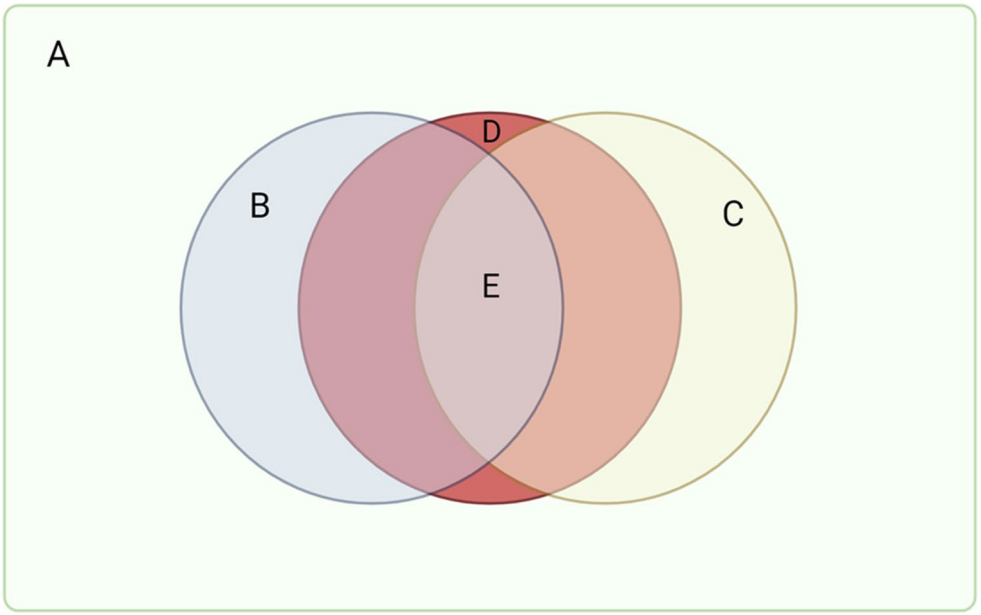


Fig. 1 Venn diagram of how studies were narrowed down (**A**) Medicinal properties of plants. (**B**) Medicinal properties of alkaloids (**C**) Medicinal properties of polyphenols (**D**) Areca catechu-related studies discussing medicinal properties (**E**) Medicinal properties of alkaloids and polyphenols from Areca catechu plant (Created using Biorender.com)

Inclusion criteria

Studies were included if they met the following criteria:

1. Original experimental research (in vitro, in vivo or in humans) reporting the medicinal or pharmacological properties of *Areca catechu* extracts or compounds derived from *A. catechu*.
2. The study explicitly identified or quantified one or more constituents isolated from *A. catechu* (for example, polyphenols, flavonoids, procyanidins, and arecoline) and linked those constituents to biological activity. Studies that tested only generic compounds not shown to be derived from *A. catechu* were excluded.
3. No restrictions were applied on country of origin, language or publication date.
4. Studies investigating the therapeutic benefits of arecoline independently without mention of areca nuts were included.

This approach ensures that we capture both whole-extract evidence (which reflects real-world preparations) and mechanistic/compound-level evidence while avoiding the attribution of activity to compounds that were not shown to originate from *A. catechu*. Studies of arecoline are limited, given its role as a principal bioactive compound of *A. catechu*. Review articles, commentaries, and reports without primary experimental data were excluded.

Results and discussion

Screening and review

Following a comprehensive online search using the queries listed in Tables S1–S4 for the Cochrane Library, Embase, PubMed, and Web of Science, along with additional references from cited studies and review articles, a total of 262 studies were identified. Of these, 18 were duplicates across databases and were manually removed by one of the investigators via the online tool rayyan.ai. The remaining 244 studies were screened on the basis of titles, abstracts, and, where necessary, full texts. A total of 137 studies met the inclusion criteria and were retained, while 107 were excluded. All 137 eligible studies were successfully retrieved. A flow diagram depicting the number of identified, screened, retrieved, and included studies for this review is shown in Fig. 2.

Upon categorization, we found that the greatest proportion of publications focused on the antioxidant, antimicrobial, and neuropharmacological properties of areca nut (AN), each comprising 16% of the total studies analysed (Fig. 3). Most studies were in English, and three studies were in Chinese and were translated via Google Translate. Studies notably originated from Taiwan, Indonesia, Thailand, India, China, South Korea, and Japan. The distribution and classification of the included studies are shown in Fig. 4. In cases where multiple medicinal properties were addressed within a single article, classification was based

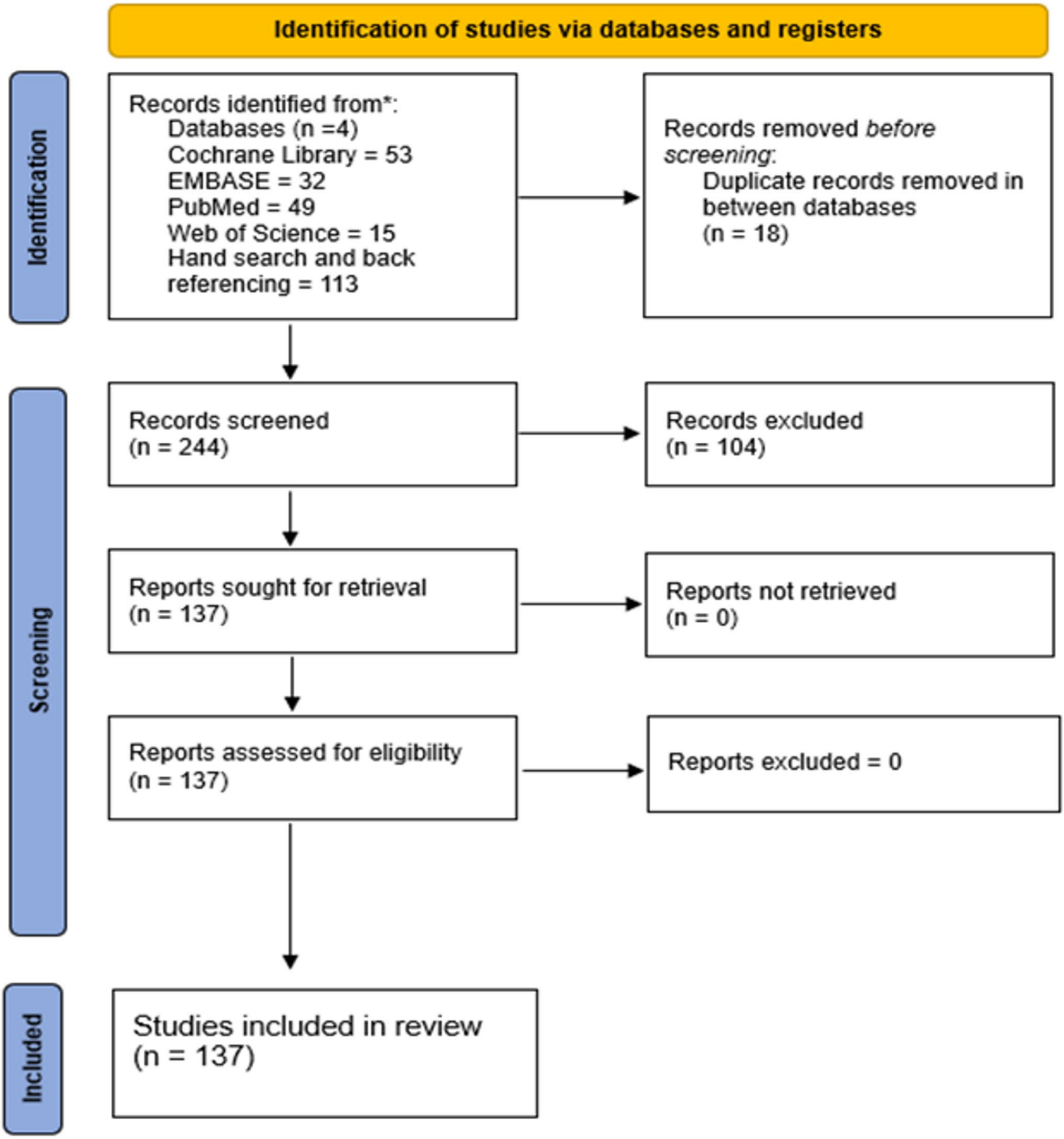


Fig. 2 Flowchart of identification, screening, and inclusion of papers

on the primary focus as determined by the investigator's judgment. The subsequent sections detail the medicinal properties supported by three or more studies; others with fewer studies (<=2) were placed under 'Other Benefits'. An analysis of publication trends revealed a marked increase in research activity between 2010 and 2019 and 2019–2024 compared with the earlier periods of 1950–2000 and 2000–2010 (Fig. 5). Furthermore, ethanolic areca nut extract (51 studies) was mostly employed across studies, followed by aqueous (35 studies) and methanolic (27 studies) extracts (Fig. 6). In vitro study-type (85) and animal-based (45) studies were conducted mostly across different medicinal and biological effects, suggesting mostly preclinical evidence, whereas human-based (12) studies were collected

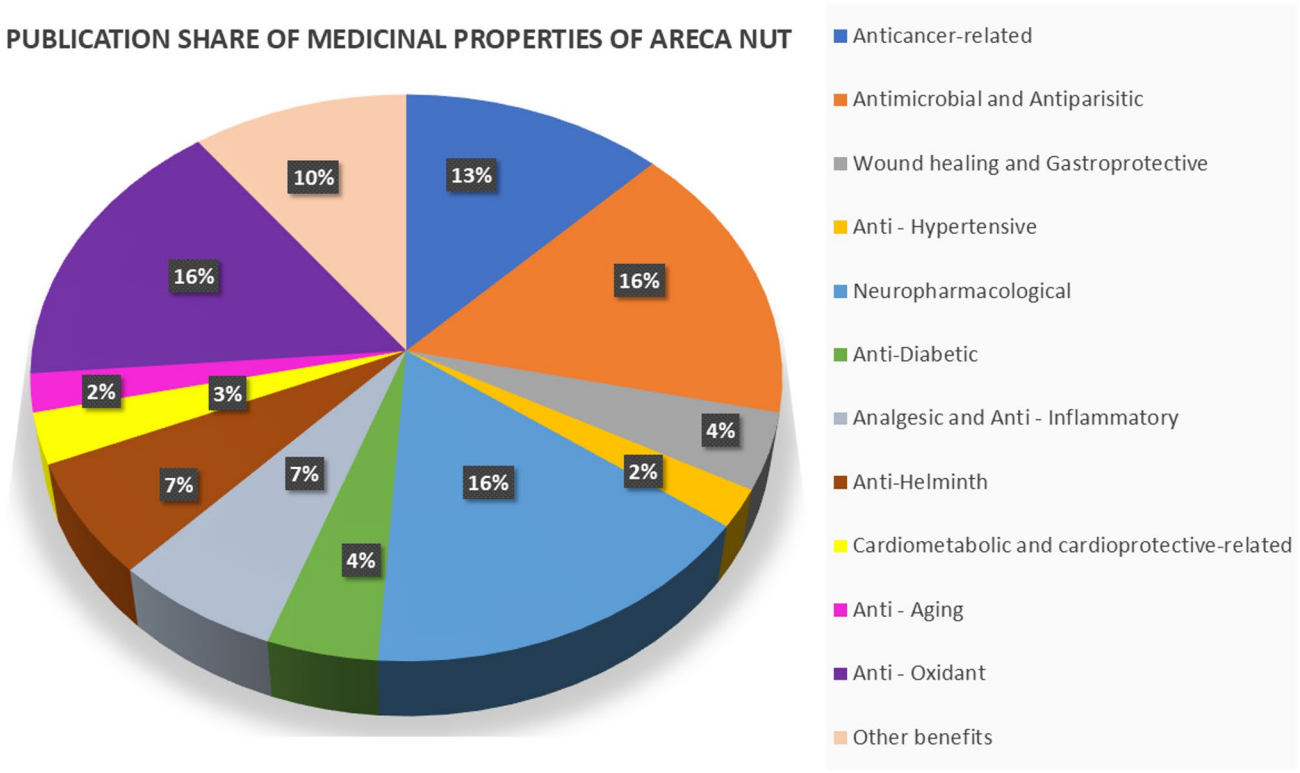


Fig. 3 Percentage of studies collected, discussing medicinal properties of areca nut (AN)

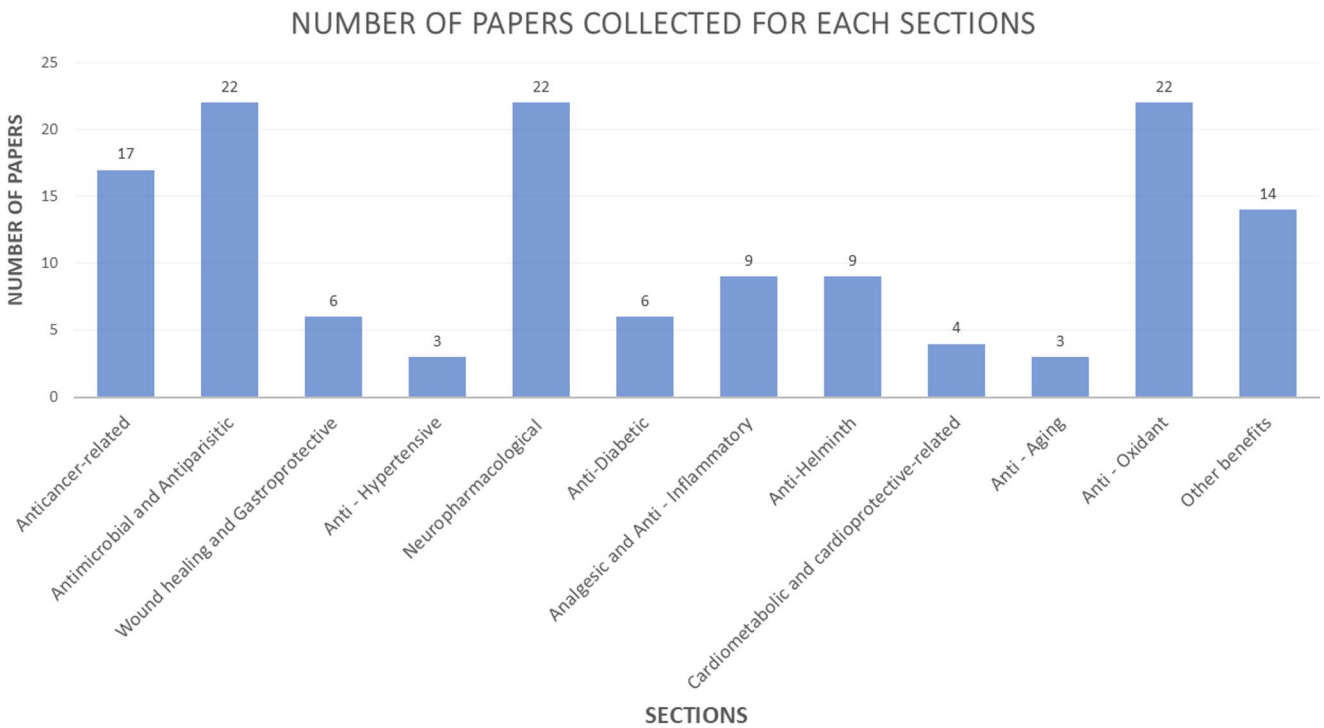


Fig. 4 Numbers of papers collected for each section of medicinal property discussed

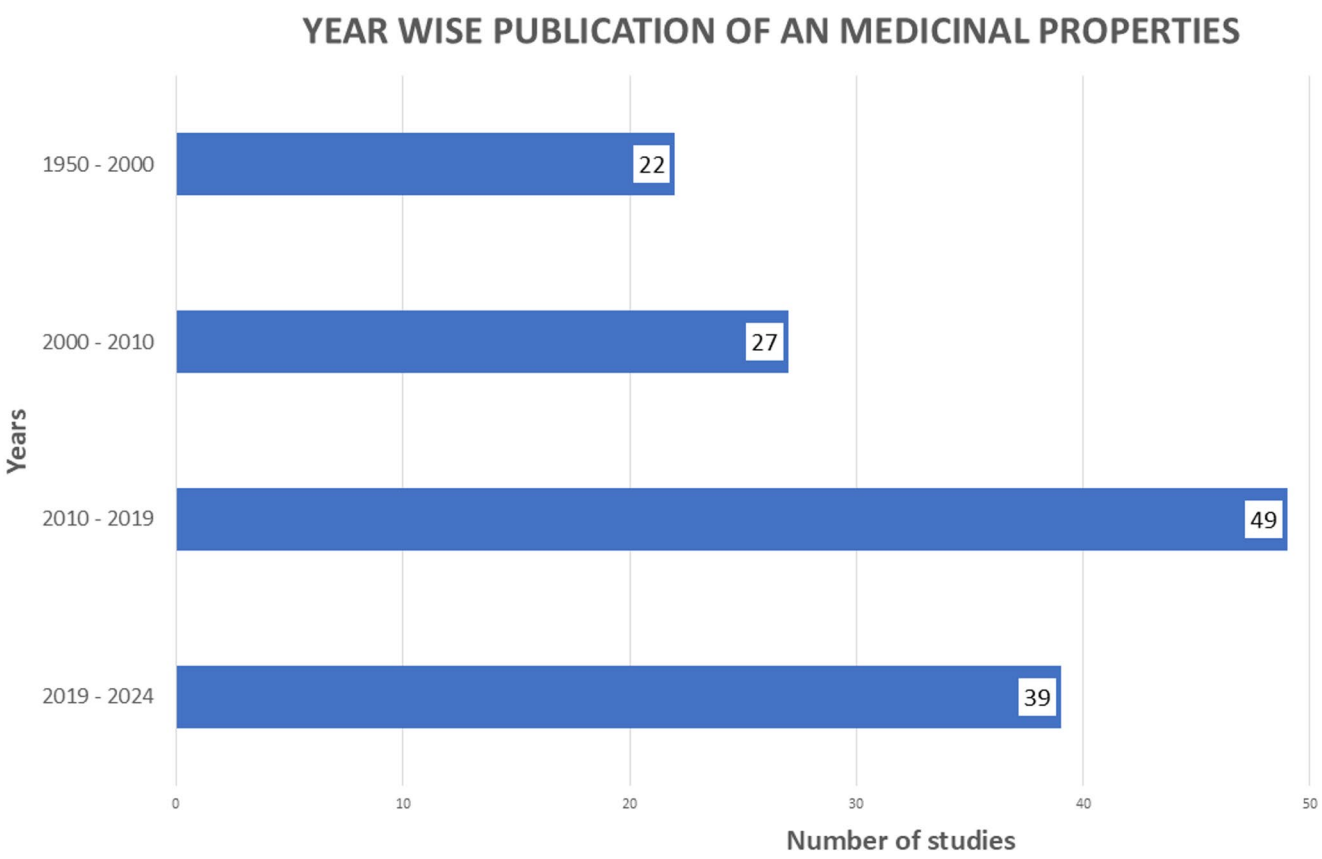


Fig. 5 Year-wise publication of studies discussing areca nut (AN) medicinal properties

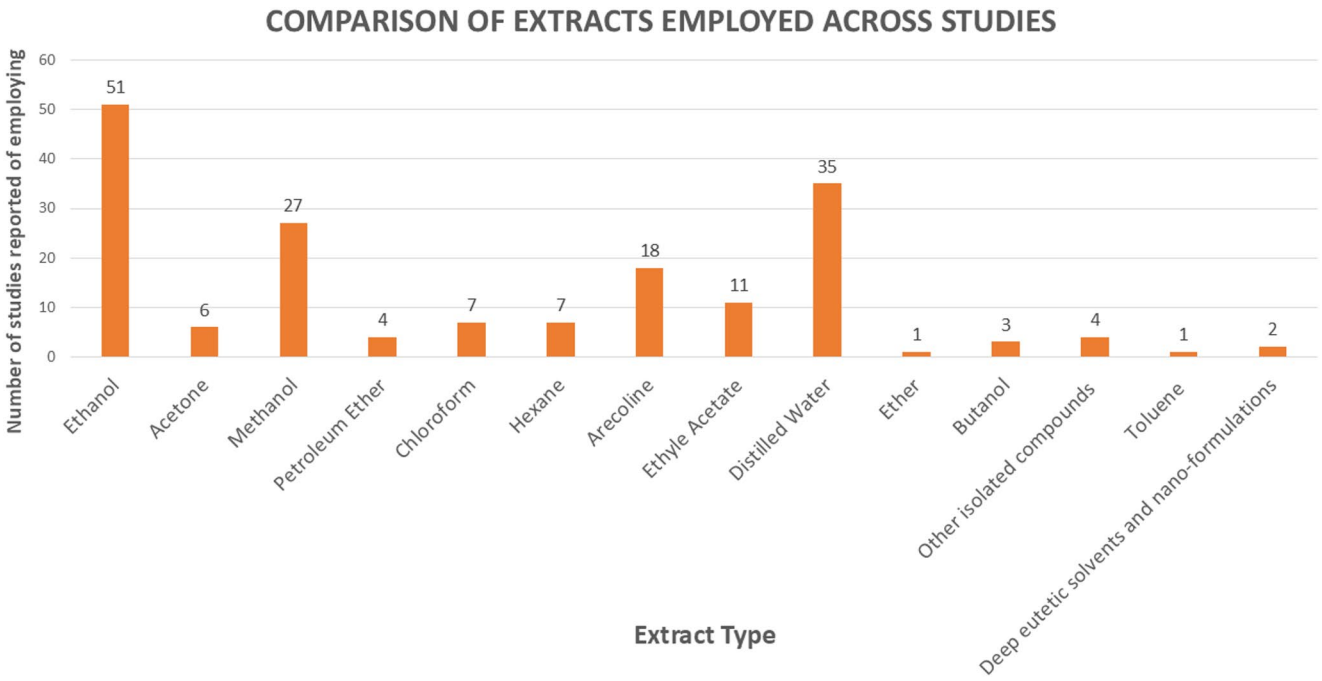


Fig. 6 Comparison of extracts employed across studies

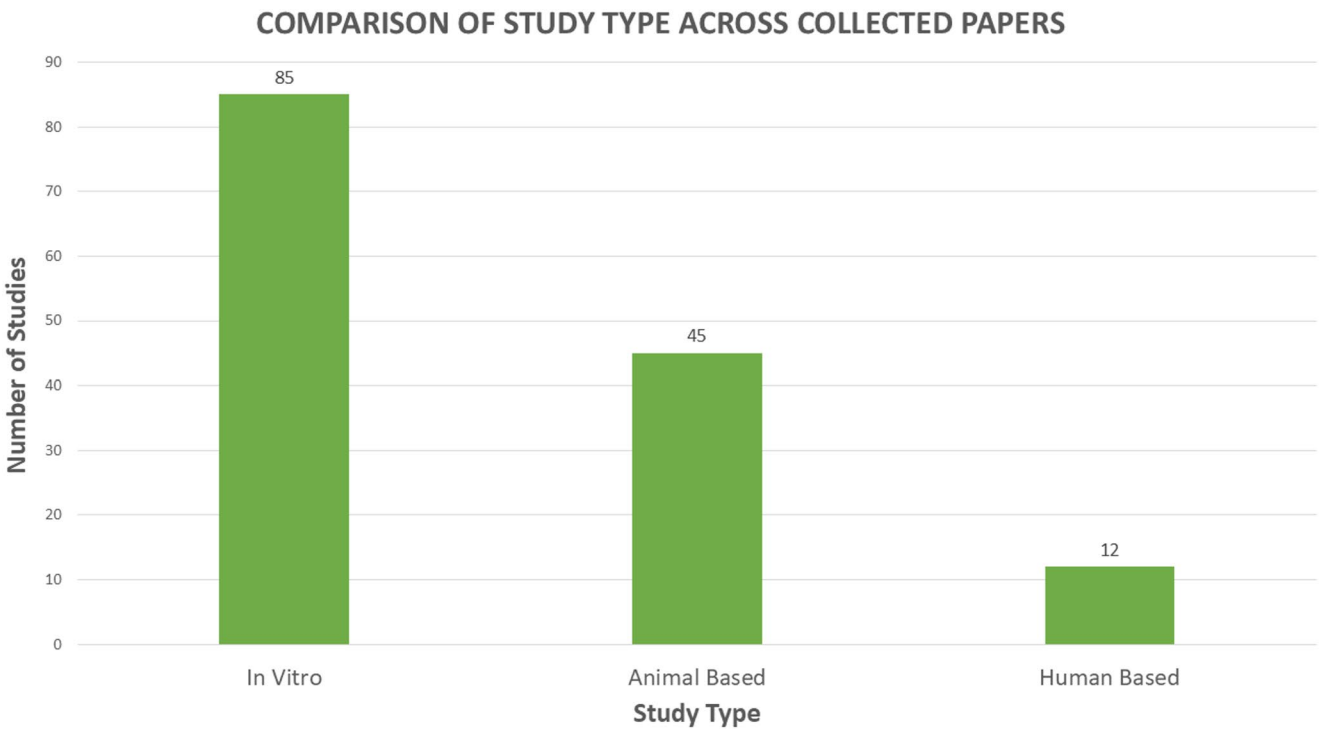


Fig. 7 Comparison of study type across available literature

but lacked sufficient clinical relevance (Fig. 7). A detailed summary of studies on antiaging, antidiabetic, antihypertensive, anti-inflammatory and analgesic, wound healing and gastroprotective, antihelminth and cardiometabolic and cardioprotective effects is given in Table 1. A summary of the anticancer effects and the neuropharmacological, antimicrobial and antiparasitic, antioxidant, and other benefits are given in Tables 2, 3, 4 and 5, and 6, respectively. A quality appraisal is also shown for the studies in Table 7. A formal risk-of-bias assessment using a single standardized tool was not performed because the included studies were methodologically heterogeneous and spanned multiple experimental domains for which no single appraisal instrument was appropriate. To address study quality more transparently, the evidence was instead evaluated narratively according to study design, extract characterization, model relevance, and major methodological limitations. The review question was defined a priori to focus specifically on the reported medicinal and beneficial biological effects of areca nut-derived materials. Accordingly, studies addressing therapeutic or beneficial outcomes were prioritized for inclusion in the main synthesis, whereas the broader toxicological and carcinogenic literature was not reviewed exhaustively as a separate systematic evidence stream. However, because areca nut is associated with important toxicological and carcinogenic concerns, these issues are acknowledged and discussed in the manuscript as essential for interpreting the reported beneficial findings.

The medicinal and therapeutic properties of Areca nut (*Areca catechu* L.)

Anti-aging

Areca nut-derived preparations have been investigated for several skin-related activities relevant to antiaging, including the inhibition ofextracellular matrix-degrading enzymes, protection against UV-B-induced photoaging, and improvement of hydration- and elasticity-related parameters. However, these findings arise from the use of distinct experimental systems, including enzyme-based assays, animal-photodamage models, and cell-based or instrument-based cosmetic assessments; therefore, the results should not be interpreted asequivalent evidence of antiaging efficacy.

One line of evidence concerns the inhibition of enzymes involved in the degradation of skin structural components. An areca nut extract (ANE)-labelled CC-517 significantly inhibited both porcine pancreatic elastase (PPE) and human neutrophil elastase (HNE), outperforming ursolic acid and oleanolic acid in these assays. Lineweaver–Burk analysis suggested competitive inhibition, and the effect was attributed to phenolic constituents capable of interacting with the extended substrate binding sites of the enzymes. CC-517 also showed antihyaluronidase activity through a noncompetitive mode of inhibition on the basis of measurements of *N*-acetylglucosamine release from sodium hyaluronate [21]. These findings indicate that areca-derived phenolic-rich

Table 1 Bioactive compounds, solvent used for extraction and medicinal properties of Areca nut

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvents used for Extraction	Medicinal Properties	Stage of the seed used	References
1	ANE	80% ethanol	Anti - aging	NA	[21]
2	ANE - procyanidins	80% acetone	Anti - aging	Tender AN	[22]
3	ANE – CC516	90% ethanol	Anti - aging	NA	[23]
4	ANE	70% ethanol	Anti - diabetic	Mature AN	[24]
5	ANE	Petroleum ether, chloroform and methanol	Anti - diabetic	AN leaf (stage not mentioned)	[28]
6	ANE	70% ethanol	Anti - diabetic	Mature AN	[25]
7	ANE	70% ethanol	Anti - diabetic	AN flower (stage not mentioned)	[27]
8	ANE - procyanidins	NA	Anti – diabetic	NA	[29]
9	ANE	50% ethanol	Anti - diabetic	NA	[26]
10	ANE – (Areca – II – 5 – C) catechin, epicatechin and tannins	NA	Anti - hypertensive	Mature AN	[30]
11	Arecoline	NA	Anti - hypertensive	NA	[32]
12	ANE - flavonoids	75% ethanol	Anti – hypertensive, anti – diabetic and antioxidant	Tender AN (seed, flower and husk)	[31]
13	ANE	96% ethanol	Anti - inflammatory	Old and young AN	[40]
14	ANE	Chloroform and methanol	Anti - inflammatory	AN leaf from Mangalore (stage not mentioned)	[39]
15	ANE	Methanol	Antinociceptive	AN leaves and stem (stage not mentioned)	[33]
16	ANE - procyanidins	80% acetone	Anti - inflammatory	Tender AN	[35]
17	ANE	50% ethanol	Anti – inflammatory, antioxidant and hepatoprotective	NA	[41]
18	ANE	50% ethanol	Analgesic and antioxidant	NA	[34]
19	ANE	70% methanol	Anti – inflammatory and analgesic	NA	[36]
20	ANE	70% ethanol	Anti - inflammatory	AN leaf (stage not mentioned)	[37]
21	ANE – CC – 516	Ethanol	Anti – inflammatory and anti - melanogenesis	NA	[38]
22	ANE	Water	Anti – ulcerogenic	NA	[47]
23	ANE	70% ethanol	Wound healing	NA	[42]
24	ANE	70% ethanol	Wound healing	NA	[45]
25	ANE	70% ethanol	Wound healing	NA	[43]
26	ANE	70% ethyl alcohol	Wound healing	Mature AN	[46]
27	ANE – arecoline, polyphenols	Chloroform and 80% methanol	Wound healing	NA	[44]
28	ANE	80% ethanol	Anti – helminth (*Fasciola spp.*)	Mature AN	[48]
29	AN	NA	Anti - helminth	Mature AN	[57]
30	ANE	70% ethanol	Anti – helminth (*Ascaris lumbricoides*)	NA	[58]
31	ANE	hexane, chloroform, ethyl acetate and ethanol	Anti – helminth (*Cotylophoron cotylophorum*)	NA	[59]
32	ANE	Distilled water	Anti – helminth (*Ascaridia galli*)	NA	[51]
33	ANE	Water	Anti – helminth (*Ascaridia galli*)	NA	[55]
34	ANE	Water	Anti – helminth (*Fasciola gigantica*)	NA	[49]
35	ANE	95% ethanol	Anti – helminth, anti – microbial and antioxidant	AN root (stage not mentioned)	[50]
36	ANE - lauric, myristic, palmitic, and oleic acids	50% acetone	Anti - helminth	NA	[56]
37	ANE	95% ethanol	Cardioprotective	NA	[60]
38	ANE	95% ethanol	Cardioprotective	NA	[61]
39	ANE	95% ethanol	Cardioprotective	NA	[62]
40	ANE	95% ethanol	Cardioprotective	AN inflorescence (stage not mentioned)	[63]

ANE Areca nut extract, *AN* Areca nut and *NA* – not available (AN seed used, in case of stage of seed used)

Table 2 Anticancer properties and its mechanisms of bioactive compounds from Areca nut

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvent used for Extraction	Type of cancer	Mechanism	Model	Stage of the seed used	References
1	ANE	NA	Hepatocellular cancer	ROS production with lime at alkaline pH leads to modification in DNA 8-OH-dG	HepG2, HepJ5, Mahlavu cell lines and nude mice xenograft	Ripe areca nut	[72]
2	Arecoline	NA	Basal Cell Carcinoma	Decrease in IL-6, which results in cell cycle arrest in G2/M due to low CDK1 activity due to CDc25C low levels. Also, pro-apoptotic due to caspase-3 activation and decrease in levels in Bcl3	BCC-1/KMC, HaCaT (no effect), BALB/c mice xenograft	NA	[66]
3	Arecoline	NA	Prostate cancer	Cell cycle arrest of RWPE-1 and PC-3 in G2/M phase and LnCaP in G_0/G1 phase due to probable ROS pathway induce by arecoline	RWPE-1, PC-3, LNCaP cells	NA	[65]
4	ANE and Arecoline	NA	Oropharyngeal	G2/M cell cycle arrest	KB cells	NA	[64]
5	30–100 KDa ANE	Squeezed juice resuspended in water	Oral cancer	Autophagy induced by ROS	CE81T/VGH, Jurkat leukemia T cells	Tender AN	[73]
6	ANE	96% ethanol	Oral Cancer	Induce apoptosis by expressing caspase-3 enzyme	HSC-2, HSC-3	NA	[69]
7	Arecoline	NA	Laryngeal cancer	N - Nitoso compounds derived from Arecoline interact with DNA	Hep2 cells	NA	[82]
8	ANE	Water and methanol	Breast cancer	Cytotoxic	MCF-7 cells	NA	[77]
9	Arecoline	NA	Head, neck, lung, prostate cancer and leukaemia	ACAT1 inhibitor	Human cancer cells, peripheral blood samples and mouse model (not specified)	NA	[76]
10	ANE	95% ethanol	Cholangiocarcinoma	Apoptosis, caspase 3, cPARP, CHK2 and p53 increased action	RMCCA1	NA	[68]
11	AN	NA	Oral cancer	Observed no induction of malignant tumor in hamster cheek pouch	Syrian hamsters (*Mesocricetus auratus*)	NA	[80]
12	ANE, processed and unprocessed	Water	Oral, pharyngeal and oesophageal cancer	No tumors observed in mice except for unprocessed AN showed weak carcinogenicity at high doses	Swiss albino mice	Ripe and Unripe	[81]
13	Arecoline	NA	Oral cancer	Cell cycle arrest and apoptosis	KB cells	NA	[78]
14	30–100 K Da ANE and arecoline	Squeezed juice resuspended in water	Mouth, bladder, and oesophagus	Autophagy, apoptosis and phosphorylation of mTOR – Ser^{2448}	OECM – 1, SCC – 9, UB – 09, T24 and CE81T/VGH	Tender AN	[75]
15	30–100 K Da ANE – proteoglycans	Squeezed juice resuspended in water	Mouth, bladder, and oesophagus	Autophagy, apoptosis	NA	Tender AN	[74]

Table 2 (continued)

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvent used for Extraction	Type of cancer	Mechanism	Model	Stage of the seed used	References
16	ANE – ether extract – catechin, epicatechin, leucocyanidins – n – butyl extract – proanthocyanidins	Water, ether, and n – butyl alcohol	Gastric or oesophageal cancer	Inhibit endogenous N – nitroso compounds formation in gut	2 human volunteers	Dry AN	[79]
17	ANE	96% ethanol	Oral cancer	Cell cycle arrest, inhibit proliferation and apoptosis	HSC 2, HSC 3	NA	[67]

ANE Areca nut extract, *AN* Areca nut and *NA* not available (AN seed used, in case of stage of seed used), *ACAT1* acetyl-CoA acetyltransferase 1, *cPARP* cleaved poly (ADP-ribose) polymerase, *CDK* cyclin dependent kinases, *CHK* checkpoint kinase, *mTOR* mammalian target of rapamycin, *Bcl-2* B cell lymphoma – 2, *Hep* hepatocellular carcinoma, *HaCaT* Human Adult low Calcium high Temperature keratinocytes, *BCC* Basal cell carcinoma, *BALB* Bagg Albino, *HSC* human squamous cell carcinoma, *LNCaP* Lymph Node Carcinoma of the Prostate, *PC* prostate cancer, *CE81T/VGH* Cheng-En 81 Tumor, Veterans General Hospital, *MCF-7* Michigan Cancer Foundation-7, *RMCCA* Rat Cholangiocarcinoma Cell Line, *OECM* Oral Epidermoid Carcinoma Model, *SCC* Squamous Cell Carcinoma, *T24* transitional cell carcinoma of the bladder

preparations may interfere with enzymes relevant to elastin and hyaluronan degradation. However, enzyme inhibition assays provide only mechanistic evidence at the biochemical level and do not by themselves establish functional anti-aging effects in living skin.

A second line of evidence relates to UV-B-induced photoaging. Procyanidin-rich ANE mitigated UV-B-induced skin alterations in CD-1 mice, including keratinocyte hyperproliferation, increased epidermal thickness, sebaceous gland enlargement, and collagen degradation, as assessed by H&E (haematoxylin and eosin) and Masson's trichrome staining. The extract also downregulated UV-B-induced expression of COX-2 (cyclooxygenase-2), the matrix metalloproteinases MMP-2 and MMP-9, and the tissue inhibitor TIMP1, suggesting reduced inflammatory and matrix-degrading responses [22]. These findings support a possible photoprotective effect of areca-derived preparations in an experimental model of UV-B damage. Nevertheless, such observations are specific to induced photoaging conditions in animals and cannot be directly extrapolated to broader antiaging effects in humans.

Additional studies evaluated a different preparation, CC-516, in relation to hydration, elasticity, wrinkling, and melanogenesis. This extract, reported to contain approximately 13% proline, improved skin hydration and elasticity and reduced wrinkling, as measured using a corneometer, cutometer, and visiometer. It also inhibited elastase activity over a concentration range of 10–250 µg/mL and increased collagen content and fibroblast proliferation at a 10^{-4} dilution [23]. In B-16 melanoma cells, CC-516 inhibited tyrosinase activity and reduced melanin-related outcomes, with activity greater than that of arbutin but lower than that of kojic acid [22]. Taken together, these findings suggest that some areca-derived preparations may influence skin-related functional parameters as well as select biochemical pathways linked to matrix maintenance and pigmentation. However, because these observations combine cosmetic instrument-based measurements, cell-based assays, and partly characterized extract systems, they remain preliminary and do not clarify which constituents are primarily responsible for the observed effects.

Collectively, the available studies suggest that areca nut-derived preparations may exert skin-related bioactivities through several preclinical pathways, including inhibition of matrix-degrading enzymes, attenuation of UV-B-induced tissue damage, and modulation of hydration, elasticity-, and pigmentation-related parameters. However, these findings are derived from heterogeneous experimental systems that reflect different biological levels of analysis and are not directly comparable. Enzyme assays primarily indicate biochemical interactions with specific targets, UV-B mouse studies address photodamage in an induced animal model, and hydration or pigmentation studies involve cosmetic, cellular, or formulation-level outcomes rather than disease-level validation. Therefore, the current evidence supports only preliminary antiaging-related activity in preclinical settings. This interpretation is further limited by incomplete metabolite characterization, uncertainty regarding the active constituents, and the absence of robust human clinical studies.

Anti-diabetic effects

Compounds with hypoglycemic activity may lower blood glucose levels through different mechanisms, including inhibition of carbohydrate digestion, modulation of hepatic glucose production, or protection against pancreatic and metabolic injury. The studies reviewed here suggest that areca nut-derived extracts may influence glucose-related pathways across enzymatic, cellular, and animal models; however, these models represent different biological processes and should not be interpreted as equivalent evidence of antidiabetic efficacy.

Table 3 Neuropharmacological properties and its mechanism of bioactive compounds from Areca nut

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvents used for Extraction	Action	Stage of the seed used	References
1	ANE	Ethanol, water, hexane	Anti – depressant, MAO inhibition	NA	[83]
2	ANE – Arecoline, epicatechin, syringic acid.	Ethanol	Anti - neuroinflammatory	NA	[85]
3	ANE – Gallic acid, epicatechin, catechin, syringic acid, isoguvacine, arecoline, guvacine, guvacoline, arecaidine	Aqueous	Anti – epilectic seizures and modulation of cognitive function	NA	[86]
4	Arecoline	NA	Attenuates Schizophrenia	NA	[87]
5	Arecoline	NA	Reverses cortisol level in DST related to endogenous depression	NA	[102]
6	Arecoline	NA	Memory improvement in Alzheimer's patients	NA	[89]
7	Arecoline	NA	Cognitive function improvement in Alzheimer's disease	NA	[91]
8	Arecoline	NA	Improves memory retention	NA	[92]
9	Arecoline	NA	Cognitive function improvement in Alzheimer's disease	NA	[90]
10	AN chewing	NA	Helps to alleviate symptoms	NA	[98]
11	Arecaidine, Guvacine	NA	Inhibits uptake of GABA and β – alanine	NA	[88]
12	ANE	50% aqueous ethanol	Anti – migraine by inhibition of iNOS	NA	[99]
13	Arecoline	NA	Enhances human serial learning	NA	[97]
14	ANE – catechin, tannic acid, gallic acid, diosgenin, isoguvacine	70% Aqueous methanol	Anti – platelet and acetylcholine esterase inhibition	Dried AN	[100]
15	Arecoline	NA	REM sleep induction	NA	[103]
16	ANE	Water	Anti – Alzheimer's, inhibits amyloid β and BACE1	NA	[93]
17	Arecoline	NA	Anti – Alzheimer's	NA	[94]
18	Arecoline	NA	Cognitive function improvement in Alzheimer's disease	NA	[95]
19	ANE - arecoline	Methanol	Increase in spatial memory and learning	Wet and Dry AN	[104]
20	Arecoline	NA	Cognitive function improvement in Alzheimer's disease	NA	[96]
21	ANE - saponins	aqueous, ethyl acetate, hexane, and dichloromethane: acidified, basified and neutral	Anti – depressant, via elevation of serotonin and noradrenaline levels	NA	[84]
22	ANE	70% aqueous methanol	AChE inhibition	NA	[101]

ANE Areca nut extract, *AN* Areca nut and *NA* not available (AN seed used, in case of stage of seed used), *MAO* monoamine oxidase, *DST* dexamethasone suppression test, *GABA* Gamma-Aminobutyric Acid, *REM* rapid eye movement, *BACE1* beta-secretase 1, *AChE* acetylcholinesterase

Ethanolic areca nut extract (ANE) from mature nuts was reported to inhibit intestinal disaccharidase enzymes involved in monosaccharide generation and absorption. In vitro, ANE inhibited α-glucosidase-related activity, with IC_{50} values of 12 µg/mL for maltase and 30 µg/mL for sucrase. In male Wistar rats, ANE (250–500 mg/kg body weight) significantly suppressed postprandial glucose absorption at 30 and 60 min, an effect attributed mainly to tannin-rich constituents [24]. These findings suggest that one possible glucose-lowering mechanism of ANE lies in

Table 4 Anti-microbial properties of areca nut extracts, bioactive compounds and its mechanisms

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvent used for Extraction	Action	Stage of the seed used	References
1	ANE - Cyclohexane Heptane, 2,4-bis(1,1-dimethylethyl)-Phenol Lauric acid Tetradecanoic acid Diethylhexylphthalate	80% methanol, 80% ethanol and water	Anti–microbial, against *E.coli*, *S. aureus*, *S.enterica*, *E. aerogenes*.	NA	[105]
2	ANE – Polyphenols - Catechin Epicatechin Epigallocatechin gallate	90% methanol fractionated with hexane, chloroform, ethyl acetate, and ethanol	Anti-tuberculosis (*Mycobacterium tuberculosis* H37Rv)	AN (Mangalore variety) stage not mentioned	[121]
3	Copper nanoparticles from ANE	methanol	Anti – bacterial and Anti – Oxidant	Mature AN	[125]
4	AN essential oil	NA	Anti – microbe (*S.mutans*)	Immature green AN (Sanya, China)	[109]
5	ANE	Boiled water	Anti -microbial, fungal and viral	NA	[123]
6	Polyphenols NF-86I, NF-86II	NA	Anti – microbial (*S.mutans* MT8148(c), MT6715(g) respectively)	NA	[110]
7	Peptides (65 kDA and 68kDA)	Protein isolation reagents	Anti – microbial (S. epidermidis, *E. coli* and, *P. mirabilis*)	NA	[124]
8	Terpenes Fernenol, arundoin, and mixture of stigmasterol, β – sitosterol and lauric acid	Hexane, ethyl acetate, methanol	Anti – fungal (*C.gloeosporioides*)	Mature fruit of AN	[118]
9	ANE	95% ethyl alcohol	Anti – microbial against mixed oral flora and *E. coli*, *P. vulgaris*, *P. aeruginosa*, *S. non-typhi*, *S. typhi*, *S. flexneri* and *V. Cholera*	NA	[107]
10	ANE	Water, ethanol, n- hexane	Anti – microbial (gram positive)	NA	[108]
11	ANE	butanol	Anti – malarial	NA	[120]
12	ANE - isorhamnetin, chrysoeriol, luteolin, (±)−4', 5 – dihydroxy – 3', 5', 7 – trimethoxyflavone and jacareubin	ethanol	Anti – bacterial (MRSA)	NA	[111]
13	ANE	Water, 95% alcohol, acetone and ethyl acetate	Anti – microbial (*B.cereus*, *S.aureus*, *E.coli* and *S.typhimurium*)	Ripe and unripe (Nakornchaisri, Nakornbathom province and Banpaew, Samuthprakarn province)	[106]
14	ANE	Water and alcohol	Anti – fungal	Husk	[115]
15	ANE - catechin, quercetin	96% ethanol	Immunomdulatory effect in rats infected with *S. aureus*	Ripe AN	[119]
16	ANE	Boiled water	Anti – fungal – *Candida albicans*	NA	[114]
17	ANE – quercetin, cinnamic acid	Chloroform, water, methanol and ethanol	Anti – microbal (*Bacillus subtilis)*	NA	[112]
18	ANE	Water	Anti – fungal (*Meyerozyma sp.* and *Aspergillus sp.*)	Mature AN	[116]
19	ANE	Water and methanol	Ant – viral	NA	[122]
20	BQ/ANE	Ethyl acetate	Anti - bacterial	NA	[113]
21	ANE	methanol	Anti - fungal (*Candida albicans*)	NA	[117]
22	ANE	NA (HS – SPME and SHDE methods used)	Anti – microbial (*Streptococcus canis*)	NA	[126]

ANE Areca nut extract, *AN* Areca nut and *NA* not available (AN seed used, in case of stage of seed used), *HS-SPME* headspace solid-phase microextraction, *SHDE* simultaneous hydrodistillation–extraction

Table 5 Antioxidant properties of areca nut extracts and its bioactive compounds

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvents used for Extraction	Action and assay used	Stage of the seed used	References
1	ANE	methanol, n- hexane, ethyl acetate, toluene, and chloroform.	Antioxidant – DPPH, H_2O_2, Fe^{2+} chelating and FRAP assays	NA	[135]
2	ANE	Methanol, petroleum ether, ethyl acetate and water extract	Antioxidant – H_2O_2, and reducing power assays	Mature AN fruit	[127]
3	ANE	water and ethanol (50%)	Antioxidant – H_2O_2, and FRAP assays	NA	[128]
4	ANE	70% ethanol	Antioxidant – DPPH, OH., and reducing power assays	Areca flower, husk and seed	[129]
5	ANE	methanolic and aqueous extract	Antioxidant – DPPH assay and GST activity assay in rat liver	Ripe and unripe (seeds, roots, and adventitious roots)	[131]
6	ANE – procyanidins, isorhamnetin 3-O- rutinoside and catechin	10% aqueous sample extract	Antioxidant - DPPH, FRAP, and FTC assay	Mature AN	[136]
7	ANE – alkaloid, flavonoids, pyroatecol, tannins, and gallic acid	Ethanol	Antioxidant and cytotoxic to EAC cells – NO and OH radical scavenging assay	NA	[140]
8	ANE−4-[3'-(hydroxymethyl)oxiran-2'-yl]−2,6-Dimethoxyphenol, epoxyconiferyl alcohol, isovanillic acid, protocatechuic acid, catalpinic acid, isorhamnetin, chrysoeriol, luteolin, (±)−4',5-dihydroxy-3',5',7-trimethoxyflavonone, (±)−4',5-dihydroxy-3',5',7-trimethoxyflavonone, (2*S*,3*R*)-entcatechin and jacareubin	Ethanol further portioned by water, ethyl acetate, n – butanol and light petroleum	Antioxidant – DPPH assay and cytotoxic towards SGC-7901and SMMC-7721 cell lines	NA	[141]
9	ANE	Methanol, 50% methanol and water	Antioxidant – DPPH, superoxide and reducing power assays	Mature AN	[132]
10	ANE - gallic acid, (-)-gallocatechin, (-)-epigallocatechin, D-catechin, isorhamnetin-3-*O*-galactoside, arecaine, arecoline, and guvacoline	Water, 50% acetone, 50% methanol, 50% ethanol, ethyl acetate and deep eutectic solvents	Antioxidant – ABTS, DPPH, FRAP, reducing power, CUPRAC and OH radical scavenging assays. It also exhibited anti-microbial and α – glucosidase inhibition	NA	[144]
11	ANE – arecoline, catechin and epicatechin	methanol	Antioxidant – DPPH and ABTS assay	Mature AN (Indonesia; Banda Aceh, North Sumatra, West Kalimantan and West Papua)	[137]
12	ANE – arecoline, catechin and epicatechin	80% methanol	Antioxidant – DPPH, FRAP, ABTS, OH and NO radical scavenging assays	Ripe and unripe AN (Sri Lanka; Kalutara, Kandy, Kegalle, Kurunegala, and Badulla)	[138]
13	Tri-Yannarose – contains areca nut	water	Antioxidant – DPPH, FRAP, ABTS, NBT, ORAC and MCA assays	NA	[139]
14	ANE - polyphenols	50% ethanol	Antioxidant – upregulated Nrf2 and HO1 and downregulated MAPK pathway	NA	[143]
15	ANE – epicatechin and syringic acid	70% ethanol	Antioxidant – DPPH, OH radical scavenging and reducing power assays	NA	[130]
16	ANE	70% ethanol	Antioxidant – DPPH, reducing power, and ABTS assays	NA	[145]
17	ANE	Methanol, water and butanol	Antioxidant - DPPH	Fruit (stage not mentioned)	[133]

Table 5 (continued)

Serial No.	Extracts/Oils/Bioactive compound(s)	Solvents used for Extraction	Action and assay used	Stage of the seed used	References
18	ANE – catechin, epicatechin	80% acetone	Antioxidant – ABTS, FRAP and OH radical scavenging assay	AN Mangalore variety (stage not mentioned)	[146]
19	ANE – PAP1b	Hot water extraction and ethanol precipitation	Antioxidant – DPPH and OH radical scavenging assay	NA	[147]
20	ANE	Methanol, bidistilled water, petroleum ether, methylene chloride, and ethyl acetate	Antioxidant - TEAC assay	AN (1, 2, 3, 4, 6, and 8 months), leaves, crownshafts, fruit shells (4 and 8 months), fibrous skin of mesocarp, exocarp and endocarp, root and adventitious root	[134]
21	ANE	0.1% of methanol, dichloromethane, water, petroleum ether, and ethyl acetate	Antioxidant – comet assay	AN seed, husk, flower bud, bloomed flower and leaf bud (stage not mentioned)	[148]
22	ANE	96% ethanol	Antioxidant – DPPH assay and cytotoxic towards HSC 2 and HSC 3 cells but not toxic to HaCat cells.	NA	[142]

ANE Areca nut extract, *AN* Areca nut and *NA* not available (AN seed used, in case of stage of seed used), *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *FRAP* ferric – reducing antioxidant power, *ABTS* 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), *CUPRAC* cumulative reducing antioxidant capacity, *TEAC* Trolox equivalent antioxidant capacity, *Nrf2* nuclear factor erythroid 2-related factor 2, *HO-1* heme oxygenase-1, *NBT* nitroblue tetrazolium, *MAC* metal-chelating activity, *ORAC* oxygen radical absorbance capacity, *EAC* Ehrlich Ascites Carcinoma cells, *HaCaT* Human Adult low Calcium high Temperature keratinocytes, *HSC* human squamous cell carcinoma

reducing intestinal carbohydrate digestion and postprandial glucose uptake. However, such enzyme-based and acute absorption models primarily reflect postprandial glycemic control and do not by themselves establish broader antidiabetic efficacy.

Additional studies have used animal models of chemically induced diabetes, particularly alloxan and streptozotocin (STZ), both of which predominantly damage pancreatic β-cells and are typically used to model insulin-deficient states. In Sprague–Dawley rats with alloxan-induced diabetes, ANE at 45 mg/200 g body weight improved glucose tolerance, whereas 180 mg/200 g reduced blood glucose levels [25]. Since alloxan induces reactive oxygen species (ROS)-mediated β-cell destruction, the observed effects may reflect antioxidant protection, partial preservation of β-cell function, or indirect glycemic modulation. Another study revealed that ethanolic ANE showed no acute toxicity up to 2000 mg/kg and attenuated alloxan-induced histopathological damage in the liver and kidney, such as biliary hyperplasia, arterial fibrosis, kidney necrosis, and polymorphonuclear cell infiltration, while it also showed synergy with gliclazide in Wistar rats. The authors attributed the protective effects to tannins and procyanidins, although direct compound-specific validation was limited [26]. Similarly, areca flower extracts reduced blood glucose levels in alloxan-induced diabetic rats and mice, with ethanol and aqueous extracts outperforming petroleum ether extracts and improving serum urea levels, cholesterol levels, triglyceride levels, and body weight [27]. Although these findings suggest glucose-lowering and tissue-protective effects in alloxan-based models, they remain specific to chemically induced insulin-deficient states and cannot be directly extrapolated to all forms of diabetes, particularly type 2 diabetes.

In Wistar rats with STZ-induced diabetes, areca leaf extracts prepared in petroleum ether, chloroform, and methanol were also evaluated, with the methanolic extract showing the strongest restoration of body weight and blood glucose by day 15 at 200 mg/kg body weight [28]. The extract additionally normalized AST (aspartate aminotransferase), ALT (alanine aminotransferase), SALP (serum alkaline phosphatase), serum protein, and cholesterol levels, suggesting concomitant hepatometabolic effects. Because STZ, like alloxan, largely reflects β-cell toxicity and insulin deficiency, these results again point to preclinical antihyperglycemic activity in an experimentally induced diabetic state but do not clarify whether the underlying mechanism is primarily pancreatic, antioxidant, hepatoprotective, or due to broader phytochemical interactions. The use of crude extracts and incomplete attribution to specific active constituents further limits mechanistic interpretation.

A separate line of evidence implicates hepatic glucose metabolism. Q-TOF LC–MS (quadrupole time–of–flight–liquid chromatography–mass spectrometry) revealed

Table 6 Beneficial effects of areca nut extracts and its major groups of secondary metabolites

Serial No.	Extracts/Oils/ Bioactive compound(s)	Solvents used for Extraction	Action	Stage of the seed used	References
1	ANE – alkaloids, tannins, phytosterols, and saponins	95% alcohol	Aphrodisiac	Tender AN	[149]
2	AN - arecoline	NA	Suppresses hunger and manage power balance	NA	[150]
3	Arecoline	NA	Inhibits growth of 3T3 – L1 preadipocytes	NA	[151]
4	Arecoline	NA	Proteasome inhibitor	NA	[152]
5	ANE – catechin, tannic acid, arecoline	NA	Cholinergic activity and spasmolytic effect	NA	[155]
6	ANE - gel	Aqueous ethanol	Glaucoma treatment	NA	[153]
7	ANE	Double distilled water	Platelet aggregation	NA	[154]
8	ANE	methanol	Anti - fatigue	NA	[156]
9	ANE - soap	96% ethanol	Anti – fungal (*Candida albicans)*	Tender AN	[157]
10	ANE	ethanol	Anti - allergic	Ripe AN	[158]
11	AN	NA	Anti - venom	Ripe AN	[159]
12	ANE - polyphenols	50% ethanol	Anti – venom (*Naja kaouthia*)	NA	[160]
13	ANE	ethanol	Anti - hypoxic	NA	[161]
14	ANE - polyphenols	NA	Anti - hypoxic	NA	[162]

ANE Areca nut extract, *AN* Areca nut and *NA* – not available (AN seed used, in case of stage of seed used)

procyanidins (monomers to hexadecamers) in ANE, and in cyclic adenosine monophosphate (cAMP)/dexamethasone-induced diabetic hepatocytes, these compounds suppressed gluconeogenesis by downregulating PEPCK and glucose-6-phosphatase mRNA expression [29]. In fasted mice, ANE reduced hepatic phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6 Pase) mRNA (messenger ribonucleic acid) expression and decreased blood glucose while promoting the phosphorylation of glycogen synthase kinase-3β (GSK-3β), potentially through protein kinase B (Akt) or through 5′-adenosine monophosphate-activated protein kinase subunit alpha (AMPKα)-related signalling pathways. These findings suggest that areca-derived procyanidin-rich preparations may modulate hepatic glucose output. Nevertheless, hepatocyte and short-term fasting models primarily provide mechanistic evidence at the cellular and metabolic levels and cannot substitute for comprehensive in vivo or clinical validation.

Collectively, the available evidence indicates that areca nut-derived extracts may affect glucose homeostasis through multiple preclinical pathways, including the inhibition of intestinal carbohydrate digestion, the attenuation of hyperglycemia in chemically induced insulin-deficient animal models, and the suppression of hepatic gluconeogenesis. However, these findings arise from heterogeneous experimental systems that are not directly comparable and do not represent the same diabetic phenotype. Enzyme inhibition assays address mainly postprandial glucose handling, whereas alloxan- and STZ-based studies largely focus on β-cell injury and insulin-deficient states rather than the full pathophysiology of human diabetes, especially type 2 diabetes. Hepatocyte studies further suggest metabolic relevance but remain reductionist. Therefore, the current literature supports only preliminary glucose-modulating activity in preclinical settings, while robust evidence for clinically meaningful antidiabetic efficacy remains lacking. This interpretation is further constrained by variations in extract type, dose, duration, and incomplete identification of the specific bioactive constituents responsible for the observed effects.

Antihypertensive effects

Areca-derived preparations have been investigated for antihypertensive-related activity mainly through two preclinical pathways: inhibition of angiotensin-converting enzyme (ACE) signalling and modulation of endothelial *NO*–cGMP (nitric oxide–cyclic guanine monophosphate) signalling. However, these findings arise from different experimental systems, including chemically characterized extracts, hypertensive animal models, and isolated vascular or endothelial assays, and therefore, these findings should not be interpreted as equivalent evidence of antihypertensive efficacy.

One line of evidence involves ACE inhibition by procyanidin-rich areca fractions. An areca nut extract fraction, Areca II–5–C, demonstrated antihypertensive-related activity and was reported to contain high levels of polymerized procyanidins composed of flavan-3-ol units such as (−)-epicatechin and (+)-catechin. At 15 mg/kg body weight, Areca II–5–C significantly inhibited ACE activity in spontaneously

Table 7 Summary appraisal of included studies by study type and evidence level

Serial No.	Study type	Evidence level	References
1	in vitro	Preclinical Evidence	[21]
2	Animal based	Preclinical Evidence	[22]
3	in vitro and instrument based	Preclinical Evidence	[23]
4	in vitro	Preclinical Evidence	[24]
5	Animal based	Preclinical Evidence	[28]
6	Animal Based	Preclinical Evidence	[25]
7	Animal Based	Preclinical Evidence	[27]
8	in vitro	Preclinical Evidence	[29]
9	Animal Based	Preclinical Evidence	[26]
10	Animal Based	Preclinical Evidence	[30]
11	in vitro	Preclinical Evidence	[32]
12	in vitro	Preclinical Evidence	[31]
13	in vitro	Preclinical Evidence	[40]
14	in vitro	Preclinical Evidence	[39]
15	Animal Based	Preclinical Evidence	[33]
16	in vitro	Preclinical Evidence	[35]
17	Animal Based	Preclinical Evidence	[41]
18	Animal Based	Preclinical Evidence	[34]
19	Animal Based	Preclinical Evidence	[36]
20	Animal Based	Preclinical Evidence	[37]
21	Animal Based	Preclinical Evidence	[38]
22	Animal Based	Preclinical Evidence	[47]
23	Animal Based	Preclinical Evidence	[42]
24	in vitro and Animal Based	Preclinical Evidence	[45]
25	Animal Based	Preclinical Evidence	[43]
26	Animal based	Preclinical Evidence	[46]
27	Animal Based	Preclinical Evidence	[44]
28	in vitro	Preclinical Evidence	[48]
29	Animal Based	Preclinical Evidence	[57]
30	Animal Based	Preclinical Evidence	[58]
31	in vitro	Preclinical Evidence	[59]
32	in vitro	Preclinical Evidence	[51]
33	in vitro	Preclinical Evidence	[55]
34	in vitro	Preclinical Evidence	[49]
35	in vitro	Preclinical Evidence	[50]
36	Animal Based	Preclinical Evidence	[56]
37	Animal Based	Preclinical Evidence	[60]
38	Animal Based	Preclinical Evidence	[61]
39	Animal Based	Preclinical Evidence	[62]
40	in vitro	Preclinical Evidence	[63]
41	in vitro	Preclinical Evidence	[72]
42	in vitro and Animal Based	Preclinical Evidence	[66]
43	in vitro	Preclinical Evidence	[65]
44	in vitro	Preclinical Evidence	[64]
45	in vitro	Preclinical Evidence	[73]
46	in vitro	Preclinical Evidence	[69]
47	in vitro	Preclinical Evidence	[82]
48	in vitro	Preclinical Evidence	[77]
49	in vitro and Animal Based	Preclinical Evidence	[76]
50	in vitro	Preclinical Evidence	[68]
51	Animal Based	Preclinical Evidence	[80]
52	Animal Based	Preclinical Evidence	[81]
53	in vitro	Preclinical Evidence	[78]
54	in vitro	Preclinical Evidence	[75]
55	in vitro	Preclinical Evidence	[74]

Table 7 (continued)

Serial No.	Study type	Evidence level	References
56	Human Based	Insufficient Clinical Evidence	[79]
57	in vitro	Preclinical Evidence	[67]
58	Animal Based	Preclinical Evidence	[83]
59	in vitro	Preclinical Evidence	[85]
60	Animal Based	Preclinical Evidence	[86]
61	Animal Based	Preclinical Evidence	[87]
62	Human Based	Clinical Evidence	[102]
63	Human Based	Clinical Evidence	[89]
64	Human Based	Clinical Evidence	[91]
65	Animal Based	Preclinical Evidence	[92]
66	Human Based	Clinical Evidence	[90]
67	Animal Based	Preclinical Evidence	[98]
68	Animal Based	Preclinical Evidence	[88]
69	Animal Based	Preclinical Evidence	[99]
70	Human Based	Clinical Evidence	[97]
71	Animal Based	Preclinical Evidence	[100]
72	Human Based	Clinical Evidence	[103]
73	in vitro	Preclinical Evidence	[93]
74	Human Based	Clinical Evidence	[94]
75	Human Based	Clinical Evidence	[95]
76	Animal Based	Preclinical Evidence	[104]
77	Human Based	Clinical Evidence	[96]
78	Animal Based	Preclinical Evidence	[84]
79	Animal Based	Preclinical Evidence	[101]
80	in vitro	Preclinical Evidence	[105]
81	in vitro	Preclinical Evidence	[121]
82	in vitro	Preclinical Evidence	[125]
83	in vitro	Preclinical Evidence	[109]
84	in vitro	Preclinical Evidence	[123]
85	in vitro	Preclinical Evidence	[110]
86	in vitro	Preclinical Evidence	[124]
87	in vitro	Preclinical Evidence	[118]
88	in vitro	Preclinical Evidence	[107]
89	in vitro	Preclinical Evidence	[108]
90	Animal Based	Preclinical Evidence	[120]
91	in vitro	Preclinical Evidence	[111]
92	in vitro	Preclinical Evidence	[106]
93	in vitro	Preclinical Evidence	[115]
94	Animal Based	Preclinical Evidence	[119]
95	in vitro	Preclinical Evidence	[114]
96	in vitro	Preclinical Evidence	[112]
97	in vitro	Preclinical Evidence	[116]
98	in vitro	Preclinical Evidence	[122]
99	in vitro	Preclinical Evidence	[113]
100	in vitro	Preclinical Evidence	[117]
101	in vitro	Preclinical Evidence	[126]
102	in vitro	Preclinical Evidence	[135]
103	in vitro	Preclinical Evidence	[127]
104	in vitro	Preclinical Evidence	[128]
105	in vitro	Preclinical Evidence	[129]
106	in vitro	Preclinical Evidence	[131]
107	in vitro	Preclinical Evidence	[136]
108	in vitro	Preclinical Evidence	[140]
109	in vitro	Preclinical Evidence	[141]

Table 7 (continued)

Serial No.	Study type	Evidence level	References
110	in vitro	Preclinical Evidence	[132]
111	in vitro	Preclinical Evidence	[144]
112	in vitro	Preclinical Evidence	[137]
113	in vitro	Preclinical Evidence	[138]
114	in vitro	Preclinical Evidence	[139]
115	in vitro	Preclinical Evidence	[143]
116	in vitro	Preclinical Evidence	[130]
117	in vitro	Preclinical Evidence	[145]
118	in vitro	Preclinical Evidence	[133]
119	in vitro	Preclinical Evidence	[146]
120	in vitro	Preclinical Evidence	[147]
121	in vitro	Preclinical Evidence	[134]
122	in vitro	Preclinical Evidence	[148]
123	in vitro	Preclinical Evidence	[142]
124	Animal Based	Preclinical Evidence	[149]
125	Human based	Observational Clinical Evidence	[150]
126	in vitro	Preclinical Evidence	[151]
127	in vitro	Preclinical Evidence	[152]
128	in vitro	Preclinical Evidence	[155]
129	Animal Based	Preclinical Evidence	[153]
130	Animal Based	Preclinical Evidence	[154]
131	Animal Based	Preclinical Evidence	[156]
132	in vitro	Preclinical Evidence	[157]
133	in vitro	Preclinical Evidence	[158]
134	Human Based	Observational Insufficient Preclinical Evidence	[159]
135	in vitro	Preclinical Evidence	[160]
136	in vitro	Preclinical Evidence	[161]
137	in vitro	Preclinical Evidence	[162]

hypertensive rats (SHRs) and normotensive Wistar Kyoto rats (WKYs). The effect of the measured ACE-related endpoint was stronger in SHRs than in controls, although captopril was markedly more effective at restoring body weight. No significant vascular effects were observed in WKYs, and the extract did not alter norepinephrine-, bradykinin-, or acetylcholine-related responses [30]. These findings suggest that polymerized procyanidin-rich areca fractions may contribute to blood pressure-related effects through ACE-associated mechanisms in hypertensive experimental settings. However, comparisons with captopril should be interpreted cautiously because the endpoints assessed were not fully equivalent, and the findings do not establish clinical antihypertensive efficacy.

Additional evidence comes from phytochemically characterized ethanolic extracts of areca flowers, husks, and seeds. UHPLC–MS/MS (ultrahigh-performance liquid chromatography–tandem mass spectrometry) analysis revealed that flowers were rich in cynaroside, luteolin, and diosmetin; husks contained high levels of schaftoside and diosmetin; and seeds were enriched in catechin, procyanidin B1/B2, and L-epicatechin. ACE inhibition was measured using HHL (hippuryl–*L*–histidyl–*L*–leucine) as a substrate for fluorescence detection, and the ACE inhibitory activity of the seed extracts was stronger than that of the flower or husk extracts. Individual compounds, including epicatechin, rutin, taxifolin, kaempferol, isoquercitrin, and procyanidin B2, were also associated with antihypertensive-related effects [31]. Taken together, these findings support the view that catechin- and procyanidin-rich seed-derived preparations may be the most relevant areca source for ACE-related activity. Nevertheless, because these data are based largely on extract profiling and enzyme inhibition assays, the relative contributions of individual compounds, oligomeric mixtures, and synergistic extract effects remain unresolved.

A separate line of evidence concerns vascular relaxation through *NO*–cGMP signalling. Arecoline was reported to relax human umbilical artery and vein rings and to increase eNOS (endothelial nitric oxide synthase) and cGMP levels, suggesting endothelium-dependent vasorelaxant activity. However, in human umbilical vein endothelial cells (HUVECs), arecoline at concentrations of 100–1000 mM inhibited cell proliferation and induced G2/M arrest, indicating marked cytotoxic or antiproliferative effects at high concentrations [32]. This creates an important interpretive limitation: while arecoline may influence vascular tone

through *NO*–cGMP signalling under certain experimental conditions, the coexistence of endothelial growth-inhibitory effects at high exposure levels raises significant safety and dose–response concerns. Accordingly, vascular relaxation findings should not be interpreted independently of the broader toxicological context.

Collectively, the available evidence suggests that areca-derived fractions may influence blood pressure-related pathways through preclinical mechanisms involving ACE inhibition and endothelial *NO*–cGMP signalling. However, these findings derive from heterogeneous models that are not directly comparable. ACE inhibition assays and hypertensive rat studies primarily indicate possible interactions with renin–angiotensin-related mechanisms, whereas isolated vascular and endothelial cell models address vasorelaxation and cellular signalling under controlled experimental conditions. Therefore, the evidence supports only preliminary antihypertensive-related activity in preclinical systems rather than established therapeutic relevance. This interpretation is further limited by variability in extract type and composition, incomplete isolation of the active constituents, nonequivalent physiological endpoints, and the potential for dose-dependent toxicity, particularly in the case of arecoline.

Anti-inflammatory and analgesic effects

Areca catechu-derived preparations have been investigated for anti-inflammatory and analgesic-related activity across a broad range of preclinical systems, including acute nociceptive assays, carrageenan-based inflammatory models, macrophage systems, enzyme-related assays, and supportive hepatoprotective models. Collectively, these studies suggest that areca-derived extracts may influence inflammatory signalling through several pathways, including COX-2/5-lipoxygenase (5-LOX), mitogen-activated protein kinase (MAPK)/nuclear factor kappa B (NF-κB), and hyaluronidase-associated mechanisms. However, these models represent different biological levels of analysis and should not be interpreted as equivalent evidence of anti-inflammatory or analgesic efficacy.

One line of evidence comes from animal pain and acute inflammation models. In Swiss albino mice with acetic acid-induced gastric pain, methanolic extracts from areca nut stems and leaves reduced pain in a dose-dependent manner, with leaf extracts showing greater activity than stem extracts and aspirin [33]. Additional hydroalcoholic extracts also showed activity in the hot plate test, formalin-induced paw licking, and carrageenan-induced paw edema, suggesting effects in both central and peripheral nociceptive models [34]. These findings indicate that some areca-derived preparations may possess antinociceptive activity in acute preclinical pain settings. However, such models primarily reflect short-term nociceptive and inflammatory responses and do not by themselves define the precise molecular basis of analgesic action.

A second group of studies examined inflammatory signalling pathways more directly. In oral squamous carcinoma (SAS) cells, 80% acetone areca nut extract reduced COX-2 and extracellular signal-regulated kinase (ERK) phosphorylation at lower concentrations, whereas higher concentrations induced COX-2 expression, MAPK activation, and NF-κB translocation. The use of the ERK inhibitor PD98059 supported the involvement of the ERK pathway in COX-2 regulation. In a carrageenan-induced rat air pouch model, the same extract showed dose-dependent anti-inflammatory effects and was reported to be rich in B-type procyanidins [35]. Similarly, a 70% ethanolic extract inhibited COX-2 and 5-LOX, suppressed prostaglandin E_2 (PGE_2), and reduced inflammation in carrageenan-, arachidonic acid-, formalin-, acetic acid-, serotonin-, and histamine-based models, with the aqueous fraction showing the strongest activity [36]. Notably, the extract had little effect on serotonin- or histamine-induced inflammation, suggesting greater activity in pathways associated with prostaglandins and later inflammatory phases. Taken together, these studies support a possible anti-inflammatory role of areca-derived preparations through the modulation of eicosanoid-related and MAPK-associated signalling. Nevertheless, the findings remain model specific, and concentration-dependent bidirectional effects in SAS cells indicate that the direction of response may vary with exposure level and biological context.

Additional studies provide supportive but heterogeneous evidence. In RAW264.7 macrophages stimulated with LPS, areca leaf ethanol extract downregulated iNOS (inducible nitric oxide synthase), COX-2, and NF-κB (nuclear factor kappa B) while also reducing carrageenan-induced paw swelling in rats [37]. Compared with prednisolone and indomethacin, a different preparation, CC-516, inhibited hyaluronidase activity but had weaker effects on croton oil- and arachidonic acid-induced ear edema [38]. Chloroform and methanolic leaf extracts also inhibited protein denaturation and stabilized RBC membranes, with arecoline and apigenin identified as active constituents [39]. Ethanolic extracts from young and mature nuts similarly inhibited protein denaturation, with young nuts showing somewhat stronger activity [40]. In addition, areca nut extract reduced ALT, AST, and malondialdehyde (MDA) levels and improved histological injury in CCl_4-exposed nude Wistar rats, suggesting that hepatoprotective effects may coexist with broader anti-inflammatory activity [41]. While these findings collectively suggest that areca-derived preparations may interact with inflammatory processes at several levels, they arise from diverse systems, ranging from macrophage signalling

to protein stability assays and hepatic injury models, and therefore do not support a single unified mechanism.

Collectively, the available evidence suggests that Areca catechu-derived extracts may exert anti-inflammatory and analgesic-related effects through several preclinical pathways, including modulating COX-2/5-LOX and MAPK/NF-κB signalling, attenuating acute inflammatory responses, inhibiting hyaluronidase-associated matrix degradation, and reducing the expression of selected injury-related biomarkers. However, these findings are derived from highly heterogeneous experimental systems that are not directly comparable. Acute nociceptive assays, carrageenan-based edema models, macrophage signalling studies, protein denaturation assays, and hepatoprotective injury models each address different aspects of inflammatory biology and support different levels of inference. Accordingly, the current literature supports only preliminary anti-inflammatory and antinociceptive activity in preclinical settings. This interpretation is further limited by differences in extract type, solvent system, dose, assay conditions, and incomplete identification of the specific active constituents responsible for the observed effects.

Wound-healing and gastroprotective effects

Areca catechu-derived preparations have been investigated for tissue repair-related activity in both cutaneous wound healing and gastric injury models. Across these studies, the reported effects include enhanced wound contraction, epithelialization, collagen-associated repair, antimicrobial activity in topical formulations, and attenuation of oxidative damage in alcohol-induced gastric lesions. However, these findings arise from the use of different experimental methods, such as topical burn models, incision/excision wound models, and gastric ulcer models; therefore, these findings should not be interpreted as equivalent evidence of a single wound-healing mechanism.

One line of evidence concerns cutaneous wound healing in burn and surgical wound models. In albino Wistar rats with burn wounds, areca nut extract (ANE) improved wound contraction and epithelialization, with oral doses of 100–300 mg/kg body weight resulting in greater healing than dexamethasone treatment did, and topical 2% ANE also enhanced recovery [42, 43]. Additional studies in incision, excision, and dead-space wound models reported that arecoline and ANE-associated alkaloid and polyphenol-containing preparations increased the tensile strength, dry weight, and hydroxyproline content of granulation tissue in incision and excision wounds but had more limited effects on dead-space wounds [44]. These findings suggest that some areca-derived preparations may support cutaneous repair through improved tissue contraction and collagen-associated maturation. However, the differences observed across burn, incision, excision, and dead-space wound models indicate that the apparent efficacy is context-dependent and may not reflect a uniform wound-healing effect across all tissue-repair settings.

Topical formulations provide further but still preclinical evidence. Ointments containing 2.5% and 5% ANE were reported to inhibit the growth of several bacterial species, including *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Acinetobacter baumannii*, *Escherichia coli*, and *Staphylococcus aureus*, with activity comparable to that of neomycin sulfate in disk diffusion assays. In a grade IIA burn model in Sprague–Dawley rats, the 5% formulation was more effective for 14 days, reducing wound diameter and inflammatory cell infiltration, promoting early scab formation, and increasing neovascularization and collagen deposition [45]. Taken together, these findings suggest that topical areca-based preparations may combine antimicrobial and local tissue repair-related effects in experimental burn settings. Nevertheless, formulation-based studies are influenced by concentration, excipient composition, and local delivery conditions, which makes direct comparison with systemic extract studies difficult.

A separate group of studies examined gastric mucosal injury rather than cutaneous wound healing. In ethanol-induced gastric ulcer models, ANE reduced the levels of markers of oxidative and inflammatory injury, such as MDA, nitric oxide, myeloperoxidase, and xanthine oxidase, while restoring the levels of glutathione, sialic acid, and DNA [46]. In a related alcohol-induced gastric lesion model in Sprague–Dawley rats, ANE improved ulcer indices and increased catalase, superoxide dismutase (SOD), glutathione-S-transferase (GST), and glutathione (GSH) levels [47]. These observations are consistent with a gastroprotective effect associated with reduced oxidative stress and improved endogenous antioxidant defense. However, gastric mucosal protection in alcohol-induced ulcer models should be interpreted separately from cutaneous wound repair, as these systems represent different tissue environments, mechanisms of injury, and therapeutic endpoints.

Collectively, the available evidence suggests that *Areca catechu*-derived preparations may exert tissue-protective effects in preclinical models through several pathways, including enhancing cutaneous wound contraction and collagen-associated repair, providing antimicrobial support in topical formulations, and attenuating oxidative injury in gastric mucosal damage. However, these findings are derived from heterogeneous systems that are not directly comparable. Burn wound models, incision/excision wound assays, topical antimicrobial formulations, and ethanol-induced gastric lesion models address different aspects of tissue injury and recovery and therefore support different levels of

inference. Accordingly, the current literature supports only preliminary wound-healing- and gastroprotective-related activity in preclinical settings. This interpretation is further limited by variability in dose units, formulation type, model design, and incomplete identification of the specific active constituents responsible for the observed effects, as well as the need for broader safety evaluation before translational application.

Anti-helminth effects

Areca catechu-derived preparations have been investigated for anthelminth-related activity across a wide range of preclinical and veterinary models, including fluke mortality studies, ovicidal and larvicidal assays, surrogate worm paralysis models, field stool-based observations, and enzyme-target experiments. Collectively, these studies suggest that areca-derived extracts may affect helminths through several possible pathways, including through tegumental damage, paralysis, disruption of nutrient handling, ovicidal effects, and interference with detoxification-related enzymes. However, these systems represent different parasite taxa, life stages, host contexts, and experimental endpoints and therefore should not be interpreted as directly comparable evidence of a single anthelminthic mechanism.

One group of studies examined direct effects on adult helminths, particularly liver flukes and worm paralysis models. Areca nut extract (ANE) was reported to be highly effective against *Fasciola hepatica* and *Fasciola gigantica*, with complete efficacy against *F. gigantica* in the reported model and activity exceeding that of some commercial comparators, such as albendazole and oxyclozanide. Motility scoring and H&E staining revealed marked structural injury, including tegument separation, shrinkage, vacuolation, disruption of villi, loss of tegumental spines, and damage to reproductive and intestinal structures [48, 49]. In a separate model, ethanolic extracts of areca root induced paralysis and death in *Pheretima posthuma* more rapidly than albendazole did [50]. These findings are consistent with direct parasiticidal effects in adult helminth or surrogate worm systems, potentially involving surface disruption and neuromuscular impairment. Nevertheless, differences between trematode, nematode, and surrogate annelid models limit direct comparisons of potency and mechanism across studies.

A second line of evidence concerns ovicidal and larvicidal effects. Aqueous ANE containing arecoline, tannins, and proanthocyanidins showed strong ovicidal activity against *Ascaridia galli* eggs and disrupted multiple developmental stages, including morula, tadpole, vermiform, and larval forms [51–54]. Morphological studies have also described deformities in treated *A. galli* eggs and associated structures [55]. A 50% acetone extract also showed larvicidal activity against dog roundworms, and GC–MS analysis revealed fatty acids, aliphatic alcohols, and tannins, with the strongest activity associated with medium-chain fatty acids such as lauric acid and with selected aliphatic alcohols [56]. These studies suggest that areca-derived preparations may interfere with helminth development and survival at early life stages, possibly through membrane-disruptive or physicochemical effects. However, the attribution of activity to individual constituents remains tentative in most cases because the tested preparations were chemically complex mixtures.

Further evidence comes from host-level or applied veterinary observations. In poultry and ruminants, the results of stool-based studies suggested that compared with albendazole, mature areca preparations could reduce or eliminate a range of helminths or helminth eggs in chickens, goats, and sheep, with broader apparent activity in some settings, although Valbazen was more effective against pinworms. In chickens, doses above 1 g/kg body weight were associated with declining health, indicating tolerability [57]. Similarly, treatment of *A. galli*-infected chickens was associated with improved hematological parameters and body weight recovery, which is consistent with improved host conditions following deworming [54]. These findings suggest possible practical antiparasitic relevance in livestock settings, but they should be interpreted cautiously because field-type observations integrate parasite burden, host response, dose tolerance, and husbandry conditions rather than isolation of a single direct anthelminthic effect.

A separate mechanistic line of evidence concerns biochemical targets. Compared with pyrantel pamoate, which acts primarily through neuromuscular paralysis, ethanolic ANE was proposed to impair nutrient absorption in *Ascaris lumbricoides* from pigs, with a 30% solution reportedly eradicating worms within 6–12 h [58]. In *Cotylophoron cotylophorum*, ANE at 0.5 mg/mL inhibited glutathione-S-transferase (GST) activity, suggesting that ANE interferes with the detoxification capacity of the parasite [59]. These findings indicate that areca-derived preparations may affect helminths through mechanisms beyond gross surface damage or paralysis, including disruption of metabolic or detoxification-related pathways. However, such mechanistic inferences remain preliminary and may not be generalizable across helminth species or life stages.

Collectively, the available evidence suggests that Areca catechu-derived preparations may exert anthelminth-related activity through several preclinical and veterinary pathways, including direct tegmental injury, paralysis-associated effects, ovicidal and larvicidal activity, interference with nutrient-related or physicochemical processes, and inhibition of detoxification-associated enzymes. However, these findings are derived from highly heterogeneous systems

involving different parasite taxa, developmental stages, host species, and assay formats and are therefore not directly comparable. Adult fluke mortality studies, egg-stage ovicidal assays, larvicidal experiments, surrogate worm paralysis models, stool-based livestock observations, and GST inhibition assays each support different levels of inference. Accordingly, the current literature supports only preliminary anthelminth activity in heterogeneous experimental settings. This interpretation is further limited by variations in extract type, dose, tolerance, host context, and incomplete validation of the specific active constituents responsible for the observed effects.

Cardiometabolic and cardioprotective-related effects

Areca catechu-derived preparations have been investigated for their preclinical cardiometabolic activity through two main pathways: reducing intestinal cholesterol levels and lipid absorption and attenuating the oxidative modification of low-density lipoprotein (LDL). These findings suggest that areca-derived extracts may influence biochemical processes relevant to atherosclerotic risk. However, the available evidence is limited to preclinical enzymatic, dietary, and oxidation models and therefore should not be interpreted as direct evidence of cardioprotective efficacy.

One line of evidence relates to intestinal lipid and cholesterol handling. Ethanolic areca nut extract (ANE) was fractionated into chloroform, ethyl acetate, n-butanol, and aqueous fractions, among which the n-butanol fraction showed the strongest in vitro inhibition of pancreatic cholesterol esterase (pCEase), followed by the aqueous fraction. In Sprague–Dawley rats fed a cholesterol-enriched diet, 0.5% (w/w) ANE reduced intestinal pCEase activity and decreased plasma cholesterol levels, whereas plasma triglyceride levels were not significantly altered. The extract also inhibited ACAT2 (acyl CoA–cholesterol acetyltransferase) but not ACAT1, and radiolabelled cholesterol was retained predominantly in the intestine rather than appearing in the circulation, suggesting reduced intestinal absorption [60]. These findings are consistent with a possible hypocholesterolemic mechanism involving the modulation of intestinal cholesterol esterification and absorption. However, they remain limited to dietary and enzyme-related preclinical models and do not establish broader cardiovascular benefits.

Additional studies support a similar intestinal mechanism. Two formulations, Areca I (95% ethanolic extract) and Areca II (n-butanol plus aqueous fractions), reduced plasma cholesterol levels, plasma triglyceride levels, and pCEase activity in Sprague–Dawley rats, with radiolabelled cholesteryl oleate again accumulating more in the intestine than in blood [61]. In a related study, 0.5% ANE also reduced plasma triglyceride levels and pCEase activity, inhibited ACAT, and increased intestinal retention of radiolabelled triolein, suggesting reduced lipid absorption [62]. Taken together, these studies indicate that areca-derived preparations may consistently affect intestinal lipid handling in cholesterol-fed rat models, although the magnitude of the effects is modest and varies according to fraction and formulation. The data also suggest that activity is distributed across multiple extract fractions rather than being attributable to a single clearly validated constituent.

A separate line of evidence concerns antioxidant protection against LDL oxidation. Areca inflorescence extracts prepared using boiling water, ambient water, and ethanol were tested for their ability to delay Cu^{2+}-induced LDL oxidation. The boiling-water extract showed the strongest activity, delayed LDL oxidation, and reduced malondialdehyde formation in the thiobarbituric acid reactive substances (TBARS) assay and exhibited ferric reducing and metal-chelating properties. The reported phenolic compounds included gallic acid, coumalic acid, epicatechin, fumaric acid, naringenin, and rutin, with epicatechin identified as the most abundant [63]. These findings suggest that some areca-derived preparations may reduce oxidative processes relevant to LDL modification, which is mechanistically relevant to atherosclerotic biology. Nevertheless, LDL oxidation assays represent a biochemical model of oxidative susceptibility rather than direct evidence of in vivo cardiovascular protection.

Collectively, the available evidence suggests that *Areca catechu*-derived preparations may exert cardiometabolic-related activity in preclinical settings through two main pathways: reducing intestinal cholesterol and lipid absorption and attenuating LDL oxidative modification. However, these findings are derived from heterogeneous experimental systems that are not directly comparable. Enzyme inhibition assays and cholesterol-fed rat studies primarily support effects on intestinal lipid handling, whereas LDL oxidation models address antioxidant and metal-chelating properties relevant to lipoprotein stability. Accordingly, the current literature supports only preliminary cardiometabolic or cardioprotective-related activity at the mechanistic level rather than established cardioprotective efficacy. This interpretation is further limited by modest effect sizes, variation among fractions and formulations, incomplete identification of the active constituents, and the absence of robust in vivo cardiovascular outcome studies or clinical validation.

Anticancer-related effects

Areca catechu-derived preparations and arecoline have been investigated for anticancer-related activity across multiple preclinical systems, including tumor cell lines,

fraction-based autophagy studies, metabolic reprogramming models, and selected in vivo or genotoxicity-related experiments. Collectively, these studies suggest that areca-derived materials may exert antiproliferative effects through several mechanisms, including oxidative stress-associated cell cycle arrest, apoptosis-related signalling, autophagy induction, and metabolic disruption. However, these findings must be interpreted with caution because the same plant and some of its constituents, especially arecoline, are also associated with toxicological and carcinogenic concerns under other exposure contexts. Therefore, short-term cytotoxicity in tumor models should not be interpreted as direct evidence of therapeutic suitability or safety.

One group of studies examined oxidative stress-associated growth arrest and cytostasis. In oral KB epithelial cancer cells, ANE and arecoline inhibited proliferation after 24 h without clear apoptosis, an effect associated with reduced intracellular glutathione, elevated reactive oxygen species (ROS), mitochondrial membrane hyperpolarization, increased IL-6, and cell cycle arrest at G2/M; S-phase arrest was also reported at earlier time points [64]. In prostate cancer cells, arecoline induced G2/M arrest in PC-3 cells and G0/G1 arrest in LNCaP cells, with cell type-specific changes in cyclins and cyclin-dependent kinase regulators. ROS appeared to contribute to this response, as *N*-acetylcysteine attenuated the arrest phenotype. However, arecoline also induced G2/M arrest in normal RWPE-1 cells [65], indicating that the cytostatic effects were not clearly tumor-selective. Taken together, these findings are consistent with oxidative stress-associated antiproliferative activity, but they also raise important selectivity concerns, since similar growth-inhibitory effects may extend to nonmalignant cells.

A second line of evidence concerns apoptosis-related pathways in susceptible tumor cell lines. In BCC-1/KMC basal cell carcinoma cells, arecoline reduced IL-6 levels, suppressed IL-6/STAT3 signalling, increased p53 and p21, inhibited cdc25C activity, and triggered apoptosis, while no comparable cytotoxicity or arrest was observed in HaCaT keratinocytes in that study [66]. In oral squamous carcinoma models, ANE induced G1 arrest in HSC-3 cells and sub-G1 arrest and apoptosis in HSC-2 cells, accompanied by reduced Ki-67 expression [67]. In cholangiocarcinoma RMCCA1 cells, ANE increased caspase-3, cleaved PARP, p53, and CHK2 levels, together with ERK1/2, p38, and Akt signalling [68]. In HSC-2 and HSC-3 cells, ANE-associated apoptosis was also linked to caspase-3 activation and phosphatidylserine externalization [69–71]. These findings suggest that, in some tumor cell contexts, areca-derived preparations may activate apoptosis-related signalling rather than merely inducing growth arrest. Nevertheless, the direction and magnitude of the response remain cell line dependent, and the extent to which these effects reflect therapeutic selectivity rather than generalized cytotoxic stress remains uncertain.

A third group of studies highlights autophagy-related and fraction-dependent effects. In hepatocellular carcinoma cells, ANE induced ROS-associated autophagy and apoptosis, with increased Beclin-1 expression, LC3-II conversion, p62 degradation, BAX upregulation, and Bcl-2 downregulation [72]. Additional ANE fractions in the 30–100 kDa and ≥100 kDa range induced autophagic features, including cytoplasmic vacuolization, LC3-II accumulation, and acidic vesicle formation, across several cell lines and peripheral blood lymphocytes, and proteoglycans were proposed as major active components of the 30–100 kDa fraction [73, 74]. In other tumor cell systems, ANE also inhibited mTOR phosphorylation and promoted autophagy, whereas arecoline was more often linked to apoptosis-associated changes such as caspase-3 activation, chromatin condensation, and micronucleation [75]. These observations suggest that different areca-derived fractions may trigger distinct stress responses, with autophagy appearing more prominent in some high-molecular-weight preparations and apoptosis more evident with arecoline in certain settings. However, because these responses depend strongly on the fraction type, dose, and cell system, they do not support a single unified anticancer mechanism.

Additional evidence implicates metabolic reprogramming and general cytotoxicity. Arecoline was reported to inhibit ACAT1 tetramerization and alter PDH acetylation, thereby suppressing glycolysis and promoting oxidative phosphorylation, with associated antiproliferative effects in vitro and in vivo [76]. Standard cytotoxicity assays also revealed that aqueous ANE was toxic not only to MCF-7 cells but also to Vero cells [77], and in KB cells, arecoline caused dose-dependent outcomes ranging from S/G2/M arrest at lower concentrations to apoptosis and necrosis at higher concentrations [78]. These findings support the view that areca-derived materials can disrupt tumor cell survival through multiple stress-related pathways. Moreover, the observed toxicity toward non-tumor-derived cell systems and the dose-dependent shift from cytostasis to overt cytotoxicity further underscore the need to distinguish tumor-selective effects from broader cellular injury.

A separate and essential consideration concerns long-term safety, genotoxicity, and exposure context. Although ANE was reported to reduce urinary N-nitroso-L-proline levels in a human nitrosation model, an effect attributed to catechin, epicatechin, and proanthocyanidins [79] does not negate the broader concern that arecoline and areca-related exposures may generate harmful nitrosated intermediates under certain conditions. In long-term animal studies, chronic betel quid exposure in hamsters did not result in

malignant tumors in one model [80], whereas weak carcinogenicity was observed in Swiss albino mice exposed to high-dose, unprocessed, sun-dried areca nut, while processed variants were less harmful [81]. Arecoline in combination with sodium nitrite under acidic conditions also generated weakly genotoxic N-nitroso compounds and suppressed DNA and protein synthesis in Hep2 cells [82]. Taken together, these data indicate that the biological significance of areca-derived preparations depends strongly on the processing, chemical environment, dose, and exposure context. Accordingly, the anticancer-related cytotoxicity observed in short-term experimental systems cannot be interpreted independently of the broader carcinogenic and genotoxic concerns associated with areca exposure.

Collectively, the available literature indicates that *Areca catechu*-derived preparations and arecoline can exert antiproliferative effects in preclinical models through multiple mechanisms, including oxidative stress-associated cell cycle arrest, apoptosis-related signalling, autophagy induction, and metabolic disruption. However, these findings arise from highly heterogeneous systems that differ in cell type, fraction composition, dose and end point, and they do not consistently demonstrate tumour selectivity. Importantly, the same body of literature also contains evidence of toxicity toward nonmalignant cells, dose-dependent genotoxic or necrotic effects, and context-dependent carcinogenic concerns related to areca exposure and nitrosation. Therefore, the current evidence supports only preliminary anticancer-related activity in experimental settings and does not establish therapeutic safety or translational suitability. Any future consideration of areca-derived anticancer applications would require rigorous activity-guided fractionation, direct comparison with normal-cell controls, careful dose–response evaluation, and dedicated long-term toxicological assessment.

Neuropharmacological effects

Areca catechu-derived preparations and alkaloids have been investigated for a broad range of neuropharmacological-related effects, including antidepressant-like activity, modulation of monoaminergic and cholinergic systems, neuroinflammatory and oxidative pathways, anticonvulsant and GABAergic actions, myelination-related effects, and cognitive outcomes, in preclinical models and limited human studies. However, these findings arise from highly heterogeneous systems, including rodent behavioral assays, inflammatory cell models, zebrafish seizure paradigms, tissue-slice preparations, small human infusion studies, and observational field data. Therefore, they should not be interpreted as equivalent evidence of unified neurotherapeutic efficacy.

One line of evidence concerns antidepressant-like and monoamine-related effects. Fractionated ethanolic areca nut extract, including hexane and aqueous fractions, reduced immobility time in forced swim and tail suspension tests in rodents without major locomotor stimulation at selected doses, and brain homogenate assays revealed marked monoamine oxidase (MAO) inhibition [83]. In additional studies, ethanolic and aqueous extracts also reduced immobility in the forced swim test, whereas aqueous preparations increased hippocampal serotonin, 5-HIAA (5-hydroxyindoleacetic acid), and noradrenaline levels [84]. These findings suggest that some areca-derived preparations may exert antidepressant-like effects in rodent screening models, potentially through monoaminergic mechanisms involving MAO-related activity and altered neurotransmitter balance. However, forced swim and tail suspension paradigms primarily provide evidence for behavioural screening and do not by themselves establish antidepressant efficacy in humans. In addition, differences in formulation-dependent tolerability, including localized tissue injury with ethanolic preparations in some settings, indicate that biological activity must be interpreted alongside safety and route-of-administration considerations.

A second group of studies suggests anti-inflammatory, anticonvulsant, and neuroprotective activity. In BV-2 microglia, ANE suppressed anthracene-induced reactive oxygen species and inflammatory cytokine expression while inhibiting JNK, p38, and NF-κB signalling and increasing HO-1 (heme oxygenase-1) expression [85]. In adult zebrafish exposed to pentylenetetrazole (PTZ), aqueous ANE delayed seizure onset, inhibited acetylcholinesterase, increased GABA levels and antioxidant defences, reduced glutamate levels and lipid peroxidation, and attenuated histopathological neuronal injury [86]. These findings are consistent with possible neuroprotective effects mediated through anti-inflammatory, antioxidant, and neurotransmitter-related pathways. Nevertheless, microglial cell assays and zebrafish seizure models provide mechanistic or screening-level evidence and cannot be directly extrapolated to clinical anticonvulsant or neuroprotective efficacy.

Additional evidence concerns GABAergic transmission and myelination-related effects. Arecoline increased myelin basic protein expression in the frontal cortex of cuprizone-treated mice and improved Y-maze performance [87]. In spinal cord and cerebellar slice preparations from cats, arecaidine and guvacine inhibited GABA and β-alanine uptake, enhancing GABAergic transmission, and high-dose arecaidine attenuated bicuculline-induced seizures [88]. These findings suggest that areca alkaloids may modulate inhibitory neurotransmission and myelination-related processes in selected experimental settings. However, the diversity of models, species, and doses makes it difficult to infer a single

coherent therapeutic mechanism, and the relevance of high-dose anticonvulsant effects to safe pharmacological application remains uncertain.

A separate set of studies explored cognition- and Alzheimer's-related outcomes. Small randomized or controlled human studies reported dose-dependent cognitive improvement with intravenous arecoline in some patients with Alzheimer's disease, particularly at lower doses, although the compound showed rapid metabolism, a short plasma half-life, and a narrow apparent therapeutic window [89–91]. Additional work reported changes in local cerebral glucose utilization and neurovascular coupling in animal models [92], while aqueous ANE inhibited β-amyloid aggregation and BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) activity and protected PC12 cells from oxidative injury [93]. Further small human studies have suggested that verbal memory, picture recognition, or scopolamine-impaired learning are beneficial at selected doses, whereas prolonged or high-dose infusions produce mixed outcomes and psychomotor suppression [94–97]. Taken together, these observations suggest possible cholinergic and cognition-related activity, but the evidence remains limited by small sample sizes, intravenous administration, short-term designs, formulation dependence, and dose-related adverse effects. Accordingly, these findings should be interpreted as preliminary translational signals rather than evidence of an established therapeutic benefit in Alzheimer's disease or cognitive impairment.

Other studies indicate broader central and peripheral pharmacology. A field study in Micronesia revealed milder schizophrenia symptom scores among betel nut chewers, although the observational design and potential confounding substantially limit interpretation [98]. Additional extracts inhibited antimigraine-related inducible nitric oxide synthase (iNOS), platelet aggregation, and acetylcholinesterase-related activity and enhanced gastrointestinal motility [99–101]. Arecoline also induced cortisol escape in a dexamethasone suppression model and promoted REM sleep initiation in a scopolamine-sensitive manner, suggesting cholinergic and hypothalamic–pituitary–adrenal involvement [102, 103]. Compared with dry ANE, wet ANE improved radial arm maze performance in rats, possibly reflecting compositional differences such as increased arecoline content [104]. These findings indicate that areca-derived preparations affect multiple neural and peripheral systems, but they also underscore the breadth and non-selectivity of their pharmacology. As a result, the current evidence does not support a single unified neuropharmacological profile.

Collectively, the available literature suggests that *Areca catechu*-derived preparations and alkaloids have diverse neuropharmacological-related effects, including monoaminergic, anti-inflammatory, anticonvulsant, GABAergic, cholinergic, and cognition-related effects, in experimental settings. However, these findings derive from highly heterogeneous models that are not directly comparable and support different levels of inference. Rodent behavioral assays, inflammatory cell models, zebrafish seizure studies, tissue-slice preparations, small human infusion studies, and observational field reports each provide distinct but limited evidence. Accordingly, the current literature supports only preliminary neuropharmacological activity with restricted translational relevance. This interpretation is further constrained by rapid arecoline metabolism, narrow dose ranges, potential dose-dependent toxicity, broad peripheral pharmacology, and incomplete identification of the specific active constituents responsible for the observed effects.

Antimicrobial and Antiparasitic effects

Areca catechu-derived preparations have been investigated for a broad range of antimicrobial- and antiparasitic-related activities, including antibacterial, antibiofilm, antifungal, antiviral, antimalarial, food-preservation, and plant-protective effects. However, these findings arise from highly heterogeneous systems, including disk diffusion and MIC (minimum inhibitory concentration)/MBC (minimum bactericidal concentration) assays, animal infection models, food challenge studies, plant–pathogen experiments, isolated-compound analyses, and formulation-enhanced preparations. Therefore, they should not be interpreted as evidence of a single coherent antimicrobial profile.

One line of evidence concerns antibacterial and oral health-related activity. Multiple aqueous, methanolic, ethanolic, acetone, alcohol, and ethyl acetate extracts inhibited common bacterial pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, and *Salmonella* spp., and selected enteric organisms, although the potency varied according to the solvent, geographic source, and test organism, and in several studies, it remained lower than that of standard antibiotics such as gentamicin or penicillin [105–108]. Essential oils from areca nut reduced *the* virulence-related properties of *Streptococcus mutans*, including surface hydrophobicity, glucosyltransferase activity, biofilm formation, and extracellular polysaccharide production, while specific isolated polyphenolic inhibitors reduced insoluble glucan synthesis [109, 110]. Additional extracts or compounds, including jacareubin, quercetin, cinnamic acid, and ethyl acetate fractions from Sri Lankan betel quid, showed activity against MRSA (methicillin-resistant *Staphylococcus aureus*), oral biofilms, and *Porphyromonas gingivalis* [111–113]. Taken together, these findings suggest that areca-derived preparations may be particularly relevant to topical or oral-care-related antimicrobial applications,

especially where antibiofilm or antivirulence effects are important. However, the evidence remains strongly fraction- and assay dependent, and direct comparisons across studies are limited by inconsistent methodologies and a lack of standardized head-to-head testing.

A second group of studies suggests antifungal, food-preservation, and plant-protective activities. Areca extracts inhibited *Candida albicans* in several formulations, reduced aflatoxin production by *Aspergillus flavus*, and in some cases showed synergistic activity with chitosan [114–117]. Methanolic, ethanolic, and aqueous extracts also reduced microbial growth in food-preservation challenge studies, including cake-storage models, suggesting possible preservative-related effects in a food matrix [105]. In addition, pericarp extracts inhibited *Colletotrichum gloeosporioides* both in vitro and in mango fruit, with activity exceeding that of benomyl in one anthracnose model [118]. These findings indicate that some areca-derived preparations may have practical relevance in fungal control, food preservation, and plant–pathogen suppression. Nevertheless, such applications require separate considerations of safety, formulation stability, sensory impact, and real-world matrix effects, which were not consistently addressed in the available studies.

Another line of evidence concerns antiparasitic and host-modulating effects. A 96% ethanolic extract improved white blood cell counts in *Staphylococcus aureus*-infected rats without major changes in hematological toxicity indicators [119]. Butanol extracts and crude areca preparations also showed antimalarial activity against *Plasmodium berghei* in mice, with moderate suppression and survival benefits [120]. These observations suggest that some areca-derived preparations may combine host-modulating and antiparasitic effects. However, the reported selectivity indices were modest, and the evidence remains preliminary, supporting only exploratory antiparasitic relevance rather than established therapeutic applicability.

Further studies reported pathogen-specific activity against mycobacteria, viruses, and other organisms. Phenolic-rich methanolic and ethanolic fractions showed selective activity against *Mycobacterium tuberculosis* H37Rv [121], whereas aqueous and methanolic extracts inhibited HIV-1 (human immunodeficiency virus) protease activity, and other preparations showed in vitro activity against Newcastle disease virus and egg drop syndrome virus [122, 123]. Antimicrobial peptides isolated from areca also inhibited *Staphylococcus epidermidis*, *E. coli*, and *Proteus mirabilis* [124]. These findings indicate that areca-derived materials contain multiple classes of potentially active compounds, including phenolics, peptides, procyanidins, triterpenes, phytosterols, fatty acids, and volatile components. However, most of this evidence remains in vitro and is highly dependent on extraction, purification, and organism-specific assay conditions.

Finally, formulation and processing approaches appear to influence potency. Compared with crude extracts, silver nanoparticles synthesized from aqueous ANE showed greater antimicrobial activity [125], and volatile-profiling methods coupled with targeted extraction identified numerous compounds with activity against *Streptococcus canis* [126]. These findings suggest that selective extraction and formulation strategies may concentrate active constituents and enhance the observed antimicrobial effects. Moreover, they further emphasize that the activity is highly preparation-dependent and cannot be generalized to all areca-derived materials.

Collectively, the available evidence suggests that *Areca catechu*-derived preparations possess broad antimicrobial- and antiparasitic-related activity in experimental systems, including antibacterial, antibiofilm, antifungal, antiviral, antimalarial, and plant-protective effects. However, these findings derive from highly heterogeneous models that are not directly comparable. Disk-diffusion assays, MIC/MBC studies, food challenge systems, animal infection models, plant–pathogen experiments, isolated-compound analyses, and nanoparticle formulations each support different levels of inference. Accordingly, the current literature supports only preliminary and context-dependent antimicrobial-related activity. This interpretation is further limited by variations in extract type, geographic source, processing, assay standardization, organism susceptibility, and incomplete validation of the specific active constituents responsible for the observed effects. Practical application, particularly in oral care, food preservation, or targeted antimicrobial formulation development, would require standardized extraction, activity-guided fractionation, dose–response evaluation, comparison with conventional agents, and careful safety assessment.

Antioxidant properties

Areca catechu-derived preparations have been widely investigated for their antioxidant-related activity through chemical assays, cell-based systems, extraction comparisons, specialized fractions, and selected DNA protection models. Collectively, these studies suggest that antioxidant activity is influenced by solvent polarity, plant part, ripeness, regional origin, extraction method, and multicomponent formulation context. However, the findings arise from heterogeneous assay systems that capture different aspects of antioxidant behavior, such as radical scavenging, reducing power, metal chelation, or cellular stress–response signalling, and therefore should not be interpreted as directly comparable measures of a single antioxidant effect.

One major line of evidence concerns solvent- and extraction-dependent variation. In multiple studies, methanolic, ethanolic, and aqueous extracts frequently showed strong antioxidant activity and high phenolic content, particularly in seed-derived preparations enriched in compounds such as epicatechin and syringic acid [127–134]. In some reports, methanolic extracts of mature or unripe seeds outperformed conventional comparators such as BHT (butylated hydroxytoluene), vitamin C, or ascorbic acid in selected assays, whereas butanol fractions showed relatively low activity [131–134]. Other studies, however, reported stronger activity in ethyl acetate, n-hexane, or chloroform extracts than in methanolic preparations [135]. Taken together, these findings suggest that polar solvents often yield phenolic-rich extracts with strong radical-scavenging or reducing activity, but the reported superiority of any one solvent is not uniform across studies. Differences in plant part, maturity, extract composition, and assay type likely account for much of the apparent inconsistency.

A second group of studies indicates that antioxidant readouts also vary according to regional source, ripeness, and multicomponent formulation. Compared with some individual components, betel quid, which includes areca nut as one component, showed greater antioxidant activity in selected assays, suggesting possible combinatorial effects [136]. Regional comparisons revealed particularly strong activity in West Papua samples in one Indonesian study [137], while Sri Lankan ripe samples often outperformed unripe samples in several antioxidant assays and were associated with catechin, epicatechin, and arecoline contents [138]. Tri-Yannarose, a multicomponent medicinal formula containing areca, also showed strong antioxidant activity with low cytotoxicity in Vero cells [139]. These findings suggest that antioxidant activity is shaped not only by extract solvent but also by geographic origin, developmental stage, and formulation context. However, such multicomponent systems complicate the attribution of activity to areca nuts alone.

Cell-based studies provide additional but distinct evidence. Ethanolic ANE and selected flavonoid-rich fractions showed direct radical-scavenging activity and were cytotoxic to selected carcinoma cell lines, such as Ehrlich ascites carcinoma, HSC-2, HSC-3, SGC-7901, and SMMC-7721, while some normal cells, such as HaCaT cells, were less affected [140–142]. In LPS-stimulated RAW264.7 macrophages, 50% ethanolic ANE upregulated Nrf2 and HO-1 while downregulating MAPK-related genes, suggesting the activation of endogenous antioxidant defense pathways in addition to direct scavenging effects [143]. These findings indicate that areca-derived preparations may act not only through chemical antioxidant activity but also through the modulation of cellular oxidative stress responses. Moreover, the coexistence of antioxidant signalling and selective cytotoxicity means that such effects should be interpreted carefully, particularly because dose, fraction type, and cell context strongly influence the balance between protective and growth-inhibitory outcomes.

A further line of evidence concerns extraction innovations and specialized fractions. Deep eutectic solvents, ultrasound-assisted extraction, and pH-controlled acetone extraction were reported to improve extraction efficiency and alter phytochemical composition, often enhancing antioxidant readouts in comparison with conventional solvent systems [144–146]. These methods appeared to shift extract profiles toward different proportions of alkaloids, phenolics, and flavonoids, thereby influencing assay performance. In addition, in chemical assays, the activity of PAP1b, a neutral polysaccharide fraction, is not confined to only low-molecular-weight phenolic fractions [147]. These findings suggest that extraction technology and fraction type substantially influence measured antioxidant behavior. However, they also further complicate cross-study comparisons unless extract composition is reported in a standardized way.

Distinct evidence also suggests that these compounds have a genetic potential. In comet assays, methanolic and methylene chloride husk extracts protected against H_2O_2-induced DNA damage [148]. These findings indicate that some chemically distinct areca-derived fractions may provide antioxidant-linked protection at the level of oxidative DNA injury, complementing the radical-scavenging and cellular signalling data described above. Nevertheless, such genetic observations remain limited and should be interpreted as preliminary evidence from specific experimental systems rather than broad evidence of in vivo antioxidant protection.

Collectively, the available literature suggests that *Areca catechu*-derived preparations possess antioxidant-related activity across multiple experimental contexts, including radical scavenging, reducing power, metal chelation, cellular oxidative stress signalling, and protection against oxidative DNA injury. However, these findings are derived from highly heterogeneous systems that are not directly comparable. Chemical assays, such as DPPH (2,2-diphenyl-1-picrylhydrazy), ABTS (2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)), FRAP (ferric reducing antioxidant power), and TEAC (Trolox equivalent antioxidant capacity), and related methods measure different antioxidant properties, whereas cell-based studies and DNA protection assays address distinct biological levels of response. Accordingly, the current literature supports only preliminary antioxidant-related activity, which is strongly dependent on the extract type, solvent, plant part, maturity, formulation, and assay choice. This interpretation is further limited by inconsistent extract characterization, varying comparator standards, and

incomplete definitions of the specific active constituents responsible for the observed effects. Future work would benefit from activity-guided fractionation, standardized extract reporting, and paired evaluation of protective versus cytotoxic responses across defined dose ranges.

Other reported medicinal effects

A range of additional biological activities, including reproductive and metabolic effects, proteasome-related activity, ocular and hemostatic effects, fatigue- and mitochondrial-related effects, antiallergic activity, antivenom-related observations, and protection against hypoxic injury, have been reported for Areca catechu-derived preparations in preclinical models and traditional-use contexts. However, these findings arise from highly heterogeneous systems, including behavioural assays, cell-based studies, topical formulations, traditional practices, venom models, and systemic animal physiology. Therefore, they should be interpreted as context-specific preliminary signals rather than as evidence of a unified therapeutic profile.

One group of studies suggests reproductive, metabolic, and proteostasis-related effects. In male Wistar albino rats, areca nut increased mounting and intromission frequencies and reduced mounting latency and postejaculatory interval, suggesting aphrodisiac-like activity in this behavioural model [149]. Other studies reported appetite suppression, modulation of energy balance, and inhibition of 3T3-L1 preadipocyte differentiation by areca nut or arecoline, indicating the possible relevance of these processes to weight-regulatory pathways [150, 151]. Arecoline tripeptides were also reported to inhibit proteasome activity through interactions with catalytic threonine residues [152]. These findings suggest that areca-derived materials may influence reproductive behavior, adipocyte-related metabolism, and proteasome-associated pathways in experimental settings. However, these endpoints represent very different biological domains and do not support a single integrated pharmacological conclusion.

Additional studies have reported ocular, hemostatic, and smooth-muscle-related effects. An ethanol ANE formulated into ocular films with chitosan and hydroxypropyl methylcellulose reduced intraocular pressure in rabbits with dexamethasone-induced glaucoma [153]. In contrast, ANE also induced platelet aggregation and thromboxane B2 production in rabbits [154], suggesting a proaggregatory hemostatic effect that may be beneficial or adverse depending on the clinical context. Previous work has also described a cholinomimetic reduction in atrial contractility caused by the arecoline and spasmolytic effects of catechin and tannic acid on smooth muscle [155]. Taken together, these findings indicate that areca-derived preparations may affect ocular, vascular, cardiac, and gastrointestinal physiology, but their direction of benefit or risk depends strongly on the formulation, dose, and intended use.

Another line of evidence concerns fatigue-related, mitochondrial, and topical antifungal effects. In sleep-deprived C57BL/6J mice, methanolic ANE improved fatigue resistance and increased ATP production in the colon, as discussed in relation to gut–liver axis function, mitochondrial health, and microbiota balance [156]. Areca-based soaps, with or without *Quercus infectoria*, also showed antifungal activity against *Candida albicans* [157]. These findings suggest that some areca-derived preparations may have supportive effects on fatigue-related metabolic stress or topical antifungal formulations. However, these models address very different biological questions, and the evidence remains formulation specific and preliminary.

A separate group of studies suggests antiallergic and immunomodulatory effects. Ethanolic ANE reduced anaphylactic responses and inhibited the expression of inflammatory mediators such as TNF-α, MAPK, and ERK1/2 in RBL-2H3 mast cells and ICR mice while also downregulating FcεRI expression and reducing IgE-mediated mast-cell degranulation [158]. These findings are consistent with the possible modulation of IgE-dependent allergic pathways. Nevertheless, the current evidence remains preclinical and does not establish clinical efficacy for allergic disease.

Traditional-use reports and controlled venom studies provide another distinct evidence stream. Processed unripe areca nut ("chikni supari") has been used traditionally as a topical antivenom material, with color changes after application interpreted as toxin-related interactions [159]. In controlled venom studies, ANE reduced necrotic activity in *Naja kaouthia* venom models and markedly inhibited acetylcholinesterase activity, with tannin-rich fractions being suggested as possible contributors [160]. These findings suggest that condensed tannin-rich areca preparations may interact with venom-related injury processes. However, traditional reports are not equivalent to controlled pharmacological validation, and the exact mechanism, specificity, and safety of venom neutralization remain insufficiently defined.

Further evidence suggests protective effects in hypoxia and high-altitude injury models. In rats exposed to hypoxic or hypobaric conditions, ethanolic ANE improved blood gas parameters, reduced lung water and inflammatory infiltration, preserved tissue architecture, and increased antioxidant enzyme activity while reducing the levels of malondialdehyde and inflammatory markers [161, 162]. These findings are consistent with antioxidant- and anti-inflammatory-related protection against hypoxic injury in preclinical models. However, these studies involved relatively high doses and short-term animal exposure systems;

thus, their relevance to safe therapeutic applications in humans remains uncertain.

Collectively, the available literature suggests that *Areca catechu*-derived preparations may exert a wide range of additional biological effects in experimental settings, including behavioral, metabolic, ocular, hemostatic, immunomodulatory, topical, antivenom-related, and hypoxia-protective effects. However, these findings derive from highly heterogeneous systems that are not directly comparable and support different levels of inference. Behavioural assays, cell-based mechanistic studies, topical formulations, traditional-use observations, venom models, and systemic physiology studies each address distinct biological questions. Accordingly, the current literature supports only preliminary and context-dependent evidence for these additional reported activities. This interpretation is further limited by variations in extract composition, route of administration, dose, and endpoint selection, as well as the need for more explicit safety evaluation, particularly for systemic applications and alkaloid-rich preparations.

Safety, toxicological considerations, and future directions

From the studies collected, major gaps can be identified, which limits the translation of the beneficial effects discussed in this review. A standardized extract characterization, activity-guided fractionation and direct comparison of isolated compounds vs. crude extracts is required to establish mechanistic claims. Dose–response and long-term therapeutic window studies, normal-cell and toxicity panels, would aid in carefully designed clinical studies, where justified, as most studies were preclinical therapeutic claims that were not plausible. Additionally, the pharmacokinetics and metabolism of areca nut and its constituents need to be investigated closely.

Although the results of the present review summarize the reported beneficial biological effects of areca nut, these findings should not be interpreted as a recommendation for therapeutic use or as evidence of overall safety. A growing body of literature indicates that areca nut and its constituents may also exert harmful, genotoxic, and carcinogenic effects under certain exposure conditions. For example, ANE has been reported to induce HIF-1α expression in oral cancer cells, leading to autophagy that may protect cells from ANE-induced apoptosis [163]. Activation of the MEK1/ERK/c-Fos pathway has likewise been implicated in promoting survival and altering cell cycle progression in oropharyngeal cancer cells [164]. These findings suggest that the biological effects of areca-derived preparations are not uniformly beneficial and may, in some contexts, support rather than suppress cell survival.

Additional toxicological evidence further limits therapeutic interpretation. ANE has been associated with genotoxicity in Swiss albino mice, with effects linked to glutathione depletion, reactive oxygen species generation, and increased damage following longer exposure [165]. In vitro, ANE has also been shown to induce 8-hydroxydeoxyguanosine formation, indicating oxidative DNA damage [166]. In animal studies, areca nut administration produced oral and gastric lesions in hamsters [167], whereas observational data from Guam and Saipan reported a higher frequency of potentially malignant oral disorders among areca nut chewers [168]. Arecoline administration in Wistar rats for 14 consecutive days also resulted in dose-dependent toxicity, with adverse effects observed at high doses (1000 mg/kg) but not at lower doses (100 mg/kg) under the reported study conditions [169]. In addition, meta-analytic evidence has linked areca nut chewing with metabolic disorders and chronic kidney disease, further underscoring the broader systemic safety concerns associated with exposure [170, 171]. At the neuropharmacological level, arecoline has also been shown to excite ventral tegmental area dopaminergic neurons, a finding discussed in relation to dependent and cessation-related research [172].

On the basis of the available literature, these findings indicate that the beneficial biological activities discussed in this review must be interpreted within a broader toxicological context. The current literature does not justify therapeutic recommendation, and the coexistence of reported bioactivity with genotoxic, carcinogenic, metabolic, and dose-dependent toxic effects highlights the need for caution, particularly for systemic use and alkaloid-rich preparations.

Several major gaps in the literature also limit the translation of the reported beneficial effects. Many studies rely on crude extracts with incomplete phytochemical characterization, making it difficult to assign activity to specific constituents or to distinguish the effects of isolated compounds from those of complex mixtures. Standardized extract characterization, activity-guided fractionation, and direct comparison of isolated compounds versus crude extracts are therefore needed to support these mechanistic claims. In addition, dose–response studies, therapeutic window assessments, long-term toxicity evaluations, and normal-cell safety panels are needed before any meaningful clinical interpretation can be made. Pharmacokinetic and metabolic studies are also limited and should be prioritized, particularly for arecoline and other major alkaloids. Overall, future research should focus on standardized preparation methods, mechanistic validation, defined safety profiling, and carefully designed clinical studies only where the preclinical evidence is sufficiently robust to justify further translation.

Conclusion

A comprehensive search was conducted across four major databases, the Cochrane Library, EMBASE, PubMed, and Web of Science, along with references from additional studies and reviews to explore the medicinal properties and mechanisms of action of areca nuts (*Areca catechu* L.). Following a systematic screening based on predefined inclusion criteria, 137 studies were selected for analysis. Among these, research on antioxidant, antimicrobial, and neuropharmacological properties each accounted for the highest percentage of publications, at 16%. A notable increase in publications on the medicinal applications of *Areca catechu* was observed between 2010 and 2019. This review systematically discusses the known mechanisms and therapeutic potential of *Areca catechu* in terms of its anticancer-related effects; antimicrobial and antiparasitic, anthelminthic, antioxidant, antihypertensive, antidiabetic, cardiometabolic and cardioprotective-related effects; and antiaging, wound healing and gastroprotective, neuropharmacological, analgesic, and anti-inflammatory effects, along with other health-related benefits. In addition, the review highlights various safety and toxicological considerations regarding areca nut consumption and future directions for the current literature on areca nut.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11694-026-04393-9.

Acknowledgements We thank Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India and FIST, DST, New Delhi and K-FIST, VGST, Govt. of Karnataka and DBTBUILDER (BT/INF/22/SP43065/2021), Govt. of India for the facilities. The authors (NKR, MK, SU and AK) are grateful to MAHE for providing Dr. T.M.A. Pai Ph.D. scholarship. AK is grateful to ICMR grant (No. 59/08/2022-TRM/BMS) for financial assistance as Project Associate I respectively We are indebted to Dr. B.S. Satish Rao, Professor and Director, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, India, for his encouragement and support.

Funding Open access funding provided by Manipal Academy of Higher Education, Manipal. The author declare that no funds, grants, or other support were received during the preparation of this manuscript. Open access funding provided by Manipal Academy of Higher Education (MAHE), Manipal-576104, Karnataka, India.

Declarations

Ethical Statement Not applicable since this study did not employ any animals or human subjects.

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. P.C. Gupta, S. Warnakulasuriya, Addict. Biol. **7**, 77–83 (2002). https://doi.org/10.1080/13556210020091437
2. S.M. Amudhan, H. Begum, K.B. Hebbar, Int. J. Pharm. Sci. Res. **3**, 4151–4157 (2012). www.ijpsr.com
3. K.S. Bhat, S. Bhat, P.K. Kalladka, Int. J. Sci. Res. Methodol. **17**, 95–109 (2021). www.ijsrm.humanjournals.com
4. A. Ansari, T. Mahmood, P. Bagga, F. Ahsan, A. Shamim, S. Ahmad, M. Shariq, S. Parveen, Food Front. **2**, 163–183 (2021). https://doi.org/10.1002/fft2.70
5. K. Patidar, R. Parwani, S. Wanjari, A. Patidar, JOMFP 19, 69–76 (2015). https://doi.org/10.4103/0973-029X.157205
6. S.S. Strickland, Addict. Biol. **7**, 85–97 (2002). https://doi.org/10.1080/13556210120091446
7. Directorate of Arecanut and Spices Development, DASD Annual Report 2020–2021, (2021)
8. A.G. Mathew, V.S. Govindarajan, Phytochemistry. **3**, 657–665 (1964)
9. H. Sun, W. Yu, H. Li, X. Hu, X. Wang, Nutrients. **16**, 695 (2024). https://doi.org/10.3390/nu16050695
10. G. Nonaka, F. Hsu, I. Nishioka, J. Chem. Soc. Chem. Commun. 781–783 (1981)
11. S.P. Pathak, S.S. Mathur, Fat, J. Sci. Food Agric. **5**, 461–465 (1954)
12. V. Raghavan, H.K. Baruah, Econ. Bot. **12**, 315–345 (1958)
13. International Agency for Research on Cancer, Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 85), (2004)
14. International Agency for Research on Cancer, IARC Monographs Volume 128: Acrolein, Crotonaldehyde, and Arecoline, (2021)
15. K. Senevirathna, R. Pradeep, Y.A. Jayasinghe, S.M. Jayawickrama, R. Illeperuma, S. Warnakulasuriya, R.D. Jayasinghe, Clin. Pract. **13**, 326–346 (2023). https://doi.org/10.3390/clinpract13020030
16. P. Zhang, N.Q.E. Chua, S. Dang, A. Davis, K.W. Chong, S.S. Prime, N. Cirillo, Int. J. Mol. Sci. **23**, 1637 (2022). https://doi.org/10.3390/ijms23031637
17. K.S. Bhat, P. Kumar, K.S. Bhat, IJDMSR 4, 21–32 (2022). https://doi.org/10.35629/5252-04042132
18. K.S. Bhat, A. Devasya, M. Sarpangala, Int. J. Food Sci. Nutr. **2**, 46–51 (2017). www.foodsciencejournal.com
19. K.S. Bhat, S. Bhat, IJMHR. **4**, 35–40 (2018). www.medicalsciencejournal.com
20. M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J.M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, BMJ. **372**, 71 (2021). https://doi.org/10.1136/bmj.n71

21. K.-K. Lee, J.-J. Cho, E.-J. Park, J.-D. Choi, Int. J. Cosmet. Sci. **23**, 341–346 (2001)
22. C.-L. Weng, C.-C. Chen, H.-H. Tsou, T.-Y. Liu, H.-T. Wang, Drug Chem. Toxicol. **45**, 353–359 (2022). https://doi.org/10.1080/01480545.2019.1696813
23. K.-K. Lee, J.-D. Choi, Int. J. Cosmet. Sci. **21**, 285–295 (1999). https://doi.org/10.1046/j.1467-2494.1999.196563.x
24. H. Begum, V. Mohideen, Pharmacogn Mag. **4**, 223–227 (2008). https://www.researchgate.net/publication/286629146
25. M.Y. Musdja, A. Nurdin, A. Musir, I.O.P. Conf, Ser. Earth Environ. Sci. **462**, 012036 (2020). https://doi.org/10.1088/1755-1315/462/1/012036
26. S.A. Al-Omran, S. Dharmashree, K.V. Anil Kumar, S. Nagaraja, J. Pharmacol. Pharmacother. **15**, 69–77 (2024). https://doi.org/10.1177/0976500X241231365
27. R. Ghate, V.P. Patil, S. Hugar, N.H. Matha, N.V. Kalyane, Asian Pac. J. Trop. Dis. **4**, 148–S152 (2014). https://doi.org/10.1016/S2222-1808(14)60430-8
28. S. Mondal, S. Bhattacharya, M. Biswas, JAPER 2, 10–17 (2012)
29. P.-L. Huang, C.-W. Chi, T.-Y. Liu, FCT. **55**, 137–143 (2013). https://doi.org/10.1016/j.fct.2012.12.057
30. J.-I. Inokuchi, H. Okabe, T. Yamauchi, A. Nagamatsu, G.-L. Nonaka, I. Nishioka, Life Sci. **38**, 1375–1382 (1986)
31. F. Song, M. Tang, H. Wang, Y. Zhang, K. Zhu, X. Chen, H. Chen, X. Zhao, Ind. Crops Prod. **189**, 115787 (2022). https://doi.org/10.1016/j.indcrop.2022.115787
32. F.-C. Kuo, D.-C. Wu, S.-S.F. Yuan, K.-M. Hsiao, Y.-Y. Wang, Y.-C. Yang, Y.-C. Lo, J. Perinat. Med. **33**, 399–405 (2005). https://doi.org/10.1515/JPM.2005.072
33. M.R. Barman, M.S. Uddin, S. Akhter, M.N. Ahmed, Z. Haque, S. Rahman, F. Mostafa, M. Zaman, F.A. Noor, M. Rahmatullah, ANAS 5, 223–226 (2011). https://www.researchgate.net/publication/215610973
34. A.M. Bhandare, A.D. Kshirsagar, N.S. Vyawahare, A.A. Hadambar, V.S. Thorve, FCT. **48**, 3412–3417 (2010). https://doi.org/10.1016/j.fct.2010.09.013
35. P.-L. Huang, C.-W. Chi, T.-Y. Liu, FCT. **48**, 306–313 (2010). https://doi.org/10.1016/j.fct.2009.10.014
36. S. Khan, M.H. Mehmood, A.N.A. Ali, F.S. Ahmed, A. Dar, A.-H. Gilani, J. Ethnopharmacol. **135**, 654–661 (2011). https://doi.org/10.1016/j.jep.2011.03.064
37. K.P. Lee, G.W. Sudjarwo, J.-S. Kim, S. Dirgantara, W.J. Maeng, H. Hong, Nutr. Res. Pract. **8**, 267–271 (2014). https://doi.org/10.4162/nrp.2014.8.3.267
38. K.K. Lee, J.-D. Choi, Int. J. Cosmet. Sci. **21**, 275–284 (1999). https://doi.org/10.1046/j.1467-2494.1999.196590.x
39. N.G. D'Souza, J. Fernandes, S. D'Souza, Int. J. Pharm. Sci. Res. **12**(9), 5065–5071 (2021). https://doi.org/10.13040/IJPSR.0975-8232.12
40. L. Legasari, A. Wati, D.F. Yani, J. Stannum, Sains Ter. Kim. **5**, 93–99 (2023). https://doi.org/10.33019/jstk.v5i2.4376
41. P. Pithayanukul, S. Nithitanakool, R. Bavovada, Molecules. **14**, 4987–5000 (2009). https://doi.org/10.3390/molecules14124987
42. D.K. Verma, M. Bharat, D. Nayak, T. Shanbhag, V. Shanbhag, R.S. Rajput, Int. J. Pharmacol. Clin. Sci. **1**, 74–78 (2012). www.ijpcs.net
43. M. Bharat, D.K. Verma, V. Shanbhag, R.S. Rajput, D. Nayak, A. Amuthan, Int. J. Pharm. Sci. Rev. Res. **25**, 145–148 (2014). www.globalresearchonline.net
44. S. Azeez, S. Amudhan, S. Adiga, N. Rao, N. Rao, L.A. Udupa, KMJ. **39**, 48–52 (2007). https://www.researchgate.net/publication/284789478
45. N.M.D. Sandhiutami, F. Fahleni, N. Miftahurrohmah, N.K.A. Widhiyasari, A. Azalia, I. Amalia, J. Herbmed Pharmacol. **12**, 388–398 (2023). https://doi.org/10.34172/jhp.2023.42
46. H.V. Begum, S.M. Amudhan, Pharmacologyonline. **1**, 97–1006 (2008). https://www.researchgate.net/publication/287941825
47. R.R.N. Anthikat, A. Michael, Int. J. Pharm. Sci. Res. **2**, 165–170 (2011). www.ijpsr.com
48. E.C. Yamson, G.A.S.P. Tubalinal, V.V. Viloria, C.N. Mingala, J. Adv. Vet. Anim. Res. **6**, 44–49 (2019). https://doi.org/10.5455/javar.2019.e310
49. N. Jeyathilakan, K. Murali, A. Anandaraj, S.A. Basith, Indian J. Anim. Sci. **80**, 1070–1074 (2010)
50. A.A. Baby, R.R. K, Int. J. Pharm. Pharm. Sci. **6**, 486–489 (2014). http://www.webalice.it/siamseeds/Database/Areca-catechu-
51. C.B. Salvedia, Thai J. Agric. Sci. **56**, 38–46 (2023)
52. J.H. Lorent, J. Quetin-Leclercq, M.-P. Mingeot-Leclercq, Org. Biomol. Chem. **12**, 8803–8822 (2014). https://doi.org/10.1039/c4ob01652a
53. L. Greiffer, E. Liebau, F.C. Herrmann, V. Spiegler, Sci. Rep. **12**, 18850 (2022). https://doi.org/10.1038/s41598-022-23566-2
54. T. Nyambuya, R. Mautsa, S. Mukanganyama, BMC Complement. Altern. Med. **17**, 124 (2017). https://doi.org/10.1186/s12906-017-1636-0
55. W.W. Mubarokah, W. Nurcahyo, J. Prastowo, K. Kurniasih, Vet. World. **12**, 877–882 (2019). https://doi.org/10.14202/vetworld.2019.877-882
56. F. Kiuchi, N. Miyashita, Y. Tsuda, K. Kondo, H. Yoshimura, Chem. Pharm. Bull. (Tokyo). **35**, 2880–2886 (1987)
57. M.G.G. Tangalin, AJHR 1, 230–243 (2011). https://doi.org/10.7828/ajoh.v1i1.166
58. I. Ismail, E.I. Sunaryo, B. Kordja, A. Nurkhotimah, S. Mahmuddin, J. Res. Pharm. **28**, 571–578 (2024). https://doi.org/10.29228/jrp.719
59. K.M. Dhanraj, L. Veerakumari, J. World, Pharm. Pharm. Sci. **4**, 1117–1125 (2015). www.wjpps.com
60. Y.B. Park, S.-M. Jeon, S.-J. Byun, H.-S. Kim, M.-S. Choi, Life Sci. **70**, 1849–1859 (2002)
61. S.-M. Jeon, H.-S. Kim, T.G. Lee, S.-H. Ryu, P.-G. Suh, S.-J. Byun, Y.B. Park, M.-S. Choi, Ann. Nutr. Metab. **44**, 170–176 (2000). www.karger.com
62. S.-J. Byun, H.-S. Kim, S.-M. Jeon, Y.B. Park, M.-S. Choi, Ann. Nutr. Metab. **45**, 279–284 (2001). www.karger.com
63. W. Chen, C. Zhang, Y. Huang, F. Cheng, Y. Shen, R. Wang, M. Tang, Y. Zheng, S. Zhao, Int. J. Food Sci. Nutr. **63**, 236–241 (2012). https://doi.org/10.3109/09637486.2011.620946
64. M.C. Chang, Y.S. Ho, P.H. Lee, C.P. Chan, J.J. Lee, L.J. Hahn, Y.J. Wang, J.H. Jeng, Carcinogenesis. **22**, 1527–1535 (2001)
65. L.J. Shih, J.Y. Wang, J.Y. Jheng, A.C. Siao, Y.Y. Lin, Y.W. Tsuei, Y.C. Kuo, C.P. Chuu, Y.H. Kao, Int. J. Mol. Sci. **21**, 1–18 (2020). https://doi.org/10.3390/ijms21239219
66. L.-W. Huang, B.-S. Hsieh, H.-L. Cheng, Y.-C. Hu, W.-T. Chang, K.-L. Chang, Toxicol. Appl. Pharmacol. **258**, 199–207 (2012). https://doi.org/10.1016/j.taap.2011.11.001
67. L.M. Sari, G.P. Subita, E.I. Auerkari, JRMDS 9, 279–306 (2021). www.jrmds.in
68. S. Leelawat, K. Leelawat, Oncol. Lett. **13**, 961–966 (2017). https://doi.org/10.3892/ol.2016.5488
69. L.M. Sari, G.P. Subita, E.I. Auerkari, F1000Res. **7**, 723 (2018). https://doi.org/10.12688/f1000research.14856.1
70. D. Mandal, P.K. Moitra, S. Saha, J. Basu, FEBS Lett. **513**, 184–188 (2002). https://doi.org/10.1016/S0014-5793(02)02294-9
71. H.M. Hankins, R.D. Baldridge, P. Xu, T.R. Graham, Traffic. **16**, 35–47 (2015). https://doi.org/10.1111/tra.12233
72. P.-L. Wei, C.-S. Hung, H.-H. Lu, U. Batzorig, C.-Y. Huang, Y.-J. Chang, Int. J. Med. Sci. **18**, 3452–3462 (2021). https://doi.org/10.7150/ijms.61570
73. M.-H. Lin, W.-F. Hsieh, W.-F. Chiang, W.-Z. Hong, Y.-R. Hsu, Y.-C. Cheng, T.-C. Chen, K.-C. Hsu, P.Y. Lina, S.Y. Liu, Y.C. Liu,

Oral Oncol. **46**, 822–828 (2010). https://doi.org/10.1016/j.oraloncology.2010.08.002
74. M.-H. Lin, S.-Y. Liu, Y.-C. Liu, Autophagy. **4**, 967–968 (2008). https://doi.org/10.4161/auto.6821
75. S.-Y. Liu, M.-H. Lin, Y.-R. Hsu, Y.-Y. Shih, W.-F. Chiang, C.-H. Lee, T.-H. Chou, Y.-C. Liu, J. Biomed. Sci. **15**, 823–831 (2008). https://doi.org/10.1007/s11373-008-9273-8
76. J. Fan, R. Lin, S. Xia, D. Chen, S.E. Elf, S. Liu, Y. Pan, H. Xu, Z. Qian, M. Wang, C. Shan, L. Zhou, Q.Y. Lei, Y. Li, H. Mao, B.H. Lee, J. Sudderth, R.J. DeBerardinis, G. Zhang, T. Owonikoko, M. Gaddh, M.L. Arellano, H.J. Khoury, F.R. Khuri, S. Kang, P.W. Doetsch, S. Lonial, T.J. Boggon, W.J. Curran, J. Chen, Mol. Cell. **64**, 859–874 (2016). https://doi.org/10.1016/j.molcel.2016.10.014
77. C.C. Anajwala, R.M. Patel, S.L. Dakhara, J.K. Jariwala, J. Adv. Pharm. Technol. Res. **1**, 245–252 (2010). http://www.ncbi.nlm.nih.gov/pubmed/22247852
78. P.-H. Lee, M.-C. Chang, W.-H. Chang, T.-M. Wang, Y.-J. Wang, L.-J. Hahn, Y.-S. Ho, C.-Y. Lin, J.-H. Jeng, Toxicology. **220**, 81–89 (2006). https://doi.org/10.1016/j.tox.2005.07.026
79. H.F. Stich, H. Ohshima, B. Pignatelli, J. Michelon, H. Bartsch, J. Natl. Cancer Inst. **70**, 1047–1050 (1983). http://jnci.oxfordjournals.org/
80. L.J. Dunham, K.M. Herrold, J. Natl, Cancer Inst. **29**, 1047–1067 (1962). https://doi.org/10.1093/jnci/29.6.1047
81. A.R. Rao, P. Das, Int. J. Cancer. **43**, 728–732 (1989)
82. K.K. Wary, R.N. Sharan, Int. J. Cancer. **47**, 396–400 (1991)
83. A. Dar, S. Khatoon, G. Rahman, Atta-Ur-Rahman Phytomedicine. **4**, 41–45 (1997)
84. G. Abbas, S. Naqvi, S. Erum, S. Ahmed, A. Atta-Ur-Rahman, Dar, Phytother Res. **27**, 39–45 (2013). https://doi.org/10.1002/ptr.4674
85. S. Janpaijit, M. Sukprasansap, T. Tencomnao, A. Prasansuklab, Nutrients. **16**, 2882 (2024). https://doi.org/10.3390/nu16172882
86. A.P.R. Nadig, M. Suman, S. Sahyadri, K.L. Mehdi, Krishna, ADTM 23, 1137–1152 (2023). https://doi.org/10.1007/s13596-022-00664-0
87. Z. Xu, A. Adilijiang, W. Wang, P. You, D. Lin, X. Li, J. He, Neuroreport. **30**, 134–138 (2019). https://doi.org/10.1097/WNR.0000000000001172
88. D. Lodge, G.A.R. Johnston, D.R. Curtis, S.J. Brand, Brain Res. **136**, 513–522 (1977)
89. S. Asthana, N.H. Greig, H.W. Holloway, K.C. Raffaele, A. Berardi, M.B. Schapiro, S.I. Rapoport, T.T. Soncrant, Clin. Pharmacol. Ther. **60**, 276–282 (1996)
90. K.C. Raffaele, A. Berardi, P.P. Morris, S. Asthana, J.V. Haxby, M.B.S.S.I. Rapoport, T.T. Soncrant, Prog Neuropsychopharmacol. Biol. Psychiatry. **15**, 643–648 (1991)
91. K.C. Raffaele, J. Asthana, A. Berardi, J.V. Haxby, P.P. Morris, M.B. Schapiro, T.T. Soncrant, Neuropsychopharmacology. **15**, 163–170 (1996)
92. K. Maiese, H.H. Holloway, D.M. Larson, T.T. Soncrant, Brain Res. **641**, 65–75 (1994)
93. R.J. Sullivan, J.S. Allen, C. Otto, J. Tiobech, K. Nero, BJPsych. **177**, 174–178 (2000)
94. T.T. Soncrant, K.C. Raffaele, S. Asthana, A. Berardi, P.P. Morris, J.V. Haxby, Psychopharmacol. (Berl). **112**, 421–427 (1993)
95. P.N. Tariot, R.M. Cohen, J.A. Welkowitz, T. Sunderland, P.A. Newhouse, D.L. Murphy, H. Weingartner, Arch. Gen. Psychiatry. **45**, 901–905 (1988). http://archpsyc.jamanetwork.com/
96. J.E. Christie, A. Shering, J. Ferguson, A.I.M. Glen, BJPsych. **138**, 46–50 (1981)
97. N. Sitaram, H. Weingartner, J.C. Gillin, Science. **201**, 274–276 (1978)
98. M. Bozorgi, Z. Najafi, S. Omidpanah, A. Sadri, Z. Narimani, F.H. Moghadam, N. Edraki, T. Akbarzadeh, M. Saeedi, Bol. Latinoam. Caribe Plantas Med. Aromat. **20**, 406–415 (2021). https://doi.org/10.37360/blacpma.21.20.4.30
99. A. Bhandare, A. Kshirsagar, N. Vyawahare, P. Sharma, R. Mohite, J. Ethnopharmacol. **136**, 267–270 (2011). https://doi.org/10.1016/j.jep.2011.04.039
100. M.N. Ghayur, S.F. Kazim, H. Rasheed, A. Khalid, M.I. Jumani, M.I. Choudhary, A.H. Gilani, J. Chin. Integr. Med. **9**, 619–624 (2011)
101. A.H. Gilani, M.N. Ghayur, Z.S. Saify, S.P. Ahmed, M.I. Choudhary, A. Khalid, Life Sci. **75**, 2377–2389 (2004). https://doi.org/10.1016/j.lfs.2004.03.035
102. G.A. Charles, P.J. Orsulak, A.J. Rush, C.L. Fulton, Biol. Psychiatry. **37**, 811–816 (1995)
103. N. Sitaram, A.M. Moore, T.C. Gillin, Sleep. **1**, 83–90 (1978)
104. M. Joshi, K. Gaonkar, S. Mangoankar, S. Satarkar, Int. Curr. Pharm. J. 2012, 128–132 (2012). http://www.icpjonline.com/documents/Vol1Issue6/01.pdf
105. N. Jam, R. Hajimohammadi, P. Gharbani, A. Mehrizad, Biomed. Res. Int. 2021, 6663399 (2021). https://doi.org/10.1155/2021/6663399
106. A. Karphrom, S. Suknaisilp, P. Pradeepasaena, S. Tantratian, International Conference on the Role of Universities in Hands-On Education Rajamangala University of Technology Lanna, Chiang-Mai, Thailand 209–14 (2009)
107. A.A. Chin, D.F. Clariza, B.S. Renalyn, S.S.B. Marie, F.T. Regine, R.M. Frederick, Int. J. Res. Ayurveda Pharm. **4**, 876–880 (2013). https://doi.org/10.7897/2277-4343.04620
108. M.A. Rahman, P. Sultana, M.S. Islam, M.T. Mahmud, M.M.O. Rashid, F. Hossen, Banglad J. Microbiol. **31**, 19–23 (2014)
109. S. Liu, T. Zhang, Z. Li, Y. Wang, L. Liu, Z. Song, Front. Cell. Infect. Microbiol. **13**, 1140689 (2023). https://doi.org/10.3389/fcimb.2023.1140689
110. M. Iwamoto, K. Uchino, T. Toukairin, K. Kawaguchi, T. Tatebayashi, H. Ogawara, Y. Tonosaki, Chem. Pharm. Bull. (Tokyo). **39**, 1323–1324 (1991)
111. Z. Xing, M. Wen-li, Z. Yan-bo, L. Jian, D. Wen-jun, D. Hao-fu, J. Trop. Subtrop Bot. **17**, 74–76 (2009)
112. S. Shamim, M. Khan, IRJP. **8**, 29–37 (2017). https://doi.org/10.7897/2230-8407.0810178
113. M.P. Paranagama, N.S. Piyarathne, T.L. Nandasena, S. Jayatilake, A. Navaratne, B.P. Galhena, S. Williams, J. Rajapakse, K. Kita, BMC Complement. Med. Ther. **20**, 259 (2020). https://doi.org/10.1186/s12906-020-03048-6
114. R.R.N. Anthikat, A. Michael, V.A. Kinsalin, S. Ignacimuthu, IJPCR 4, 1–3 (2014)
115. M.B. Cyriac, P. Vidya, I. Varghese, M. Shantaram, M. Jose, Int. J. Res. Ayurveda Pharm. **3**, 81–84 (2012). www.ijrap.net
116. P. Dewi, D.R. Indriyanti, L. Herlina, A.S. Gunawan, C.E. Lusiana, J. Teknol. **84**, 133–138 (2022). https://doi.org/10.11113/jurnalteknologi.v84.17252
117. R. Putriningrum, A. Nurhidayati, T. Umarianti, K.D. Listyaningsih, W.R. Agustin, IJPMBS 5, 142–145 (2016). https://doi.org/10.18178/ijpmbs.5.2.142-145
118. P. Yenjit, M. Issarakraisila, W. Intana, K. Chantrapromma, Postharvest Biol. Technol. **55**, 129–132 (2010). https://doi.org/10.1016/j.postharvbio.2009.09.003
119. L.M. Sari, R.F. Hakim, Z. Mubarak, A. Andriyanto, Vet. World. **13**, 134–140 (2020). https://doi.org/10.14202/vetworld.2020.134-140
120. J.-H. Jiang, S.-Y. Jung, Y.C. Kim, S.R. Shin, S.T. Yu, H. Park, KJPP 23, 495–498 (2009)
121. A. Raju, S. De, M. Ray, M. Degani, Int. J. Mycobacteriol. **10**, 13–18 (2021). https://doi.org/10.4103/ijmy.ijmy_199_20
122. I.T. Kusumoto, T. Nakabayashi, H. Kida, H. Miyashiro, M. Hattori, T. Namba, K. Shimotohno, Phytother Res. **9**, 180–184 (1995)
123. R.R.N. Anthikat, A. Michael, JYP 1, 42–45 (2009). https://doi.org/10.4103/0975-1483.51874

124. D.J. Hazarika, K. Sood, Der Pharmacia Lettre. **7**, 1–7 (2015). www.scholarsresearchlibrary.com
125. B. Pradeep, P. Hemba, A.K. Jagadeesh, C.G. Ramakakanavar, S. Nayak, C.V. Rao, J. Agri Nat. **53**, 386–394 (2019)
126. M. Machová, T. Bajer, D. Šilha, K. Ventura, P. Bajerová, Molecules. **26**, 7422 (2021). https://doi.org/10.3390/molecules26247422
127. A. Hannan, S. Karan, T.K. Chatterjee, Int. J. Pharm. Pharm. Sci. **4**, 420–427 (2012)
128. N. Safriani, N.M. Erfiza, N. Arpi, IJASEIT 6, 285–288 (2016)
129. W.-M. Zhang, B. Li, L. Han, H.-D. Zhang, Afr. J. Biotechnol. **8**, 3887–3892 (2009). http://www.academicjournals.org/AJB
130. W.-M. Zhang, W.-Y. Huang, W.-X. Chen, L. Han, H.-D. Zhang, Molecules. **19**, 16416–16427 (2014). https://doi.org/10.3390/molecules191016416
131. M.N. Hamsar, S. Ismail, M.N. Mordi, S. Ramanathan, S.M. Mansor, Free Rad Antiox. **1**, 28–33 (2011). https://doi.org/10.5530/ax.2011.1.6
132. C.-C. Li, E.-S. Lin, Afr. J. Biotechnol. **9**, 7831–7836 (2010). https://doi.org/10.5897/ajb10.864
133. H. Hong, J.H. Lee, S.K. Kim, Asian-Australas, J. Anim. Sci. **31**, 1677–1684 (2018). https://doi.org/10.5713/ajas.17.0903
134. P. Wetwitayaklung, T. Phaechamud, C. Limmatvapirat, S. Keokitichai, NUJST 14, 1–14 (2006)
135. A.A. Kumar, S.S.S. Abuthahir, H.Y. Aboul-Enein, Pharmacia. **69**, 447–451 (2022). https://doi.org/10.3897/pharmacia.69.e77829
136. N.N. Sazwi, T. Nalina, Z.H.A. Rahim, BMC Complement. Altern. Med. **13**, 351 (2013). http://www.biomedcentral.com/1472-6882/13/351
137. E.F. Sari, G.P. Prayogo, Y.T. Loo, P. Zhang, M.J. McCullough, N. Cirillo, Sci. Rep. **10**, 16254 (2020). https://doi.org/10.1038/s41598-020-73337-0
138. S.C. Rangani, R.A.U.J. Marapana, G.S.A. Senanayake, P.R.D. Perera, M.M. Pathmalal, H.K. Amarasinghe, Appl. Food Res. **3**, 100361 (2023). https://doi.org/10.1016/j.afres.2023.100361
139. S. Sanpinit, P. Wetchakul, P. Chonsut, N. Prommee, C. Punsawad, J. Han, S. Net-anong, Antioxidants. **12**, 1428 (2023). https://doi.org/10.3390/antiox12071428
140. S. Das, S. Mukherjee, S. Choudhury, A. Bose, S. Roy, Int. J. Curr. Pharm. Res. **12**, 20–27 (2020). https://doi.org/10.22159/ijcpr.2020v12i2.37481
141. X. Zhang, W.U. Jiao, H. Zhuang, W.-L. Mei, D. Hao-Fu, Chem. Res. Chin. Univ. 2010, 161–164 (2010)
142. L.M. Sari, G.P. Subita, E.I. Auerkari, AJPCR 10, 286–291 (2017)
143. S. Yi, L. Zou, Z. Li, K. Sakao, Y. Wang, D.X. Hou, Foods. **11**, 3607 (2022). https://doi.org/10.3390/foods11223607
144. R. Wang, F. Pan, R. He, F. Kuang, L. Wang, X. Lin, J. Appl. Res. Med. Aromat. Plants. **25**, 100336 (2021). https://doi.org/10.1016/j.jarmap.2021.100336
145. L. Han, H. Zhang, S. Luo, K. Luo, Afr. J. Biotechnol. **10**, 9289–9296 (2011). https://doi.org/10.5897/ajb11.703
146. Y.V. Chavan, R.S. Singhal, J. Sci. Food Agric. **93**, 2580–2589 (2013). https://doi.org/10.1002/jsfa.6081
147. X. Ji, J. Guo, F. Pan, F. Kuang, H. Chen, X. Guo, Y. Liu, Front. Nutr. **9**, 853115 (2022). https://doi.org/10.3389/fnut.2022.853115
148. P. Toprasri, C. Chinpaisal, T. Phaechamud, Thai Pharm. Health Sci. **3**, 309–315 (2008)
149. R.R.N. Anthikat, A. Micheal, S. Ignacimuthu, J. Mens Health. **10**, 65–70 (2013). https://doi.org/10.1016/j.jomh.2012.07.003
150. S.S. Strickland, G.V. Veena, P.J. Houghton, S.C. Stanford, A.V. Kurpad, Ann. Hum. Biol. **30**, 26–52 (2003). https://doi.org/10.1080/03014460210157448
151. Z.H. Tian, J.T. Weng, L.J. Shih, A.C. Siao, T.Y. Chan, Y.W. Tsuei, Y.C. Kuo, T.S. Wang, Y.H. Kao, PLoS One. **13**, e0200508 (2018). https://doi.org/10.1371/journal.pone.0200508
152. M. Marastoni, A. Baldisserotto, A. Canella, R. Gavioli, C. De Risi, G.P. Pollini, R. Tomatis, J. Med. Chem. **47**, 1587–1590 (2004). https://doi.org/10.1021/jm0309102
153. R. Jarag, R. Jarag, G. Dhule, IJPSR 14, 1000–1016 (2023). https://doi.org/10.13040/IJPSR.0975-8232.14(12).1000-16
154. J. Jeng, S. Chen, C. Liao, Y. Tung, B. Lin, L. Hahn, M. Chang, Free Radic Biol. Med. **32**, 860–871 (2002)
155. M.N. Ghayur, A.H. Gilani, Pharmazie. **62**, 67–71 (2007). https://doi.org/10.1691/ph.2007.1.6583
156. Y. Zhang, Y. He, L. Yuan, J. Shi, J. Zhao, C. Tan, Y. Liu, Y.J. Xu, Phytomedicine. **132**, 155838 (2024). https://doi.org/10.1016/j.phymed.2024.155838
157. N.N.W. Udayani, K.A. Adrianta, I.G.M. Suradnyana, N.L.P.T. YogaCahyani, Gema Ling Kes. **22**, 35–41 (2024)
158. J.H. Lee, S.H. Chang, Y.S. Park, E. Her, H.Y. Lee, J.W. Park, J.W. Han, Y.M. Kim, W.S. Choi, J. Pharm. Pharmacol. **56**, 927–933 (2010). https://doi.org/10.1211/0022357023808
159. S.K. Gupta, A. Gupta, Indian J. Appl. Res. **3**, 381–382 (2013)
160. P. Pithayanukul, P. Ruenraroengsak, R. Bavovada, N. Pakmanee, R. Suttisri, S. Saen-Oon, J. Ethnopharmacol. **97**, 527–533 (2005). https://doi.org/10.1016/j.jep.2004.12.013
161. J. Ma, X. Du, A. Zhao, Z. Wang, Q. Guo, N. Qin, R. Wang, J. Cent. South. Univ. **47**, 512–520 (2022). https://doi.org/10.11817/j.issn.1672-7347.2022.210582
162. Y. Huo, A. Zhao, J. Song, J. Li, R. Wang, J. South. Med. Univ. **41**, 671–678 (2021). https://doi.org/10.12122/j.issn.1673-4254.2021.05.06
163. H.H. Lu, S.Y. Kao, T.Y. Liu, S.T. Liu, W.P. Huang, K.W. Chang, S.C. Lin, Autophagy. **6**, 725 (2010)
164. M.C. Chang, H.L. Wu, J.J. Lee, P.H. Lee, H.H. Chang, L.J. Hahn, B.R. Lin, Y.J. Chen, J.H. Jeng, J. Biol. Chem. **279**, 50676 (2004)
165. K. Kumpawat, S. Deb, S. Ray, A. Chatterjee, Mutat. Res. Genet. Toxicol. Environ. Mutagen. **538**, 1 (2003)
166. U.J. Nair, R.A. A'', J. Floyd, V. Nair A'', M. Bussachini ~, Friesen, H. Bartsch, A'' Chem. -Biol Interact. **63**, 157 (1987)
167. K.J. Ranadive, S.N. Ranadive, N.M. Shivapurkar, Aud, S.V. Gothoskar, *BETEL QUID CHEWING A N D ORAL CANCER: EXPERIMENTAL STUDIES ON HAMSTERS* (1979)
168. Y.C. Paulino, E.L. Hurwitz, S. Warnakulasuriya, R.R. Gatewood, K.D. Pierson, L.F. Tenorio, R. Novotny, N.A. Palafox, L.R. Wilkens, G. Badowski, BMC Oral Health (2014)
169. X. Wei, J. Zhang, J. Niu, X. Zhou, J. Li, B. Li, PLoS One **10**, (2015)
170. M. Wang, S.Y. Yu, Z. Lv, Y. Yao, Int. Urol. Nephrol. **50**, 1097 (2018)
171. F. Javed, K. AL-Hezaimi, S. Warnakulasuriya, J. Nutr. Health Aging. **16**, 445 (2012)
172. Q. Lan, P. Guan, C. Huang, S. Huang, P. Zhou, C. Zhang, Front. Pharmacol. **13**, (2022)

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.