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https://doi.org/10.31925/farmacia.2025.5.18 **ORIGINAL ARTICLE**

POTENTIAL ARECA NUT EXTRACT AS MALE SHORT-TERM ORAL CONTRACEPTION CANDIDATE: REDUCED SPERM MOTILITY WITHOUT IMPAIRMENT IN THE EPIDIDYMIS AND TESTIS

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Abstract

Areca nut is traditionally used as a male antifertility agent. However, prolonged administration of high doses has been associated with oxidative stress. This study investigated the poorly documented effects of low-dose and short-term areca nut ethanolic extract on the epididymis. Twenty fertile rats were divided into four groups: a control receiving distilled water; treatment groups administered the extract (50 mg/kg b.w.) for 7, 14, or 28 days. Epididymal DHT, CRISP1, MDA, and Nrf2 levels were measured using ELISA. Sperm parameters, epididymal and testicular histopathologies were evaluated microscopically. The ethanolic areca nut extract significantly reduced sperm motility after 7, 14, and 28 days, with fertility reduction ranging from 40% to 80%. No significant differences were observed in MDA and Nrf2 levels among the groups. Although DHT and CRISP1 levels in the treatment groups tended to decrease, the changes were not statistically significant. Short-term administration (7 and 14 days) did not affect the testicular or epididymal structure. This finding highlights the potential of low-dose areca nut extract to induce significant sperm antimotility without histological disruption, supporting its exploration as a candidate for short-term male contraception agent.

Rezumat

Nuca de Areca este utilizată tradițional ca agent antifertilitate masculin. Totuși, administrarea îndelungată a dozelor mari a fost asociată cu stres oxidativ. Acest studiu a evaluat efectele extractului etanolic de nucă de Areca, în doze mici și pe termen scurt, asupra epididimului. Douăzeci de șobolani fertili au fost împărțiți în patru grupuri: martor și tratate cu extract (50 mg/kgc) timp de 7, 14 sau 28 de zile. Nivelurile epididimale de DHT, CRISP1, MDA și Nrf2 au fost determinate prin ELISA, iar parametrii spermei și histopatologia au fost analizate microscopic. Extractul a redus semnificativ motilitatea spermatozoizilor, cu o scădere a fertilității între 40% și 80%, fără modificări semnificative ale MDA și Nrf2. Deși DHT și CRISP1 au prezentat o tendință descrescătoare, diferențele nu au fost semnificative. Administrarea pe termen scurt nu a afectat structura testiculară sau epididimală. Rezultatele susțin potențialul extractului de nucă de Areca, în doze mici, ca posibil agent contraceptiv masculin de scurtă durată.

Keywords: *Areca catechu* L, sperm motility, male antifertility

Introduction

Family planning remains essential for reproductive health; however, most available contraceptive methods are designed for women, placing a disproportionate burden on them. Long-term use of female hormonal contraceptives may cause adverse effects [1, 2]. In contrast, male contraception options remain limited. Condoms have a relatively high failure rate (13 - 20%) and low acceptance, while vasectomy is irreversible [3,4]. Several communities utilize plants as alternative male contraceptives. Various plants have been reported to exhibit antifertility effects in males. The use of natural products as a herbal contraceptive is economical, readily available, and accessible [5, 6]. Several plants are used as traditional contraceptives, one of them is the areca nut [7-10].

The areca nut, the seed of *Areca catechu L*., a palm tree widely cultivated across Asia Pacific, Africa, and North America, has long been used in traditional medicine [11, 12]. Recent findings suggest its potential as a male oral contraceptive candidate.

Several studies have reported that areca nut, when administered in high doses or for a prolonged duration, reduces sperm motility in rats [13-16], disrupts spermatogenesis [17-24], and decreases testosterone level [15, 25-27]. Conversely, low doses (e.g., 50 mg/kg body weight) have shown minimal hepatotoxicity

and nephrotoxicity [16, 20]. Areca nut toxicity appears to be linked to oxidative stress induction, as indicated by an increased malondialdehyde (MDA) or nuclear factor erythroid 2–related factor 2 (Nrf2) [22, 28-31].

While the effects of areca nut on the testis are relatively well-documented, its impact on the epididymis remains poorly understood. The epididymis plays a key role in the maturation of sperm motility [32]. The epididymis is divided into three main segments: caput, corpus, and cauda, each with distinct morphological and functional characteristics. The epididymal epithelium secretes epididymosomes containing proteins such as CRISP1 (cysteine-rich secretory protein 1) [32, 33]. CRISP1 is an androgen-dependent protein, primarily regulated by dihydrotestosterone (DHT). It binds to the sperm surface during epididymal transit, acts as a decapacitation factor by regulating sperm motility through the Cation Channel of Sperm (CatSper), and is released during capacitation in the female reproductive tract [33, 34].

An ideal male contraceptive should reduce sperm quality without damaging the testis and the epididymis. Areca nut has been reported to contain bioactive compounds, including alkaloids (arecoline, arecaidine, and guvacoline), polyphenols (flavonoids and tannins), polysaccharides, and fatty acid components [35-37]. Extraction methods can influence the composition and potency of these compounds. In this study, areca nut was extracted using ethanol, a solvent known to extract phenolic compounds with antioxidant properties [38], which may mitigate arecoline-induced toxicity.

Low-dose ethanolic areca nut extract may produce distinct effects on sperm motility and epididymal structure compared with previously reported high-dose administration. Therefore, this study aimed to investigate the impacts of a low-dose (50 mg/kg b.w.) ethanolic extract of areca nut, previously reported to be relatively safe for the liver and kidneys, on sperm motility and the epididymis over 7-day, 14-day, and 28-day treatment periods.

Materials and Methods

Collection and Preparation of Areca Nut

Green, unripe areca nuts (Batara variety) were obtained from a plantation in Jambi, Sumatra, Indonesia. The nuts were sliced and oven-dried at 50°C for 24 hours. The dried nut was ground into a fine powder and stored in an air-tight container, protected from light and moisture until further use.

Extraction

The powdered areca nuts were extracted by maceration using ethanol as the solvent, at a 1:10 ratio (w/v), where 1 gram of areca powder was immersed in 10 liters of ethanol. Maceration was carried out for 24 hours with intermittent agitation. The resulting macerate was filtered through Whatman no. 41 filter paper, and the filtrate was concentrated using a rotary evaporator (Buchi R-114) at 58°C. The concentrate was then oven-dried at 50°C for 4 × 24 hours to obtain a solid extract, which was stored in an air-tight container at 4°C until use. Phytochemical analysis of the ethanolic extract was performed using high-performance liquid chromatography (HPLC) and UV-visible spectrophotometry to determine the total alkaloid, phenolic, flavonoid, and arecoline content, following previously established methods.

Determination of Total Phenolic, Flavonoid, Arecoline, and Antioxidant Activity in Extract

The total phenolic content was determined using a previously described method with slight modifications, employing the Folin-Ciocalteu colorimetric assay and gallic acid as the standard compound. Absorbance was measured using a spectrophotometer at the maximum wavelength obtained (600 - 800 nm) [39, 40]. The total flavonoid content was quantified using the aluminium chloride colorimetric method, with quercetin as the standard, following a modified protocol from earlier studies [39, 40] The total alkaloid content was determined using the Bromocresol Green method with reserpine as the reference standard [41-43]. Absorbance for flavonoids and alkaloids was recorded at their maximum wavelength (400 - 600 nm) using a spectrophotometer.

Arecoline content was analysed using HPLC, following previously established methods [38, 44]. The HPLC system was equipped with a UV-visible detector (UV-1575) set at 216 nm, and operated in isocratic mode with a flow rate of 0.8 mL/min at 45°C. separation was performed on a C18 column (Spherisorb ODS2, 5 µm, 4.6 × 250 mm). The mobile phase consisted of 10 g of potassium dihydrogen phosphate dissolved in 990 mL of water, which was then homogenized and subsequently mixed with 3.5 mL of phosphoric acid, 8 mL of triethylamine, and 9 mL of acetonitrile. The pH was adjusted to 4.5 using triethylamine or phosphoric acid, and the solution was filtered through a 0.22 µm membrane filter before use.

The antioxidant activity of areca nut extract was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, as previously described [45, 46]. Absorbance was measured at a wavelength of 516 nm using a spectrophotometer.

Laboratory Animals

Twenty (20) adult, fertile, male Wistar albino rats (3 - 4 months old; 180 - 240 grams) were used in this study. The sample size was determined using a standard sample size calculation formula with $\alpha = 0.05$ and statistical power = 0.8 [47]. The animals were obtained from and housed at the Animal House of the Department of Pharmacology, Faculty of Medicine, Public Health, and Nursing, University of

Gadjah Mada. They were housed in clean wire-mesh cages under standard laboratory conditions (12 h light/dark cycle, temperature 25 ± 2°C), with free access to commercial rat pellets (RatBio) and clean drinking water ad libitum. All rats were acclimatized for one week before the experiment.

The animals were maintained under veterinary supervision and handled according to institutional protocols and international standards for the care and use of animals in scientific research. This study adhered to Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, the Guide for the Care and Use of Laboratory Animals (8 th edition), ARRIVE guidelines (2.0), and the principles of 3R (replacement, reduction, refinement) and 5F (freedom from hunger and thirst, fear and distress, discomfort and pain, injury and disease). Ethical approval was obtained from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, University of Gadjah Mada-Dr. Sardjito General Hospital.

Fertility Test

A fertility test was conducted by housing each male rat with a female for 4 or 8 days before the treatment period was completed. Each male was paired with its pretreatment female partner, and only females in the oestrus phase were introduced into the males' cages. Mating success was confirmed by the presence of a copulation plug or sperm in the vaginal smear collected between 8:00 and 9:00 a.m. Vaginal smear analysis for sperm detection and the oestrus phase determination followed a previously reported method [48]. Male fertility (%) was calculated by the number of males that successfully made their partner pregnant divided by the total number of rats in the group.

Experimental Protocol

The rats were randomly divided into four groups (I-IV) (n = 5) using the lottery method (simple randomization). Group I (control) received distilled water, while groups II, III, and IV received the areca nut extract at a dose of 50mg/kg body weight (kg b.w.) for 7, 14, and 28 days, respectively. The extract was administered once daily by oral gavage. This dose was selected based on previous findings indicating that doses below 50 mg/kg b.w. had no significant effect on sperm motility [16]. Treatment allocation was open-label, as laboratory personnel were aware of the administered doses.

At the end of the treatment period, body weights were recorded, and the animals were euthanized under anaesthesia overdose. The epididymis was carefully excised, cleared of surrounding tissue and blotted free of blood before weighing. One epididymis from each rat was used for sperm count, motility, morphology, the hypo-osmotic swelling (HOS) test, and histopathological analysis. The remaining epididymis was stored at -20°C for subsequent ELISA analysis of malondialdehyde (MDA), nuclear factor erythroid 2–related factor 2 (Nrf2), dihydrotestosterone (DHT), and cysteine-rich secretory protein 1 (CRISP1).

Cauda Epididymal Sperm Count, Motility, Morphology, and Hypo-Osmotic Swelling Test

The cauda epididymis was excised, and several incisions (about 1 mm) were made while suspended in 1 ml of pre-incubated normal saline solution. After 10 minutes of incubation at 37°C, sperm concentration and motility were determined. Sperm morphology assessed using Giemsa staining [49]. Abnormalities were categorized as head or tail defects. The percentages of normal and abnormal-shaped sperm were then calculated [49]. Hypo-osmotic swelling was performed to assess sperm membrane integrity according to a previously described method [50].

The ELISA Test of Epididymis Tissue

The epididymis were homogenized, and the resulting supernatant was isolated and stored at −80°C until further analysis. The concentrations of MDA, Nrf2, and DHT in the epididymis tissue homogenates were determined using ELISA kits (Elabscience, catalogue numbers E-El-0060, E-EL-R1052, E-EL-0031, respectively). The concentration of CRISP1 was measured using an ELISA kit from Mybiosource (catalog number MBS7204579). All assays were performed according to manufacturers' instructions.

Histopathological Studies

Following sperm collection, the testes and epididymis were fixed in 10% neutral buffered formalin for 24 hours. The tissues were processed routinely, embedded in paraffin wax, sectioned at a thickness of 5 μm, and stained with haematoxylin and eosin (H&E). The sections were examined under a light microscope by a pathologist to evaluate structural variations [51].

Histopathology evaluation was conducted in an open-label manner (no blinding), as the pathologist was required to identify control and treatment groups for comparative analysis. The density of sperm within the epididymal lumen was categorized as tubules with normal sperm, low sperm, and free sperm. The density of sperm was presented as a percentage of tubules with normal sperm/total tubules. The epithelial height of the epididymis was measured following a previously described method [52].

Statistical Analysis

The results were presented as the mean ± standard error (SEM). Data Normality and homogeneity were assessed using the Shapiro–Wilk and Levene's tests, respectively. Parametric data were analysed by one-way ANOVA followed by the least significant difference (LSD) post hoc test. Nonparametric data were analysed using the Kruskal–Wallis test, followed by the Mann–Whitney test. A value of $p < 0.05$ was considered statistically significant.

Results and Discussion

The phytochemical analysis of the ethanolic areca nut extract revealed the presence of total phenolic content, total flavonoid content, and total alkaloids (Table I). These finding are consistent with previous reports [35, 37].

Arecoline is the main alkaloid in areca nut and has been widely reported for its harmful effects on spermatozoa [13, 53]. The unripe areca nut extract in this study contained arecoline at 108.343 ± 0.627 mg/g extract, which is markedly higher than previously reported values in methanolic unripe areca nut extract (4 - 6 mg/g) [37]. This difference reflects the influence of extraction solvents and methods on the concentration of active compounds in the crude extracts.

The antioxidant activity of the ethanolic areca nut extract showed an IC50 value of 5.709 ± 0.002 µg/mL, comparable to other studies reporting values around 4.5 µg/mL [54]. The strong antioxidant potential of areca nut has been associated with its high total polyphenol content [37, 43].

Table I

Quantification of phytochemical groups in the ethanolic areca nut extracts

Phytochemical groups	Concentration (mean ± SD)	Units
Total phenolic content	647.213 ± 1.362	mg GAE/g extract
Total flavonoid content	1.901 ± 0.025	mg QE/g extract
Total alkaloid content	17.695 ± 0.522	mg RE/g extract
Arecoline content	108.343 ± 0.627	mg arecoline/g extract

GAE: gallic acid equivalent; QE: quercetin equivalent; RE: reserpine equivalent

The ethanolic areca nut extract significantly decreased sperm motility after 7, 14, and 28 days of administration (Table II). The reduction in motility was progressive with longer treatment duration. The extract also reduced the percentage of morphologically normal sperm, with a significant difference observed in 28 days of treatment. The types of abnormal sperm morphology include head loss, tail loss, tail bend, head-to-head agglutination, and head-to-tail agglutination (Figure 1). These abnormalities are consistent with those reported in other studies [22]. Pearson correlation analysis showed no significant correlation between sperm motility and the percentage of morphologically normal sperm.

Sperm concentration and membrane integrity were not significantly affected by areca nut extract across treatment durations (Table II). These findings suggest that the extract primarily affects sperm motility, as also reported in previous research [15,22]. The pregnancy rate in the treatment groups was reduced by approximately 20-60% supporting the idea that decreased motility contributes to reduced fertility in normal conception [55].

Table II

The effect of areca nut extract on rat sperm analysis

Variable	Groups (mean ± SEM)				p value
	Control	7 days of extract	14 days of extract	28 days of extract	
Sperm concentration (10^6 cells/mL)	19.85 ± 4.60	15.55 ± 2.19	19.10 ± 1.75	15.51 ± 2.60	0.630
Sperm motility (%)	72.82 ± 2.06^{a}	50.59 ± 3.89^{b}	35.13 ± 8.91^{b,*}	31.93 ± 1.83^{c,*}	0.004$^{\#}$
Sperm morphology (%)	66.62 ± 1.31^{a}	53.14 ± 5.39^{a}	63.06 ± 3.82^{a}	45.43 ± 6.16^{b}	0.045
Sperm membrane integrity (Positive HOS Test, %)	87.80 ± 2.61	82.80 ± 4.40	90.60 ± 3.21	84.80 ± 4.21	0.480
Male fertility after experimental (%)	100^{a}	20^{b}	20^{b}	60^{a}	0.039

Different letters identify significant differences among the groups, # analyzed with the Kruskal-Wallis Test

The effects of ethanolic areca nut extract on the epididymis tissue are shown in Table II. Areca nut has been reported to interfere with testosterone synthesis, and long-term treatment reduces serum testosterone levels [15, 25, 26]. Testosterone is converted to dihydrotestosterone in the epididymis. Dihydrotestosterone is the principal androgen responsible for maintaining the structural integrity and function of the epididymis.

The epididymis secretes various proteins that regulate sperm motility, one of which is CRISP1. CRISP1 binds to CatSper channel on the sperm membrane, preventing its activation and acting as a decapacitation factor [33, 56]. Capacitation is a sperm event that typically starts when sperm are in the oviduct of the female reproductive tract. When sperm become capacitated, there is a change in the pattern of motility, from the progressive forward motility of non-capacitated sperm to the hyperactivated motility of capacitated sperm [57].

Table III

The effect of areca nut extract on the concentration of MDA, DHT, and CRISP1 in the rats' epididymis

Variable	Groups (mean ± SEM)				p value
	Control	7 days of extract	14 days of extract	28 days of extract	
MDA caput	50.46 ± 7.28	45.23 ± 6.24	44.08 ± 4.79	48.79 ± 9.91	0.912
corpus	31.45 ± 6.65	43.31 ± 3.78	35.22 ± 5.27	31.78 ± 6.09	0.424
cauda	73.60 ± 9.70	62.72 ± 12.04	61. 89 ± 10.56	49.72 ± 6.03	0.424
NRF2 caput	543.08 ± 50.26	507.30 ± 24.39	542.82 ± 47.77	545.26 ± 22.83	0.878
corpus	470. 52 ± 26.41	420.22 ± 45.16	512.98 ± 49.37	516.88 ± 32.69	0.307
cauda	484.16 ± 18.86	433.72 ± 10.33	456.44 ± 13.49	473.44 ± 13.49	0.250#
DHT caput	346.02 ± 41.97	290.80 ± 72.18	236.74 ± 54.04	271.52 ± 33.87	0.535
corpus	264.89 ± 41.30	207.23 ± 70.34	195.23 ± 37.23	229.54 ± 33.66	0.749
cauda	124.57 ± 18.96	100.54 ± 16.09	160.16 ± 38.17	118.31 ± 13.11	0.598#
CRISP1 caput	1.27 ± 0.15	1.21 ± 0.39	0.97 ± 0.15	0.91 ± 0.22	0.643#
corpus	0.99 ± 0.27	0.98 ± 0.17	0.93 ± 0.15	1.03 ± 0.22	0.999
cauda	0.98 ± 0.08	0.98 ± 0.09	0.92 ± 0.27	0.67 ± 0.19	0.410

analysed with the Kruskal-Wallis Test

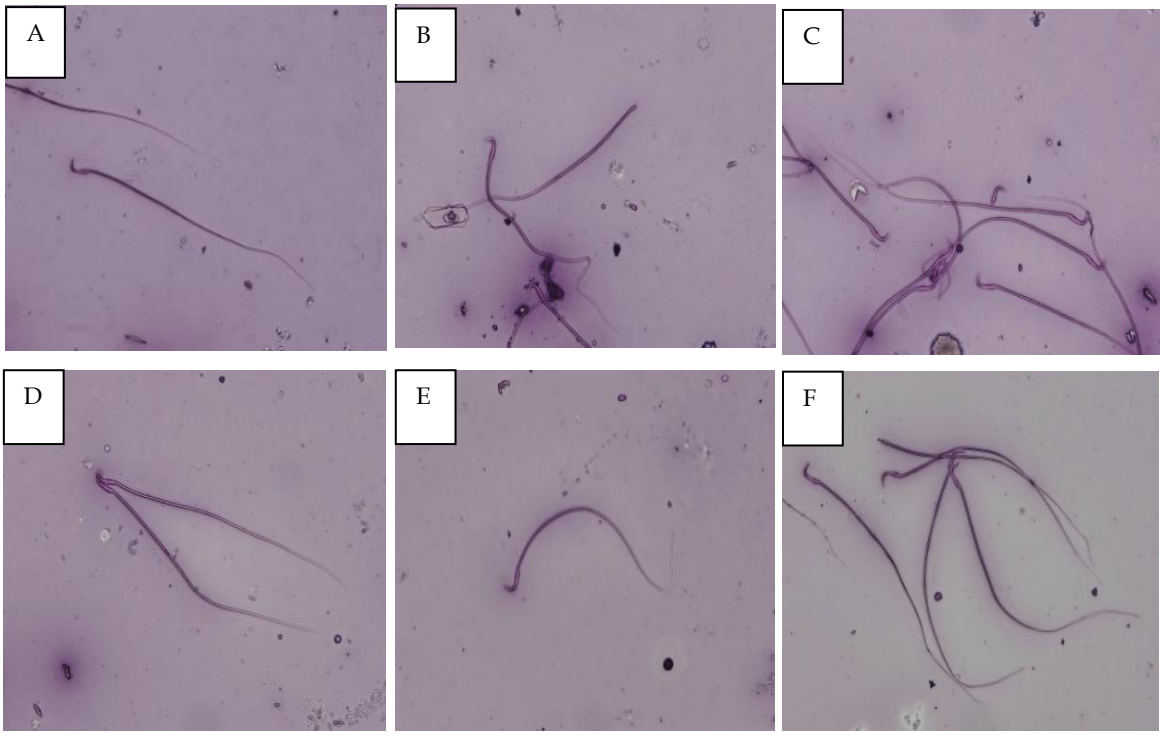

Figure 1.

Sperm morphology in control and treatment groups. Normal and abnormal morphology were present in both groups, but the treated rats showed a higher frequency of abnormalities. (A) normal sperm morphology; (B-F) abnormal morphology, including bent tail and head lost (B); tail lost, head to tail agglutination (C); head to head agglutination (D); bent tail (E); head lost, head to tail adhered, bent tail (F)

In this study, ethanolic areca nut extract caused an insignificant reduction in epididymal DHT and CRISP1 levels. This reduction appeared to be time-dependent, suggesting that more prolonged administration may further decrease DHT levels. A significant decline in androgen has been associated with reduced libido, a concern in male contraceptive development [3]. However, the short-term administration of areca nut extract (7 - 14 days) in this study resulted in only a slight, statistically insignificant reduction in androgen levels, suggesting a minimal risk of libido suppression. Further studies with greater statistical power are warranted to confirm this finding.

Administration of the extract for 28 days induced marked histopathological alterations in the testis and epididymis. Previous studies have reported conflicting results regarding the relationship between areca nut and oxidative stress [22, 58, 59]. Variations in tissue type, dosage, and extraction method likely contribute to these discrepancies [35, 59, 60].

In the present study, epididymal disruption following areca nut administration was not associated with oxidative stress, as indicated by unchanged MDA

and Nrf2 levels, two common oxidative stress markers. Histopathology examination revealed epididymal alterations characterized by simplified stereocilia, luminal sperm depletion, epithelial cell vacuolization, decreased Clear cell numbers, and the absence of inflammatory cells (Figure 2). The height of the epididymal epithelium remained unchanged (Table III). These features correspond to androgen deprivation-related changes [61].

Testicular sections from the 28-day treatment group also exhibited marked spermatogenic disruption (Figure 3). These findings indicate that ethanolic areca nut extract may impair reproductive tissues with prolonged use, suggesting its potential suitability only for short-term antifertility development.

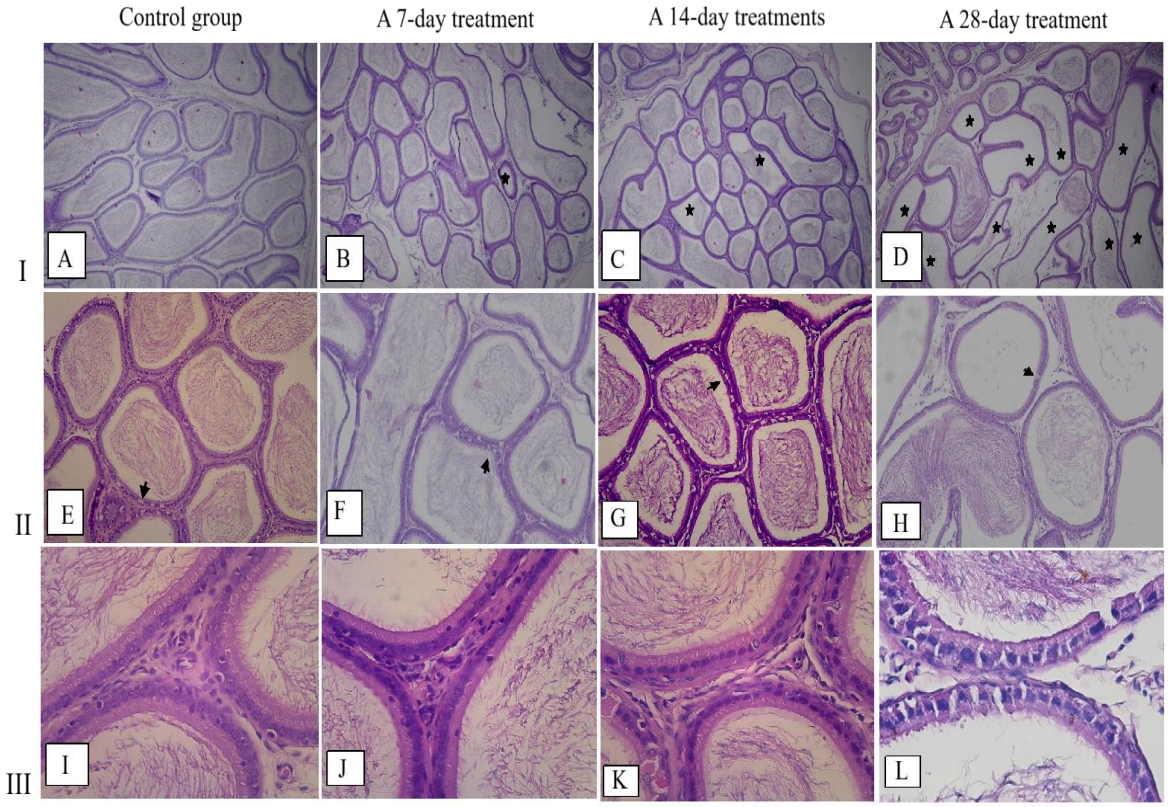

Figure 2.

Histopathology of the epididymis (H&E staining) at magnification 40x (row I), 100x (row II), and 400x (row III). Control groups (A, E, I), 7-day treatment (B, F, J), 14-day treatment (C, G, K), and 28-day treatment (D, H, L). Progressive reduction in intraluminal sperm (row I) and decreased clear cells (arrow row II) in the cauda epididymis were observed with longer treatment. The epithelial integrity and stereocilia appeared increasingly disrupted over time. (row III)

Table IV

The effect of areca nut extract on the histology of the rats' epididymis

Variable		Groups (mean ± SEM)				p value
		Control	7 days of extract	14 days of extract	28 days of extract	
Epididymis weight relative (gram)		0.168 ± 0.008^{a}	0.175 ± 0.008^{a,*}	0.149 ± 0. 008 ^{a,**}	0.137 ± 0.003 ^{b,**}	0.014
Sperma intralumen	Initial	90.32 ± 2.64^{a}	86.75 ± 2.47 ^{a}	88.24 ± 3.17 ^{a}	37.72 ± 4.69 ^{b}	0.000
	Caput	94.66 ± 2.32 ^{a}	93.18 ± 2.65 ^{a}	90.07 ± 2.68 ^{a}	45.32 ± 4.69 ^{b}	0.000
	Corpus	98.50 ± 0.53 ^{a}	97.72 ± 0.73 ^{a,*}	95.55 ± 0.77 ^{b,*}	67.84 ± 6.79 ^{c}	0.003$^{\#}$
	Cauda	99.68 ± 0.32 ^{a}	98.27 ± 0.42 ^{a}	91.36 ± 1.90 ^{a,*}	91.67 ± 1.76 ^{b,*}	0.017$^{\#}$
Height of epididymis epithelial	Initial	25.27 ± 2.06	26.695 ± 2.864	28.020 ± 3.542	33.41 ± 2.81	0.243
	Caput	17.83 ± 1.69	18.461 ± 2.033	17.397 ± 1.048	17.88 ± 0.26	0.927$^{\#}$
	Corpus	16.22 ± 1.49	15.663 ± 1.540	15.616 ± 0.981	16.46 ± 0.57	0.948
	Cauda	14.74 ± 1.55	12.944 ± 1.492	13.942 ± 0.573	15.19 ± 0.40	0.927$^{\#}$

Different letters identify significant differences among the groups, # analysed with the Kruskal-Wallis Test

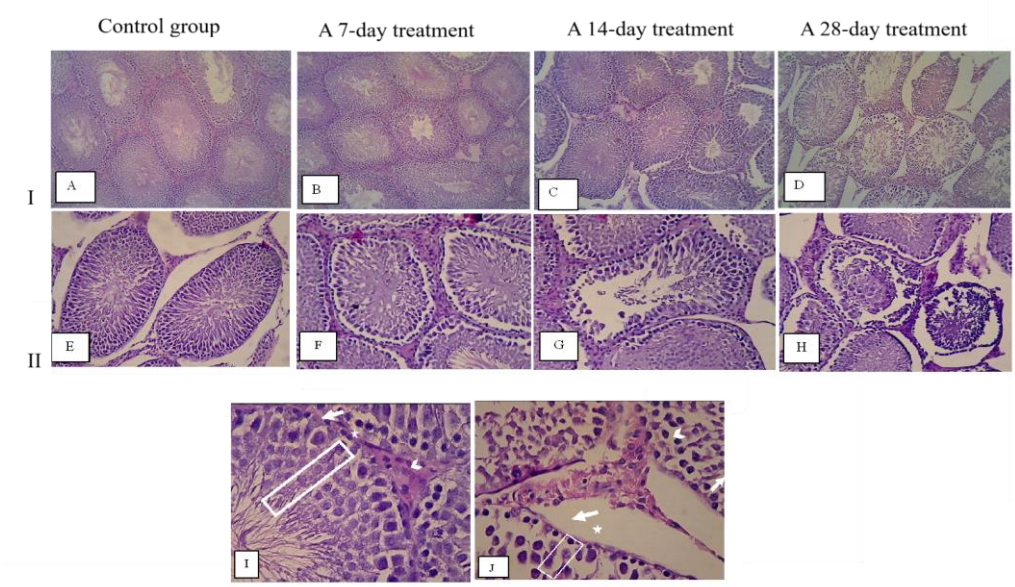

Figure 3.

Histopathology of rat testis (H&E staining) at magnification 40X (Row I), 100X (Row II), and 400X (bottom row). (A, E) Control group showing normal spermatogenesis. (B, C, F, G) The group receiving the 7-day and 14-day extract typically showed arranged germ cells with minimal disruption (<5%). (D, H) In contrast, the 28-day extract group showed marked disruption of spermatogenesis, affecting 50-75% of the tubules. (I) The control group showed normal-sized Sertoli cells (arrows), spermatogonia (stars), developing germ cells (squares), and Leydig cells in the interstitium (arrowheads). (J) The 28-day extract group showed smaller Sertoli cells (arrows), still containing spermatogonia, developing germ cells (squares), and Leydig cells (arrowheads)

Arecoline is considered the main bioactive compound responsible for the adverse reproductive effects of the areca nut. It has been shown to impair sperm motility in both in vitro [13, 53] and in vivo studies [58]. The exact mechanism is not fully understood. In vitro, arecoline at doses of 10 - 200 µg/mL induces COX-2 expression in human sperm, which may be correlated with reduced motility [13]. Arecoline may also directly interfere with mitochondrial energy metabolism in spermatozoa [62-64], or modulate ion channel expression, affecting intracellular pH, bicarbonate, and calcium ion balance [65, 66]. Several phenolic derivative was also reported to affect the spermatozoa [67]. Since plant extracts contain multiple compounds, synergistic effects among phytochemicals could contribute to the observed biological activities. Future research should identify the active compounds that reach target organs such as the epididymis, testis, seminal plasma, and spermatozoa to elucidate their combined mechanisms.

An ideal male contraceptive should be effective, safe, reversible, and have a short onset and recovery time [3]. The ethanolic areca nut used in this study reduced sperm motility without causing testis and epididymal disruption after short-term administration (7 - 14 days) at 50 mg/kg b.w. These findings suggest that the extract may serve as a potential short-term oral male contraceptive candidate. However, its unsuitability for prolonged administration and the need to assess the reversibility of its antifertility effects warrant further investigation before clinical development.

Conclusions

Ethanolic areca nut extract at a single dose of 50 mg/kg b.w., administered for 7 and 14 days, significantly reduced sperm motility without causing structural disruption in the testis or epididymis. In contrast, prolonged administration for 28 days induced marked histopathological damage to both organs. These findings indicate that ethanolic areca nut extract has potential as a short-term oral male contraceptive candidate; however, its reversibility and long-term safety must be further evaluated.

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Conflict of interest

The authors declare no conflict of interest.

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