

ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org



RESEARCH ARTICLE

Aphrodisiac Effectiveness of 70% Ethanol Extract of Caulis Lelak (*Uvaria rufa* Blume.) on Male Mice (*Mus musculus*)

Faisal Akhmal Muslikh¹, Ira Oktavia², Burhan Ma'arif³, Maximux M. Taek⁴, Dyah Aryantini²,
Nadia Pramasari², Syendriya Zeptyan Zenmas²

¹Department of Pharmacy, Faculty of Pharmacy, Hang Tuah University, Surabaya 60111, Indonesia.

²Department of Pharmacy, Faculty of Pharmacy,
Bhakti Wiyata Health Sciences Institute, Kediri 64114, Indonesia.

³Department of Pharmacy, Faculty of medicine and Health Science,
Maulana Malik Ibrahim State Islamic University, Malang 65149, Indonesia.

⁴Department of Chemistry, Faculty of Mathematics and Natural Sciences, Widya Mandira Catholic University,
Kupang 85211, Indonesia.

*Corresponding Author E-mail: ira.oktavia@iik.ac.id

ABSTRACT:

Sexual desire (SD) is often considered normal, but many men lose their sexual life due to poor health conditions. Erectile dysfunction (ED), commonly called impotence, is a condition of sexual dysfunction in the process of male sexual activity. The use of common therapies such as phosphodiesterase-5 (PDE5) inhibition will cause long-term side effects, so alternatives are needed to overcome it. One natural solution that has the potential as an aphrodisiac is Lelak (*Uvaria rufa*), a plant that is traditionally used by the people of East Nusa Tenggara, Indonesia, to overcome male sexual dysfunction. This study aims to evaluate the safety and effectiveness of *U. rufa* caulis extract as an aphrodisiac through acute toxicity tests and in vivo testing. The 70% ethanol extract of *U. rufa* caulis (EeUrC), obtained through the maceration method, was evaluated for its toxicity based on the level of mortality in zebrafish embryos referring to OECD Guideline No. 236, and its aphrodisiac activity was measured through testicular weight parameters and the number of Leydig cells (LC). The results showed that the LD₅₀ of EeUrC was 1096.7 µg/ml, which indicated relatively harmless (>1000 µg/ml), while (AA3) a dose of 1.7 mg/20 g BW of mice body weight per day was stated as the optimal dose for aphrodisiac activity. In conclusion, EeUrC is safe with mild toxicity and effective at optimal doses as an aphrodisiac.

KEYWORDS: Aphrodisiac, Dysfunction sexual, Leydig cells, Testicular weight, *Uvaria rufa*.

INTRODUCTION:

Sexual desire is generally defined as “the driving force that drives a person to engage in or avoid sexual behavior” and is viewed as a multidetermined phenomenon influenced by biological, psychological, relational, contextual, and sociological factors. Psychological research indicates a relationship between emotional disorders, such as depression, anxiety, and obsessive-compulsive disorder, and levels of sexual desire¹. Sexual desire is often considered normal and inevitable in the aging process, sexuality remains an important aspect of masculinity and is part of how men define themselves regardless of age. However, many men lose more years of active sexual life due to poor health conditions².

Received on 27.11.2024 Revised on 07.04.2025
Accepted on 11.06.2025 Published on 08.11.2025
Available online from November 13, 2025
Research J. Pharmacy and Technology. 2025;18(11):5425-5430.
DOI: 10.52711/0974-360X.2025.00782
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Sexual dysfunction (SD) in men is not a single disease. It means the entire process of male sexual activity, including desire, arousal, orgasm, or even pain³⁻⁵. Erectile Dysfunction (ED) is defined as "recurrent and persistent inability, either partial or complete, to achieve or maintain an erection firm enough to permit satisfactory sexual intercourse, despite appropriate erotic stimulation." The term ED replaces the previous definition of "impotence"⁶.

ED is one of the most common and undertreated diseases in SD³. With 20–30% of adult males globally reporting at least one sexual disorder and its incidence rising with age, male sexual dysfunction is widespread in the general population^{4,7}. In Indonesia, the prevalence of sexual dysfunction in men reaches 10% at all ages, with more than 50% occurring in men aged 50-70 years⁸.

Common treatments for sexual dysfunction often involve the use of phosphodiesterase-5 (PDE5) inhibitors, such as vardenafil, sildenafil, and tadalafil^{9,10}. PDE5 is an enzyme in the smooth muscle of the corpus cavernosum that breaks down cyclic guanosine monophosphate (cGMP) into 5'-GMP. PDE5 inhibitors increase cGMP levels, improve blood flow, and produce longer-lasting erections^{4,11,12,13}. Common side effects of PDE5 inhibitors include nasal congestion, headache, flushing, back pain, dyspepsia, and myalgia. These inhibitors can also cause severe hypotension when combined with nitrates, so nitrate users should avoid them. Rare side effects include priapism, Stevens-Johnson syndrome, sudden hearing loss and sudden visual loss^{4,14}. Treatment using plants offers strong therapeutic properties, can improve pathological conditions associated with the disease, has minimal side effects, and is inexpensive^{15,16}.

Lelak (*Uvaria rufa*) is one of the typical plants of East Nusa Tenggara (NTT), Indonesia, which is traditionally used to treat male sexual dysfunction^{17,18}. Phytochemical studies show that compounds contained in *U. rufa* include flavonoids, alkaloids, highly oxidized cyclohexane, rutin, isoquercetin, kaempferol, flavonols, quercetin, lignan glycosides, astragalins, and isoquercitrin-6-acetate¹⁷. To develop standardized herbal medicines from *U. rufa*, supporting data on safety are essential. Therefore, this study was conducted to determine the aphrodisiac effects of *U. rufa*, which has long been used traditionally in NTT, in addition to providing knowledge about its toxic effects.

MATERIALS AND METHODS:

Materials:

Plant:

The caulis of the *U. rufa* plant was sourced from

Kupang, East Nusa Tenggara, Indonesia, and its identification was conducted at the Phytochemistry Laboratory, Widya Mandira University, Kupang, Indonesia.

Chemical:

The chemicals used in this study included 70% alcohol, 70% ethanol, Tween 80, 0.5% Dimethyl sulfoxide (DMSO), distilled water, 80% alcohol, 96% alcohol, absolute alcohol, 10% formalin, ketamine, xylazine, hematoxylin, eosin, and xylol, all obtained from Merck (Darmstadt, Germany).

Animal:

Zebrafish (*Danio rerio*) embryos at 2 hours post-fertilization (hpf) and male Balb/c strain mice (*Mus musculus*), aged 12–14 months and weighing 15–30 grams, were sourced from the Healthy Animal Clinic Laboratory in Malang, Indonesia. This study was approved by the Research Ethics Committee (Animal Care and Utilization Committee) at Brawijaya University, Malang, East Java, Indonesia (Approval No. 065-KEP-UB-2024).

Methods:

Extract Preparation:

The caulis of *U. rufa* was finely ground into powder, and extraction was conducted through maceration using 70% ethanol at a powder-to-solvent ratio of 1:15. The resulting filtrate was concentrated with a rotary evaporator at 50°C, 175 psi, and 70 rpm. To obtain a thick extract, the remaining solvent was evaporated in an oven at 50°C. This process yielded 30.2 grams of dry extract from 1300 grams of simplicia, with a yield of 2.32% of 70% ethanol extract from the *U. rufa* caulis (EeUrC). For the preparation of the stock solution, 400 mg of 70% EeUrC was suspended in a solution of 0.5% DMSO and 1% Tween 80, and subsequently diluted to the desired concentrations for toxicity and activity assays.

Toxicity Test EeUrC:

In vitro toxicity tests were performed on zebrafish embryos in accordance with OECD Guideline No. 236 (2013)^{19,20}, for acute toxicity testing on zebrafish embryos over a 96-hour period. Eight-hour-old embryos at the organogenesis stage were placed in well plates containing test solutions. The test solution concentrations included extract doses of 500 ppm (TT1), 1000 ppm (TT2), 1500 ppm (TT3), and 2000 ppm (TT4), with a negative control (NC) using distilled water. Each well plate contained 20 embryos, and each concentration was tested in triplicate. The embryos were incubated at room temperature for the duration of the study¹⁸.

Aphrodisiac Activity EeUrC:

Aphrodisiac activity testing was performed by measuring testicular weight and counting Leydig cells (LC). The treatment groups consisted of a negative control group (NC), which received a 1% Tween 80 suspension in 0.5% DMSO; a positive control group (PC) which was administered a sildenafil citrate suspension at a dose of 0.13 mg/20 g body weight (BW) per day; group AA1, receiving a EeUrC at 0.425 mg/20 g BW per day; group AA2, with a dose of 0.85 mg/20 g BW; and group AA3, with a dose of 1.7 mg/20 g BW. All treatments were given orally²¹, at a volume of 0.5 ml for 28 days. At the end of the treatment period, the testicular organs were surgically removed and weighed. LC counts were conducted quantitatively using a light microscope at 400x magnification, with observations made across 5 fields of view.

Data analysis:

All tests were conducted in triplicate, and the experimental results are expressed as the mean $\pm$ standard deviation (SD). Data were analyzed using one-way ANOVA with IBM SPSS version 25, followed by a post hoc test to determine significant differences between the means. A *p*-value of less than 0.05 was considered statistically significant.

RESULT:

Toxicity Test EeUrC:

Intensive observation of the EeUrC acute toxicity test was carried out using zebrafish embryos. Because they are frequently employed as model organisms to research human genetic development and illness, zebrafish were selected^{22,23}. This is because zebrafish are a useful test animal model for researching disorders connected to humans because their genes are generally comparable to those of humans^{24,25}. Observations were carried out for 96 hours by observing signs of death in zebrafish embryos, including the presence or absence of a heartbeat, the body does not move, and abnormal morphological changes (for example, the embryo becomes cloudy or abnormally colored), then the number of deaths at 96 hours is calculated to determine the lethal dose of EeUrC.

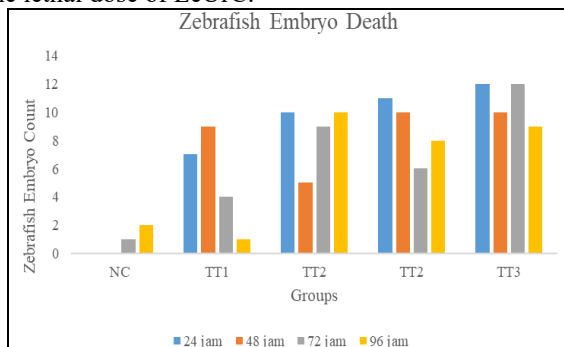


Fig 1. Total death of zebrafish embryos within 96 hours after exposure to EeUrC

Based on Figure 1 showing the results of the toxicity test using the Zebra Fish Embryo Acute Toxicity (ZFET) method, it shows that the longer the period of exposure to EeUrC, the higher the rate of embryo mortality. This is because the longer the exposure time to the test substance, the zebrafish's immune system decreases. The results of the data analysis in the acute toxicity test with SPSS 27 used probit analysis to predict concentrations in the range of death up to 96 hours. The LD₅₀ value obtained was 1096.7 μ g/mL. Based on the acute toxicity rating scale by the Fish and Wildlife Service, the acute toxicity of EeUrC is classified as relatively harmless (>1000 μ g/ml)²⁶.

Aphrodisiac Activity EeUrC:

In the observation of the aphrodisiac activity test, observations were made on testicular weight and quantitative analysis of LC. Examination of testicular weight correlates with increased testosterone (T) levels, similar studies also revealed that testicular size is positively correlated with T and LH levels²⁷. The testes are important organs for reproductive and sexual function, functioning as the main source of androgens and the site of spermatogenesis, with their development and function regulated by hormonal action through endocrine and paracrine pathways^{28,29}. The average results of testicular weight observations are presented in Figure 2.

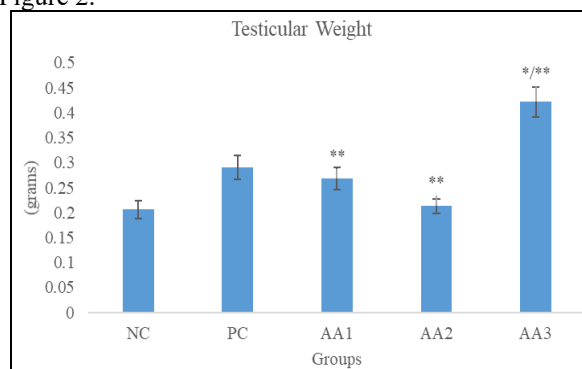


Fig 2. Average results of *Mus musculus* testicular weight. *: Sig with NC; **: Sig with PC

Figure 2 shows that the AA1, AA2, and AA3 treatment groups had higher average testicular weight results compared to the NC group, but the AA3 group had the highest average results compared to all groups, even exceeding and significantly different from NC and PC (*p* < 0.005). This shows that EeUrC most significantly affects the average testicular weight in the AA3 group.

In addition to observing the average testicular weight, observing the number of LC is also needed to determine the normality of androgen synthesis because LC are where androgen biosynthesis takes place³⁰. LC are interstitial cells of the testis that can be found between the seminiferous tubules³¹. The average results of LC count observations are presented in Figure 3.

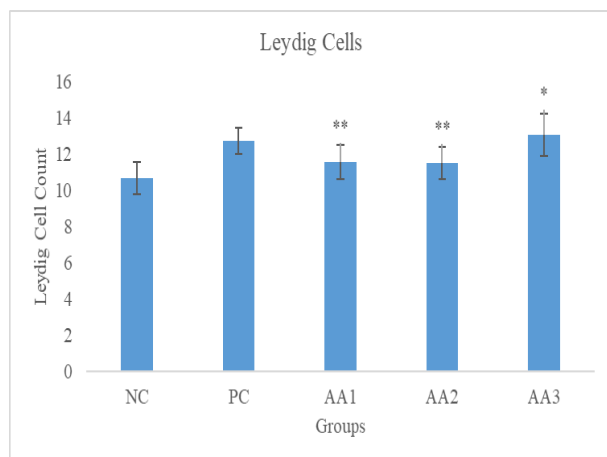


Fig 3. Average results of *Mus musculus* leydig cells. *: Sig with NC; **: Sig with PC

Figure 3 shows that the AA1, AA2, and AA3 treatment groups had a higher average number of LC compared to the NC group, but the AA3 group had the highest average result compared to all groups, even exceeding and significantly different from NC ($p < 0.005$). This is linear with the average testis weight results, which indicate that EeUrC most significantly affects the average testis weight in the AA3 group.

DISCUSSION:

Male sexual differentiation is driven by androgens secreted by LC and anti-Müllerian hormone from SC^{28,32}. Male fertility depends on the availability of T for spermatogenesis, while follicle-stimulating hormone (FSH) signaling is essential for the proliferation, differentiation, and function of SC and germ cells²⁹.

LC that differentiate during puberty increase testosterone production, which triggers SC maturation and germ cell meiosis, initiating spermatogenesis and sperm production³³. In adulthood, androgen receptors are activated, maintaining spermatogenesis. However, with aging, although sperm production continues, T secretion decreases, which is influenced by health conditions and medications²⁸.

In men, hypothalamic-pituitary-gonadal (HPG) hormones regulate T production in the testes and spermatogenesis, controlled by luteinizing hormone (LH) and FSH. Decreased sex hormones occur due to changes in the function and number of LC and SC³⁴. Male reproductive system dysfunction is also influenced by oxidative stress, apoptosis, and inflammation^{34,35}.

LH stimulates LC in the testes to produce T, while FSH stimulates SC in the seminiferous tubules, supporting nutrition and the synthesis of molecules essential for spermatogenesis. Together with T, FSH maintains spermatogenesis through the function of SC³⁶. In

addition, LC support spermatogenesis by secreting androgens and various hormones, cytokines, and growth factors³⁷.

Flavonoids are known to have pharmacological activities, such as antioxidant, anti-inflammatory, and anti-apoptotic³⁸⁻⁴¹. Oxidative imbalance can cause apoptosis, lipid peroxidation, DNA damage, and decreased sperm motility³⁹. Natural flavonoids are known to increase T levels by promoting the process of steroidogenesis and improving LC function^{42,43}. As amphipathic substances, flavonoids can penetrate the lipid layer of the membrane, protecting the acrosome membrane and spermatozoa from oxidative damage. This is important to ensure the sperm acrosome reaction required for fertilization⁴⁴, so flavonoids can play a vital role in improving this condition.

Flavonoids have antioxidant properties that support the function of the male reproductive system⁴⁵. Studies have shown that flavonoids enhance the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, which is essential for steroidogenesis, and increase StAR gene expression in LC, which plays a role in T release^{34,45}. Flavonoids also inhibit the cyclooxygenase-2 (COX-2) signaling pathway activation in rat LC by suppressing the thromboxane A2 receptor and the dosage-sensitive sex reversal-adrenal hypoplasia gene 1 (DAX-1). These effects accelerate steroidogenesis, especially in aging rats, by increasing steroidogenic acute regulatory protein (StAR) gene expression. DAX-1 decreases StAR expression and cAMP pathway activity. The NO/cyclic guanosine monophosphate (NO/cGMP) pathway can regulate steroidogenic activity, and PDE5 inhibitors have the potential to increase T secretion through LC³⁴.

CONCLUSION:

The study concluded that the 70% ethanol extract of *U. rufa* caulis demonstrated low toxicity with an LD₅₀ value of 1096.7 µg/ml. Additionally, the aphrodisiac activity test revealed that the administration of AA3 (1.7 mg/20 gBW/day) was the optimal dose, as it significantly increased testicular weight and the number of Leydig cells.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

ACKNOWLEDGMENTS:

The author extends sincere gratitude to the Directorate General of Higher Education, Research, and Technology of the Republic of Indonesia for providing funding for this research under contract No. 0459/E5/PG.02.00/2024.

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