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Sedative Hypnotic Activity of *Lagenaria siceraria* Extract on Swiss Webster White Male Mice

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ABSTRACT

***Introduction**: The rising prevalence of sleep disorders and concerns about conventional sedative medications' side effects has created an urgent need for safer therapeutic alternatives. **Aims**: This study investigated the sedative-hypnotic properties of Lagenaria siceraria fruit ethanol extract in a controlled laboratory setting using Swiss Webster male mice. **Methods**: The research employed a randomized design with 28 male mice (2-3 months old, 20-30 grams) divided into seven groups. Two control groups received either 0.5% NaCMC (negative control) or 0.013 mg/kgBW Diazepam (positive control). The remaining five experimental groups were administered L. siceraria extract at doses ranging from 21 to 49 mg/kgBW. All treatments were administered orally under controlled conditions. Statistical analysis using two-way ANOVA revealed significant differences between treatment groups ($p<0.005$). **Result**: Subsequent Duncan's test analysis demonstrated that the highest dose of L. siceraria extract (49 mg/kgBW) produced sedative-hypnotic effects comparable to the standard Diazepam treatment. This finding suggests that L. siceraria extract could potentially serve as a natural alternative to conventional sedative medications. **Conclusion**: The results of this study provide compelling evidence for the sedative-hypnotic properties of L. siceraria extract, warranting further investigation into its mechanism of action and potential therapeutic applications. Future research should focus on establishing optimal dosing regimens and evaluating long-term safety profiles before clinical implementation can be considered.*

KEYWORDS: Sedative hypnotic, *Lageneria siceraria*, diazepam, mice

INTRODUCTION

Sleep and rest are essential components of maintaining optimal health and wellbeing. Research has demonstrated that insufficient sleep significantly impairs cognitive function, particularly affecting concentration and the ability to perform daily tasks effectively (Rahma, 2016). During sleep, the body experiences a natural reduction in consciousness, utilizing this period for crucial physiological and psychological restoration. This restorative process serves as a vital protective mechanism against the adverse health effects associated with sleep deprivation

and insomnia (Ningsih & Rahma, 2014).

The treatment landscape for insomnia encompasses both pharmacological and non-pharmacological approaches. While pharmaceutical interventions, particularly sedative medications, effectively reduce anxiety, calm the nervous system, and decrease self-awareness, they are typically prescribed only for short-term use to prevent the development of chronic insomnia (Gottesman, 2013). This cautious approach stems from significant concerns regarding these medications' potential for dependence and addiction, along with notable side effects including depression, nausea, dizziness, and daytime drowsiness.

In response to these pharmaceutical limitations, there has been increasing interest in natural alternatives, particularly in Indonesia, where traditional medicine maintains a strong cultural presence. This preference for traditional remedies is deeply rooted in historical practice and generational wisdom (Munaf, 2018). One such promising natural remedy is *Lagenaria siceraria* fruit, which has demonstrated multiple therapeutic properties including cardioprotective, cardiotonic, and aphrodisiac effects, while also serving as an alternative diuretic and treatment for various conditions such as fever, asthma, and coughs. Recent scientific analysis has revealed that Lagenaria siceraria fruit extract contains a complex profile of bioactive compounds, including carbohydrates, saponins, glycosides, and flavonoids (Muhamad, 2022). Of particular significance is the presence of terpenoids, a class of secondary metabolites recognized for their sedative properties (Nugroho et al., 2011). The identification of these compounds presents a compelling opportunity for scientific investigation.

Given these promising properties, there is a compelling need to scientifically investigate the sedative-hypnotic effects of *L. siceraria*. This research aims to bridge the gap between traditional knowledge and modern scientific understanding by examining these effects in Swiss Webster strain white male mice. The study's significance lies in its potential to validate traditional uses of *L. siceraria* and possibly identify a natural alternative to conventional sleep medications, addressing the growing concern over pharmaceutical side effects and dependency.

METHODS

Preparation of Lagenaria siceraria extract

L. siceraria fruits were harvested from Pagaralam city plantations and underwent systematic preparation, beginning with the processing of 7 kg of fruits through careful washing, wet sorting, and coarse chopping. The prepared sample was then subjected to a strategic three-day extraction protocol using 96% ethanol as the solvent, with an initial volume of 3 liters. The extraction employed precisely calculated solvent ratios, beginning with a 1:5 ratio on the first day to maximize

initial compound extraction, followed by a reduced 1:4 ratio for the second and third days. The final stage involved concentrating the extract using a rotary evaporator under carefully controlled conditions, maintaining a water bath temperature of 15-20°C, pressure at 20 psi, and rotation speed at 120 rpm, ensuring optimal concentration while preserving the integrity of the extracted compounds.

Phytochemical screening

The phytochemical screening conducted in this study encompassed the identification of five key compounds: flavonoids, phenols, alkaloids, saponins, and steroid/terpenoids. The analytical methods employed were based on established protocols documented by Sulistiyarini (2020) and Astarani et al. (2013).

Sedative Hypnotic Activities

In this experimental study, which received ethical approval (registration number 0623070086), twenty-eight male Swiss Webster mice were sourced from Abduh Tikus Palembang. The mice, aged 2-3 months and weighing 20 grams, underwent a seven-day acclimatization period with adequate food and water provision. During this period, their behavior was monitored, and body weight changes remained within acceptable limits, not exceeding 10%. Prior to treatment, the mice were fasted for three to four hours while maintaining water access. The study design involved random allocation of the animals into seven groups, with four mice per group, meeting the minimum testing requirements. The treatment protocol included intravenous administration of 0.5% Na CMC as negative control (Group I), diazepam (0.0013 mg/20gBW) as a positive control (Group II), and varying doses of Lagenaria siceraria fruit ethanol extract. The experimental groups received different dosages: Group III (21 mg/kgBW), Group IV (28 mg/kgBW), Group V (35 mg/kgBW), Group VI (42 mg/kgBW), and Group VII (49 mg/kgBW). The assessment of sedative hypnotic activity employed multiple testing methods, including traction, chimney test, evasion box, and fireplace test. Researchers recorded various temporal measurements, specifically noting when the animals fell, exited, began climbing, and rose.

Data analysis

Statistical analysis was conducted using the SPSS program, following a systematic approach to data evaluation. The analysis began with a normality assessment using the Levene test to verify data homogeneity. For homogeneous data sets, a two-way ANOVA analysis was performed, followed by Duncan's test to identify significant differences between groups. The Post Hoc Test was then employed to determine statistical significance between groups, with a p-value threshold of 0.05. Results yielding p-values less than 0.05 indicated significant differences between groups, while p-values greater than 0.05 suggested no significant differences.

RESULTS AND DISCUSSION

The extraction yield results shown in Table 1 were suboptimal, likely influenced by several key process variables including extraction temperature, duration, and simplicia circulation patterns, as noted by Rani (2017).

Phytochemical screening confirmed the presence of important secondary metabolite compounds in the *L. siceraria* fruit ethanolic extract (Table 2). The analysis revealed a comprehensive profile of bioactive compounds, including flavonoids, alkaloids, saponins, tannins, and steroids. These findings align with research by Chao and Declan (2022), who classified *L. siceraria* as a vegetable with low caloric content and significant biological compounds. The presence of these compounds was confirmed through multiple chemical tests: flavonoids produced characteristic yellow coloration; alkaloids were verified using three distinct reagents (Mayer's yielding white/yellow precipitate, Wagner's producing orange-brown precipitate, and Dragendorff's showing orange-red precipitate); saponins demonstrated positive foam formation; phenols produced white precipitate; and terpenoids exhibited blue-green coloration.

The in vivo experimental results, obtained through four distinct methodological approaches, demonstrated that the ethanol extract of *L. siceraria* fruit induced sedative effects across all treatment groups. The doses ranged from 21 mg/kgBW to 49 mg/kgBW, with a clear dose-dependent relationship observed in the sedative response. As reported by Sudarsono et al. (2020), higher doses consistently produced stronger sedative effects in the test subjects, establishing a direct correlation between dosage and sedative potency.

Table 2. Preliminary phytochemical screening of *L. siceraria* extract

Test	Result
Flavanoid	+
Alkaloid	+
Saponin	+
Phenols	+
Steroid	+
Terpenoid	-

(+) means contained phytochemical compound, (-) not contained

The quantitative analysis presented in Table 3 further substantiated this dose-dependent pattern. Group V, receiving 49 mg/kgBW, exhibited the most pronounced sedative effects, followed by progressively diminishing responses in Group IV (42 mg/kgBW) and Group III (35 mg/kgBW). This pattern manifested through decreased rodent mobility and enhanced sedative activity at higher concentrations. The traction test findings, presented in Figure 1a, reinforced these observations, demonstrating an inverse relationship between sedative potency and fall time, with accelerated fall times indicating enhanced sedative effects across increasing

Table 1. Results of *Legenaria siceraria* extract yield

Sample	Simplicia (g)	Crude extract (g)	Yield (%)
Legeneria siceraria	7000	45	0.642

Table 3. Result of the average time of mice in the sedative acclimatization test

Treatment group	*Traction Test (second)*	*Chimney Test (second)*	*Evasion Box (minute)*	*Fireplace Test (second)*
Negative control	53.00±0,816	13.00±1.633	2.2575±0,16978	16.25 ±2.630
Positive control	30.00±2.449	53.00±0.816	8.2275±0,01258	51.75±2.217
Group I	40.50±1.291	38.50±1.291	4.2450±0,86735	19.25±2.217
Group II	37.75±2.363	42.50±1.291	4.9300±1.23488	24.25±6.397
Group III	35.75±2.363	44.50±1.291	6.0825±084061	37.00±3.916
Group IV	34.25±2.363	45.00±2.449	6.4650±0,95696	43.25±4.646
Group V	33.25±1.893	48.50±2.380	6.9725±1.42787	50.75±2.217

dosages (Saputri, 2021). The investigation's robustness was further supported by tube exit time analysis (Figure 1b), which revealed statistically significant differences between treatment groups and negative controls. The 49 mg/kgBW dose emerged as particularly effective, demonstrating optimal sedative enhancement. This finding was complemented by evasion box test results (Figure 1c), where the highest dose group (49 mg/kgBW) showed performance comparable to the positive control group, with extended rise times indicating pronounced sedative effects. The climbing time assessment provided additional validation through varied durations across treatment groups (Figure 1d). Using diazepam as a reference sedative in the positive control group, the study established that prolonged climbing times corresponded with increased sedative effects. This multi-parameter evaluation approach, encompassing traction, tube exit, evasion box, and climbing time assessments, provides comprehensive evidence for the sedative properties of *L. siceraria* extract, with consistent dose-dependent effects observed across all testing methodologies.

In this work, diazepam was used as the control. The pharmacological mechanism of diazepam, a benzodiazepine medication, centers on its interaction with GABA receptors and their associated systems. As explained by Friatna & Lela (2022), diazepam acts by regulating chloride ion accumulation in cellular structures, thereby influencing membrane electrical potential. Eugen (2019) further elaborates that diazepam enhances the interaction between GABA and GABA A receptors, leading to increased chloride ion conductance. This process facilitates cellular hyperpolarization and subsequent reduction in cell excitability. The detailed mechanism, as described by Mycek (2017), involves gamma-aminobutyric acid release at nerve terminals adjacent to GABA receptors on cell membranes, initiating chloride channel formation. This process elevates CT neuron thresholds, with chloride currents traversing the outer membrane to induce localized hyperpolarization. Benzodiazepine receptors, exclusively present in the central nervous system and aligned with GABA neurons, enhance GABA receptor affinity through binding interactions, resulting in more frequ-

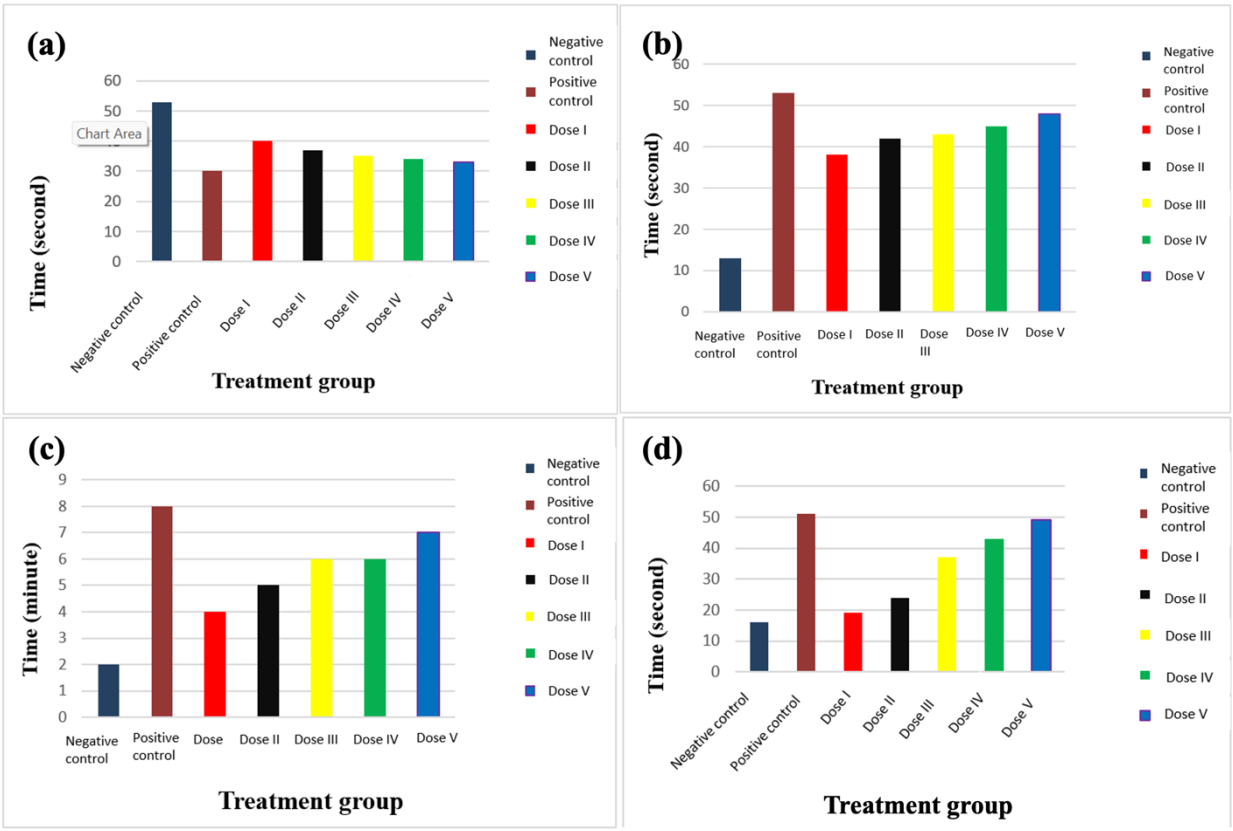

Figure 1. Sedative activity of *L. siceraria* fruit extract. (a) Traction test, (b) Chimney test, (c) Evasion box test, and (d) Fireplace test. Dose mean groups.

ent chloride channel activation and subsequent neuron inhibition.

In clinical applications, these sedative-hypnotic medications serve multiple therapeutic purposes, including pain management, anesthesia administration, seizure control, and insomnia treatment, as noted by Dewatisari & Rumiyanti (2016). The sedative properties of *L. siceraria* are primarily attributed to its flavonoid content, which functions as a GABA receptor agonist. Ikawati (2013) describes how these compounds facilitate chloride ion channel opening, leading to membrane potential changes and subsequent sedative effects. The extract's efficacy extends beyond sedation to include muscle relaxation properties, with flavonoids enhancing GABA's modulatory effects. Additionally, saponins present in the extract also contribute to its sedative properties through surface tension reduction and metabolic process interference, as documented by Harun et al. (2013). Moreover, steroids in the extract enhance GABA receptor binding affinity, promoting hyperpolarization through chloride channel activation, ultimately inducing a sleep state.

The experimental analysis, employing four distinct methodological approaches, yielded statistically robust results. The data demonstrated normal distribution and homogeneity, with two-way ANOVA revealing significant differences among treatment groups. Duncan test results indicated

significant differentiation from positive controls, with the 49 mg/kgBW dose (Group V) emerging as the most efficacious treatment concentration.

CONCLUSION

The hypnotic sedative properties of *L. siceraria* has been evaluated in male Swiss Webster mice using four techniques. According to the research findings, the fruit extract of *L. siceraria* demonstrated potential sedative and hypnotic properties when administered to male Swiss Webster mice. The study evaluated different dosages and found that 49 mg per kilogram of body weight produced the strongest sedative and hypnotic effects. Duncan's test analysis revealed a dose-dependent response, with 42 mg/kg and 35 mg/kg showing progressively lower levels of effectiveness compared to the 49 mg/kg dose.

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