Hypnotic-Sedative Effectiveness Of Ethanol Extract Keji Beling (*Strobilanthes Crispus*) In Mice With Rotarod Test As An Indicator Of Motor Impairment

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Abstrak

Insomnia is a sleep disorder that adversely affects the quality of life, mental and physical health. Treatment of insomnia often utilizes pharmacological therapies that have side effects. Keji beling (*Strobilanthes crispus*) contains secondary metabolites of flavonoids, tannins, alkaloids, saponins, and triterpenoids that have potential as natural sedatives and hypnotics. This study uses the rotarod test to detect motor impairment and evaluate the effectiveness of the ethanol extract of keji beling (EEKB) as a hypnotic-sedative agent in mice. Extraction of keji beling by maceration using 96% ethanol, the extract was tested on mice in four groups: diazepam 5 mg/kgBB, CMC Na 1%, and EEKB 600 and 1200 mg/kgBB. The parameter measured was the number of falls on the rotarod for 30 rotation/minutes after administration. EEKB showed decreased motor balance. The 1200 mg/kgBB dose produced the highest mean number of falls (25 times), followed by the 600 mg/kgBB dose (11.25 times), similar to the diazepam 5mg (16.75 times). SPSS indicated that EEKB exerted a significant hypnotic-sedative effect by modulating GABA receptors. EEKB in doses of 600 and 1200 mg/kgBB has an effectiveness comparable to diazepam as a hypnotic tranquilizer, so it has the potential to be developed as a natural-based insomnia therapy agent.

Keywords: insomnia; *strobilanthes crispus*, hypnotic-sedative, rotarod, ethanol extract

1. INTRODUCTION

A typical sleep problem is insomnia, which can affect a person's quality of life and physical and mental health. It often occurs alongside other medical problems or psychiatric conditions, such as pain or depression. Individuals who experience insomnia generally have a poorer view of their quality of life compared to those who do not. This phenomenon applies to both genders, although women tend to report insomnia complaints more often and experience a more significant decrease in quality of life than men (Langer Gary & Filer Christine, 2020). Global studies show that the prevalence of insomnia varies widely between countries, with prevalence rates ranging from 2.3% to 25.5%. Factors such as mood disorders, anxiety, and substance abuse have a strong association with insomnia. This suggests that insomnia is often associated with other mental health conditions (Aernout et al., 2021).

Treatment of insomnia usually involves a multidisciplinary approach, including behavioral interventions, improved sleep habits, psychological stress management, and

pharmacological therapy. Frequently prescribed medications Among the non-benzodiazepine hypnotics used to treat insomnia are zolpidem, eszopiclone, and zaleplon. Zolpidem, which is one of the most commonly used hypnotics, however, has some side effects that should be noted. In addition, benzodiazepines and benzodiazepine receptor agonists are also frequently used, but both have the risk of serious side effects, such as tolerance, dependence, central nervous system depression, and amnesia (Edinoff et al., 2021). Keji beling leaf (*Strobilanthes crispus*) is known among Indonesians as a plant with various properties, one of which is to treat sleep disorders or insomnia. Empirically, this plant has been used to help improve sleep quality and overcome sleep difficulties. Some recent studies have shown that keji beling leaves contain bioactive compounds that have the potential to provide sedative, anti-anxiety, and antidepressant effects, which play an important role in overcoming insomnia (Friatna et al., 2023a).

Keji beling leaves contain flavonoids, polyphenolic compounds found in various plants, including keji beling leaves. These compounds have different medicinal effects, including anti-inflammatory antioxidants and mild sedatives. Some studies reveal that flavonoids, like GABA, may affect the neurotransmitter system in the brain and influence sleep regulation. In addition, flavonoids may also help reduce anxiety, which is often a significant cause of insomnia and may improve sleep quality by calming the central nervous system (Spencer, 2008).Saponins are triterpenoid compounds found in various parts of plants, including constipated leaves. Saponins have adaptogenic properties that can reduce stress and promote relaxation. These effects are significant in overcoming insomnia caused by anxiety or stress (Li et al., 2024).

2. METHOD

Materials

Mice scales, Sudip, grinder, stopwatch, Buchner analytical balance (Lutou), oral syringe, rotary vacuum evaporator (Biobase RE-301) , Whatman filter paper and rotarod (TM-200B), 96% ethanol p.a (Merck), potassium iodide (KI) p.a (Merck), hydrochloric acid (HCl) p.a (Merck), and glacial acetic acid (CH_3COOH) p.a (Merck), iodine (I_2) (Merck), diazepam (Merck), sulfuric acid (H_2SO_4) p.a (Merck), Chloroform ($CHCl_3$) p.a (Merck), magnesium powder p.a (Merck), iron(III) chloride ($FeCl_3$) (Merck) and samples of keji beling leaves were obtained from Pagotan area, Madiun Regency, East Java.

Exctration

Keji beling leaves were dried using an oven at a low temperature (40-50°C) (Nurhaslina et al., 2022).After drying, it was pulverized into powder using a grinder. In the pulverization process, the surface area of the material to be extracted increases. This allows the active compounds to dissolve more quickly in the solvent used during extraction (Alsaud & Farid, 2020).For three days, the samples were macerated with 96% ethanol solvent. Then, it was filtered, and the remaining pulp was macerated again. The same procedure was carried out until the solvent used no longer changed color after use. The extract obtained was evaporated with a *rotary vacuum evaporator* (Hasanuddin et al., 2023).

The percentage yield of the extract was calculated using the following formula (Friatna et al., 2023):

$$\% \text{ result} = \frac{final\ weight}{initial\ weight}\ X\ 100\%$$

According to Harbome JB (1998),to test alkaloids, the ethanol extract of keji beling is added with 1% hydrochloric acid, and 1 mL of *Wagner*'s reagent is added, experiencing a reddish-brown color change, indicating that the extract has alkaloids. To perform the saponin test, the ethanol extract of keji beling is added to 10 mL of distilled water. After mixing, if there is foam, it indicates that the saponin test is positive. For steroid and triterpenoid tests, ethanol extract of keji beling was added 1 milliliter of H_2SO_4 and CH_3COOH. The presence of triterpenoids is indicated by the appearance of red in the lower layer; the green upper layer indicates the presence of steroids. The test combines the ethanol extract of keji beling with 3 mL of pure H_2SO_4 and 2 mL of $CHCl_3$ to produce terpenoids. After heating for three minutes, a positive reaction indicates the presence of terpenoids. EEKB was added into 5 milliliters of distilled water to test for tannins with a few drops of $FeCl_3$ 5%. A color change to blackish green indicates a positive reaction. Put the ethanol extract of keji beling into 100 mL of hot water to test for flavonoids, then boil for 5 minutes and filter. To 5 mL of the filtrate taken, add 0.005 mg of magnesium powder and 1 mL of concentrated HCl and shake. The color changes to yellow, red, or pink, indicating a positive reaction to flavonoids.

Activity Test

The test animals were adapted for 1 week before treatment and fasted for 18 hours while drinking. For the positive control group, diazepam was induced at a dose of 5 mg, and the recommended administration volume for rats was 0.5 mL (Sharma, 2023).In Friatna et al.'s

(2023b) study, the hexane extract of keji beling leaves was effective at 400 and 600 mg / kgBB because it has sedative-hypnotic activity.

There are four treatment groups with 6 mice in each group, namely group 1, induced with 1% CMC Na as a negative control; group 2, induced with diazepam as a positive control; and groups 3 and 4, induced with a suspension of ethanol extract of keji beling (EEKB) at a dose of 600 mg/kgBB and 1.2 g/kgBB per oral. Mice were first trained to rotarod on the first day for 15 minutes at a speed of 30 revolutions/minute. Then, after being induced with each test preparation, the patients waited for 60 minutes. After 1 hour, the mice were again placed on the rotarod for 30 minutes, rotated at the same speed, and then the fall time was calculated; this was done 7 times. The Rotarod tool measures motor coordination and balance in rats (Hasanuddin et al., 2023). ANOVA test was used to analyze the statistical data obtained. Then, *post hoc* tests were run to determine if these groups had significant differences.

3. RESULTS AND DISCUSSION

According to the determination results, the keji beling plant is known by the scientific name *Strobilanthes crispa* Blume. Extraction results with the maceration method in Table 1

Table 1. Extraction Results of Keji Beling (*Strobilanthes crispus*)

Solvent	Weight of Simplisia	Weight of Viscous Extract	Results
96% Ethanol	500 grams	51.2 grams	10.24%

The extraction results of *Strobilanthes crispus* Blume using 96% ethanol solvent in this study showed a concentrated extract yield of 10.24%, which was significantly higher than the study by (Friatna et al., 2023)who reported a yield of 0.5562% (3.65 grams of keji beling leaf thick extract). This difference is likely due to variations in extraction methods, the type of crude extract, or process parameters such as extraction time and temperature. Although the yield of keji beling thick extract in this study was higher (10.24%), this result does not necessarily reflect its pharmacological efficacy.

The results of the observation of the chemical compound content of keji beling (*Strobilanthes crispus*) extract are shown in Table 2.

Table 2. Phytochemical Screening Results of keji being (*Strobilanthes crispus*) leaf extracts

No.	Compound Check	Reagents	Observation Results	Description
1	Alkaloids	Wagner	Reddish brown	+
2	Saponins		Foaming	+
3	Triterpenoids	Acetic acid	Red color (bottom layer)	+
4	Steroids	Sulfuric acid	Green color (bottom layer)	+
5	Tannins	FeCl	Blackish green	+
6	Flavonoids	Mg and HCl	Pink	+

The results of phytochemical screening (Table 2) indicate the presence of bioactive compounds such as flavonoids, saponins, and alkaloids, which are known in the literature to potentially affect the central nervous system (CNS). Flavonoids, for example, have been reported to exhibit anti-stress and analgesic activities (Holanda et al., 2020), while saponins and alkaloids in other studies have been shown to suppress exploratory activity and influence sleep duration (Begum et al., 2020). These compounds are suspected to contribute to the sedative-hypnotic effects observed in the rotarod test (Table 3), including an increase in the number of falls in the EEKB 1200 mg/kgBB group (25.00 ± 3.559) compared to the negative control (7.75 ± 9.535). The high average number of falls at the highest dose indicates impaired motor coordination or muscle relaxation, consistent with the CNS-depressing effects of alkaloid and saponin compounds. However, the variable results in the EEKB 600 mg/kgBB group (11.25 ± 5.679) suggest the possibility of dose-dependent responses or complex interactions between active compounds in the extract. Thus, although phytochemical screening (Table 2) confirmed the presence of potential compounds, the rotarod test (Table 3) supports the hypothesis that the sedative-hypnotic effects of keji beling are mediated by the combination of bioactive compounds, with dose and extract formulation as critical factors in its efficacy.

Table 3. The average number of falls on the rotarod

Test Group	∑ Early Fall T0 (30 minutes)	∑ Last Fall T1 (30 minutes)	Average Number of Falls Mean ± SD
Group +	19	74	16.75 ± 2.362
Group -	23	12	7.75 ± 9.535
EEKB 600 mg/KgBB	8	62	11.25 ± 5.679
EEKB 1200 mg/KgBB	10	106	25.00 ± 3.559

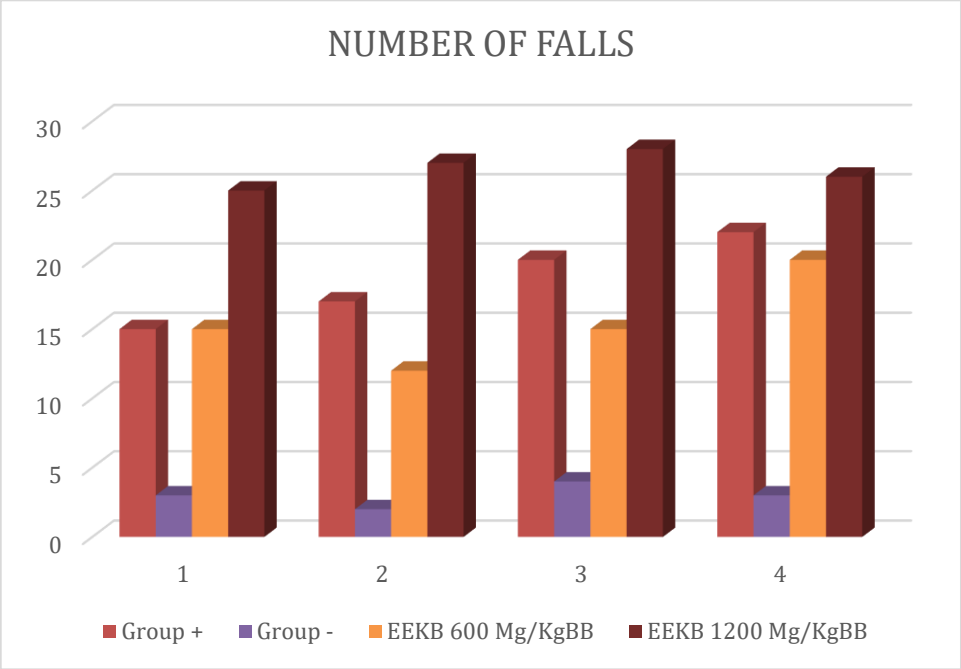

Figure 1. Number of animals falling on the rotarod

The results showed that the positive control group induced by diazepam 5 mg had an average number of falls on the rotarod of 16.75 times for 30 minutes, more than the negative control group of 7.75 times; this is because diazepam is a compound that binds to the A-type GABA receptor *ionophore* complex which is calming and reduces activity. As a sedative, diazepam is used as a central nervous system depressant used to treat sleep problems, including insomnia used to treat sleep problems, including insomnia (Alnamer et al., 2012). Diazepam works by increasing the activity of *gamma-aminobutyric acid* (GABA A) receptors, which produces a calming effect on the central nervous system. The drug is used to treat anxiety, sleep problems, alcohol withdrawal syndrome, seizures, and muscle spasms (Zhang et al., 2022). Chronic use of diazepam can lead to cognitive impairment, including decreased memory and learning functions. Studies show that diazepam can reduce *dendritic* density and neuronal complexity in the *hippocampus*, contributing to cognitive decline (Furukawa et al., 2021).Diazepam also works by modulating GABA receptors, which play a role in sedative effects and motor impairment. Modifying these receptors may affect diazepam potency and *allosteric* modulation (Blednov et al., 2020).

SPSS was used to test the data, namely *one-way ANOVA* analysis followed by *post hoc* analysis, which showed that the positive control group, EEKB 600 and 1200 mg/kgBB with the negative control group showed significant differences, while EEKB 600 and 1200 mg/kgBB with the positive control group did not show significant differences, which means that this dose

has comparable effectiveness with the positive control group. In this study, the potentiation effect of ethanol extract of keji beling can be seen in Table 3, which is decrease in motor balance as measured by the rotarod test. Ethanol extract of keji beling has produced hypnosis at doses of 600 and 1200 mg/kgBB, which can be seen from the number of falls on the rotarod for 30 minutes; this indicates that ethanol extract of keji beling produces movement-related activities resulting from brain activation, which appears as stimulation of central neurons through various neurochemical processes and increases brain metabolism, which is caused by the sedative activity of ethanol extract of keji beling through the GABAergic pathway because sedation can be produced through GABAergic transmission in experimental animals (Alnamer et al., 2012).

Diazepam, a benzodiazepine drug, produces a sedative and anti-anxiety (anxiolytic) effect by strengthening the activity of the neurotransmitter GABA in the brain. It does this by increasing GABAergic inhibition—a process that suppresses excessive neuron activity—so that the central nervous system becomes calmer (Bappi et al., 2024). Meanwhile, natural compounds such as flavonoids (e.g., chrysin and quercetin) also exhibit anxiolytic and antidepressant effects, but through different mechanisms. Chrysin, one of the flavonoids, is able to protect the body from behavioral changes due to acute stress. Although its effect on reducing anxiety is similar to diazepam, chrysin does not rely on the GABA pathway. Research shows that this compound works through non-GABA mechanisms, such as modulating stress responses or regulating certain hormone levels. Quercetin, another flavonoid, has a more complex mode of action. Although it can interact with GABAA receptors, its anxiolytic effect is even stronger when combined with compounds such as sclareol. shows that quercetin does not rely entirely on the GABA pathway but rather involves synergistic interactions with other components to produce a calming effect (Flores-Aguilar et al., 2023).

In the study of Taylor et al. (2021), therelationship between motor balance and cognitive function shows that the two aspects are interrelated and can influence each other, which shows that executive function and *visuospatial* ability have a strong relationship with balance performance. Tannins, saponins, flavonoids, alkaloids, and triterpenoids, also present in the ethanol extract of keji beling, are bioactive compounds known to have various pharmacological effects, including hypnotic and sedative effects. A study by He et al. (2020) and Khoramjouy et al. (2021) has shown that these compounds can affect the central nervous system and are in conventional medicine to treat sleep and anxiety problems. These secondary metabolite compounds affect neurotransmission in the brain, which may reduce central nervous system activity and induce sleep, while flavonoids may modulate GABA receptors, a common tranquilizer target (Khoramjouy et al.).Alkaloids and saponins also play a role in the

pharmacological network to overcome insomnia through interaction with neurotransmitter receptors (Yan Yan et al., 2022.Likewise, triterpenoids can reduce insomnia symptoms and improve sleep quality through sedative and hypnotic effects (Mayasa Vinyas et al., 2024).

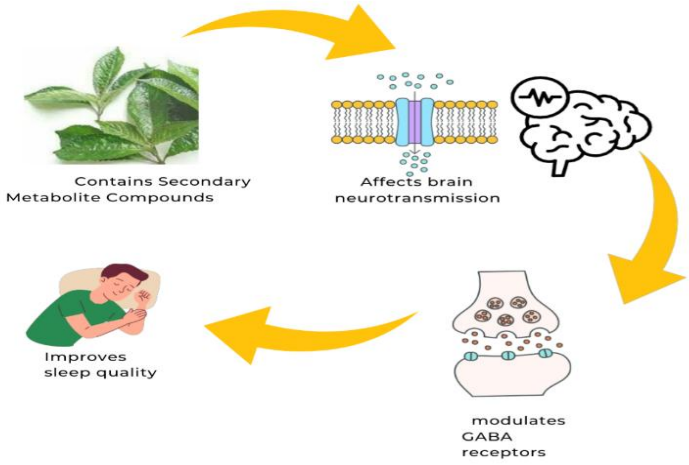

Figure 2. Mechanism of metabolite compounds in modulating GABA receptors

According to Sulastri et al. (2021), the*IR spectra* and GC-MS data of the ethyl acetate fraction of keji beling leaves are *D-limonen*e, a monoterpene essential oil. *D-limonen* has neuroprotective potential and can affect brain function through several mechanisms, namely reducing anxiety-related behavior by regulating dopaminergic and GABAergic neuron activity mediated by A2A adenosine receptors (Song et al., 2021). This compound can also contribute to health by increasing antioxidant activity and reducing inflammation so that it can contribute to improving sleep quality and overcoming insomnia (Eddin et al., 2021).

4. CONCLUSION

The dose of 1200 mg/kgBB caused the greatest average number of falls (25 times), followed by the dose of 600 mg/kgBB (11.25 times), which was comparable to the dose of diazepam 5 mg (16.75 times). EEKB modulated GABA receptors to produce a strong hypnotic-sedative effect. With a hypnotic tranquilizer efficacy similar to that of diazepam at dosages of 600 and 1200 mg/kgBB, EEKB holds promise for use as a natural insomnia treatment.

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responsibility for any shortcomings lies solely with the authors. We hope that the results of this study can contribute to the development of pharmacology, particularly in the exploration of the potential of local medicinal plants.

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