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The Administration of a Combined Extract of Gotu Kola (*Centella asiatica*) and Peppermint (*Mentha piperita*) Leaves on the Brain Cell Count of Stressed Male Mice (*Mus musculus*)

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Abstract: Chronic stress is a condition that can adversely affect the central nervous system, particularly the brain, by causing damage to neurons in the hippocampal region, which plays a crucial role in memory and learning functions. This study aimed to evaluate the neuroprotective effects of a combined extract of gotu kola leaves (*Centella asiatica*) and peppermint leaves (*Mentha piperita*) on the number of normal brain cells in male mice (*Mus musculus*) subjected to chronic stress. A Completely Randomized Design (CRD) was used with five treatment groups: a negative control group (K−) with no stress and no extract, a positive control group (K+) exposed to stress without extract administration, and three treatment groups (P1, P2, and P3) receiving the combined extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW, respectively. Stress induction was carried out using the immobilization method for 14 consecutive days, followed by extract administration for 35 days. After the treatment period, hippocampal brain tissue was collected and histologically analyzed using Hematoxylin-Eosin (H&E) staining. To assess the treatment effects, One-Way ANOVA was performed. Significant differences were found, Duncan's Multiple Range Test (DMRT) was conducted at a 5% significance level ($p < 0.05$). The results demonstrated that administration of the gotu kola and peppermint extract combination significantly reduced neuronal damage and increased the number of normal brain cells. The P3 group (300 mg/kg BW) exhibited the highest number of normal brain cells and the lowest neuronal damage scores, closely resembling the normal condition in the K-group. Therefore, the combination of gotu kola and peppermint leaf extracts shows potential as a natural neuroprotective agent in mitigating the adverse effects of chronic stress on the brain.

Keywords: *Centella asiatica*; Hippocampus; *Mentha piperita*; Mice; Neuroprotection; Stress.

Introduction

Stress is a physiological and psychological condition that can lead to a wide range of health disorders, including impaired nervous system function [1]. Chronic exposure to stress has been shown to significantly elevate cortisol levels, which can adversely affect the structure and function of the brain [2]. Among the brain regions most susceptible to the effects of stress is the hippocampus, which plays a vital role in learning and memory processes [3]. A decrease in hippocampal cell density due to stress may contribute to cognitive impairments and increase the risk of developing neurodegenerative disorders [4].

The brain serves as the central control system of the body, including its response to stressors [5]. When an individual experiences psychological or physical pressure, the hypothalamus initiates the release of stress-related hormones such as cortisol and adrenaline. These hormones prepare the body to cope with stressful situations by increasing heart rate and blood pressure [6]. Although this response is adaptive in the short term, prolonged stress can disrupt hormonal balance. As a result, brain function may decline, leading to difficulties in thinking, weakened memory, and a heightened risk of mental disorders such as anxiety and depression [7].

In recent decades, research into the use of herbal remedies as alternative therapies for mitigating the adverse effects of stress on the brain has gained momentum. Gotu kola (Centella asiatica) is a well-known medicinal plant with neuroprotective properties, traditionally used to enhance cognitive performance and protect neuronal cells from damage [8]. Its bioactive compounds, such as asiaticoside and madecassoside, possess antioxidant capabilities and stimulate neuronal cell growth [9]. Similarly, peppermint (Mentha piperita) also holds promise as a neuroprotective agent. Its key constituents, including menthol and flavonoids, are known for their calming effects and their ability to reduce oxidative stress in the nervous system [10]. The combination of gotu kola and peppermint is expected to produce a synergistic effect in safeguarding the brain from stress-induced damage.

Studies have shown that gotu kola extract exhibits adaptogenic effects by reducing cortisol levels and enhancing cognitive function and mental well-being. A study by Park et al. [11] reported that gotu kola possesses antioxidant properties that help alleviate oxidative stress, has strong anti-inflammatory effects, supports neuronal

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regeneration, may prevent neuronal cell damage, and is capable of inhibiting neurotoxicity. Additionally, Wattanathorn et al. [12] found that supplementation with gotu kola extract for 60 days improved memory and reduced anxiety in elderly individuals. Meanwhile, peppermint is known to contain menthol, which has a relaxing effect on the central nervous system [13]. Usila et al. [14] demonstrated that aromatherapy using peppermint essential oil can reduce stress and improve sleep quality in individuals experiencing anxiety. Peppermint has also been reported to relieve stress in pregnant women and alleviate symptoms such as nausea and vomiting [15]. The neuroprotective effects of gotu kola, combined with the calming properties of peppermint, suggest that this herbal combination could serve as a promising natural therapy for stress and anxiety. There has been no previous research combining these two extracts to treat hippocampal damage due to stress.

The present study aims to evaluate the effect of administering a combined extract of gotu kola and peppermint leaves on the brain cell count in stressed male mice. Histological staining techniques were employed to quantify neuronal cell density in the hippocampus and assess the extent of neuroprotection provided by the extract. It is anticipated that this combined herbal extract may be developed as a natural alternative therapy to mitigate the negative impacts of stress on the brain.

Research Methods

Research Design

This study employed a laboratory experimental design with a Completely Randomized Design (CRD). The subjects of the study were male mice aged 8–10 weeks, weighing 25–30 grams, selected using purposive sampling, and divided into five treatment groups, each consisting of 5 male mice. The first group served as the negative control (K−), which did not receive any stress or extract. The second group was the positive control (K+), which was subjected to stress without receiving any extract. The remaining three groups were subjected to stress induction along with the combination extract of gotu kola and peppermint leaves at doses of 100 mg/kg body weight (P1), 200 mg/kg body weight (P2), and 300 mg/kg body weight (P3). Stress induction was performed using the immobilization stressor method, where the mice were placed in narrow tubes for 2 hours each day for 14 days. After the stress period, the treatment groups were administered the combination extract of gotu kola and peppermint leaves orally via a gastric sonde at the specified doses for 35 days.

Preparation Stage

Extract Sample Preparation

This study used young, fresh, and green gotu kola and peppermint leaves as the primary materials for the extract preparation.

Extraction Process

The gotu kola and peppermint leaves were first dried using an oven at temperatures between 30–50°C for 6 to 8 hours. After drying, the leaves were ground using a blender into a fine powder, which was then sieved using a mesh screen number 10. The obtained powder was then extracted through maceration with 96% ethanol for three days, with periodic stirring. After the extraction period, the solution was filtered using filter paper and then evaporated using a rotary evaporator to obtain a concentrated extract.

Research Implementation Stage

Brain Tissue Isolation

On day 36, the mice were sacrificed by cervical dislocation. Subsequently, dissection was performed to retrieve the brain organ. The excised brain was first washed with NaCl physiological solution until clean, then immersed in Bouin's solution and NaCl fixative. The brain was processed into paraffin blocks and sectioned using a microtome into slices 3–5 µm thick to obtain hippocampal sections. These tissue slices were then used for histopathological analysis via Hematoxylin and Eosin (H&E) staining [16].

Hematoxilin and Eosin Staining

The staining process began with the removal of paraffin from the specimen by immersing it in silol solution twice for 30 minutes each. Rehydration was then performed by immersing the specimen in absolute alcohol for 2 minutes, followed by immersion in 95% and 70% alcohol for 1 minute each. The specimen was then washed with running water. Staining was carried out with hematoxylin for 8 minutes, followed by a 2-minute wash. The specimen was then stained with eosin for 2 minutes and rinsed again with running water. Dehydration was performed by immersing the specimen in 95% alcohol and absolute alcohol, each for 2 minutes, twice. The final step was immersion in silol twice for 2 minutes, followed by covering the specimen with a cover slip using permanent mounting medium (Permount) and labeling.

Data Analysis

The analysis was conducted quantitatively using SPSS software version 22.0 for Windows. The Kolmogorov-Smirnov test was used to assess the normality of the data. If the data were not normally distributed, the Kruskal-Wallis test was applied. This non-parametric statistical test does not assume a normal distribution and is more appropriate for ordinal data or interval data that do not meet the assumption of normality. Homogeneity of variance was tested using Levene's Test. To determine the effect of treatment, a One-Way ANOVA was conducted. If a significant difference was found, the analysis was followed by Duncan's Multiple Range Test (DMRT) at a 5% significance level ($p < 0.05$).

Results and Discussion

Hippocampal Neuron Damage Scores

Histopathological observations of hippocampal tissue in mice revealed differences in neuronal damage scores among the treatment groups. The negative control group

(K−), which was not subjected to stress or extract administration, exhibited the lowest neuronal damage score of 0.5 ± 0.12, indicating intact and healthy neuronal structures. In contrast, the positive control group (K+), which underwent stress induction without extract treatment, showed the highest neuronal damage score of 2.8 ± 0.25, indicating severe neuronal damage characterized by nuclear pyknosis, vacuolization, and cellular necrosis.

In the treatment groups receiving the combination extract of gotu kola and peppermint leaves, there was a significant reduction in neuronal damage scores with increasing doses. Group P1 (100 mg/kg body weight) showed a score of 2.1 ± 0.30, indicating moderate damage. Group P2 (200 mg/kg body weight) demonstrated improved tissue structure with a score of 1.5 ± 0.22, and group P3 (300 mg/kg body weight) recorded the lowest damage score among the treatment groups, at 0.9 ± 0.18—approaching normal conditions. These findings indicate that the combination extract has a protective effect against stress-induced neuronal damage, particularly at the highest dose.

Table 1. Hippocampal Neuron Damage Score

Group	p	Damage Score (Mean ± SD)
K− (Control Negative)	0.000	0.5 ± 0.12
K+ (Control Positive)	0.001	2.8 ± 0.25
P1 (100 mg/kg bb)	0.001	2.1 ± 0.30
P2 (200 mg/kg bb)	0.001	1.5 ± 0.22
P3 (300 mg/kg bb)	0.001	0.9 ± 0.18

Note: a value of p<0.05 indicates a significant difference

Number of Normal Hippocampal Cells

The number of normal hippocampal cells was counted across five fields of view per slide. The results showed that the negative control group (K−) had the highest number of normal cells, with 85 ± 2.6 cells per field of view. This number decreased significantly in the positive control group (K+), which recorded 46 ± 3.9 cells per field of view due to chronic stress-induced neural damage.

The treatment groups exhibited an increase in the number of normal cells compared to the positive control group. In group P1 (100 mg/kg body weight), the number increased to 60 ± 4.1; in group P2 (200 mg/kg body weight), to 72 ± 3.2; and in group P3 (300 mg/kg body weight), to 81 ± 2.5, approaching the levels observed in the negative control group. These results indicate that the combination extract of gotu kola and peppermint exerts a neuroprotective effect against stress, as evidenced by a dose-dependent increase in the number of normal cells in the hippocampal tissue.

Table 2. Number of Normal Hippocampal Cells

Group	p	Average of Normal Cells (Mean ± SD)
K− (Control Negative)	0.000	85 ± 2.6
K+ (Control Positive)	0.001	46 ± 3.9
P1 (100 mg/kg bb)	0.001	60 ± 4.1
P2 (200 mg/kg bb)	0.001	72 ± 3.2
P3 (300 mg/kg bb)	0.001	81 ± 2.5

Note: a value of p<0.05 indicates a significant difference

This study confirms that chronic stress exposure negatively affects the structure and function of neurons in the hippocampal region, which plays a crucial role in memory and learning processes. The hippocampus is particularly vulnerable to stress due to its high concentration of glucocorticoid receptors, which, when overstimulated, lead to increased free radical production and neuronal damage [17]. This phenomenon aligns with the opinion of McEwen [18], who stated that prolonged psychosocial stress results in reduced synaptic plasticity and morphological changes in neurons.

The highest neuronal damage score was found in the positive control group (K+), indicating that stress without protection accelerates neuronal degeneration. This finding is supported by Sandi [19], who reported that stress decreases the expression of BDNF and accelerates neuronal apoptosis, particularly in the CA1 and CA3 regions of the hippocampus. The lowest neuronal damage score in this study was observed in the group treated with 300 mg/kg body weight of the combination extract of gotu kola and peppermint leaves (P3), with a score of 0.9 ± 0.18. This indicates that treatment with the combination extract provided significant protective effects on neuronal structure. This score represents a substantial reduction in neuronal damage compared to the positive control group (K+), which recorded a damage score of 2.8 ± 0.25.

The administration of the gotu kola–peppermint combination extract progressively reduced tissue damage and increased the number of normal cells. Gotu kola is well known as a medicinal herb with considerable potential in alleviating stress and protecting brain cells from damage [20]. Active compounds such as asiaticoside, madecassoside, and various antioxidant flavonoids play roles in inhibiting oxidative stress induced by prolonged exposure to stress hormones. The primary mechanism by which gotu kola acts in the central nervous system is by enhancing the expression of BDNF (Brain-Derived Neurotrophic Factor), a neurotrophic factor that supports neuron survival, promotes neurogenesis, and repairs damaged synapses. A study by Wattanathorn et al. [21] showed that administration of gotu kola extract in experimental animals improved memory and cognitive function impaired by stress. Furthermore, gotu kola suppresses inflammation and apoptosis—two key contributors to brain tissue damage under chronic stress conditions [22]. Therefore, gotu kola holds promise as a natural neuroprotective agent to prevent or reverse stress-induced neural damage.

In addition, peppermint leaves have long been recognized for their therapeutic properties in relieving stress and protecting brain cells from damage. One of the main components of peppermint, menthol, has a calming effect that can reduce anxiety and stress by modulating levels of stress hormones such as cortisol [23]. Alongside menthol, other compounds such as rosmarinic acid, flavonoids, and anti-inflammatory agents in peppermint play important roles in combating oxidative stress arising from increased free radicals during stress. Research by Cho et al. [24] demonstrated that rosmarinic acid in peppermint possesses neuroprotective properties by reducing neuronal damage through the inhibition of stress-induced inflammation. This compound is also capable of lowering inflammatory cytokines such as TNF-α and IL-1β, which are known to

damage brain tissue, particularly in the hippocampus. Therefore, peppermint not only alleviates stress symptoms but also plays an essential role in preserving and restoring brain cell health compromised by chronic stress.

The protective effect was most evident at the highest dose, with group P3 exhibiting outcomes closest to normal conditions. This is consistent with findings by Gupta et al. [25], who observed that combination plant extracts with high antioxidant content are more effective in protecting brain tissue than single extracts. Administration of the gotu kola–peppermint extract at high doses (P3) mitigated damage caused by oxidative stress, which typically compromises neuronal integrity through increased free radicals and lipid peroxidation. The reduction in neuronal damage score in group P3 also suggests that higher doses of the combination extract offer maximal neuroprotection, slowing the degenerative process triggered by chronic stress exposure. This opens up the possibility of utilizing the extract combination as a potential therapeutic agent for stress-related disorders such as depression or cognitive impairment, which can cause long-term damage to brain structure.

Overall, these findings suggest that the combination of gotu kola and mint leaf extracts has potential as a natural neuroprotective agent, with mechanisms of action involving the inhibition of oxidative stress, reduction of inflammation, and stimulation of neuronal regeneration in the hippocampus. However, this study has certain limitations, such as the absence of physiological stress biomarker measurements, for instance cortisol levels, which means that the mechanisms underlying the antistress effects cannot be fully explained at a systemic level. This limitation should be taken into account when interpreting the results and the scope of the conclusions drawn.

Conclusion

Based on the results of this study, it can be concluded that administration of the combined extract of gotu kola and mint leaves exerts a protective effect against hippocampal neuronal damage induced by stress, as indicated by a p-value of <0.05. The treatment group receiving the highest dose, 300 mg/kg body weight (P3), showed the lowest neuronal damage scores compared to the other groups, indicating the effectiveness of the extract in reducing neuronal cell injury. These findings may serve as a foundation for the development of phytotherapy-based biomedical education in health sciences.

Author's Contribution

Anak Agung Istri Mas Padmiswari: Designed the research framework, conducted the research, performed data analysis, and prepared the results and discussion. Nadya Treesna Wulansari: Contributed to data analysis and prepared the results and discussion. Kadek Buja Harditya: Contributed to data analysis and prepared the results and discussion.

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