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Research article

Evaluation of the analgesic activity of the ethanol extract of sungkai (Paronema canescens Jack) leaves in the albino rat

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ABSTRACT

Paronema canescens also known as sungkai, has been traditionally used for its medicinal properties, including its analgesic effects.This study aimed to determine the analgesic effect of the ethanol extract of P. canescens leaves in rats. The analgesic effect was tested with the hot plate test. The muscarinic, dopamine and opiate receptors were investigated to examine the underlying mechanism. The rats were assigned to five groups: negative control, positive control, and treatment groups 100, 200, and 400 mg/kgbody weight (BW).The mechanism of the analgesic action for each receptor (muscarinic, dopamine, and opiate) was tested with 12 rats using the dose with the highest analgesic effect as determined by the hot plate test that had been performed before. The comparison between the 100 mg/kg BW group and the positive control showed no significant differences ($p > 0.05$), while the 200 and 400 mg/kg BW groups were significantly different ($p < 0.05$). The 200 and 400 mg/kg BW groups revealed also no significant difference ($p > 0.05$). The ethanol extract of P. canescens leaves had the highest analgesic activity at the dose of 400 mg/kg BW with an analgesic effect of 40.26%of the pain threshold. The antinociceptive mechanism of the extract through muscarinic receptors shows an increase in latency time, while dopamine and opiate receptors show a decreased latency time. It was concluded that P. canescens leaves could contribute in the future as one of the herbal medicines to analgesics.

Keywords: Analgesic, Ethanol extract, Paronema camescens, Albino rat, Hot plate test.

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INTRODUCTION

There is ongoing research on new active ingredients of traditional medicinal plants. One of these traditional medicinal plants is Sungkai (Peronema canescens Jack). In South Sumatera and Lampung, P. canescens leaves treat malaria and fever. Especially in the Musi Banyuasin Regency of South Sumatera, P. canescensleaves are used to treat hypertension and high cholesterol [1].

In Malaysia, it was used against ringworm infection [2]. In Kalimantan, it served as a medicine to treat colds, fever, intestinal worms, and toothache, and it was administered to women after parturition [3]. The use of P. canescens as toothache and fever medicine is related to its pain-relieving effects [4]. Numerous diseases are accompanied by the uncomfortable condition of pain, which is treated by administering drugs with analgesic effects. Analgesics function as anti-pain and anti-fever at the same time. Many pain relievers belonging to the class of non-steroid anti-inflammatory drugs areprescribed to reduce pain but produce side effects if consumed in the long term. This has prompted researchers to develop alternative analgesics with better effectiveness and lower side effects.

Scientific evidence on the ethanol extract of P. canescens leaves demonstrated contained phenolic and flavonoids and areactive as antioxidants [5]. P. canescens leaves have been reported to be active as antimalarial [3], antibacterial and anti-cholesterol properties [6]. Ethanol extract of P. canescens leaves had the potential to reduce blood glucose levels in mice [7].

P. canescens leaf extract in a dose of 200, 400, and 800 mg/kg BW has an immunostimulant effect both in vivo and in vitro and immunostimulators [8]. P. canescens contained steroids, phenols, flavonoids, alkaloids, and tannins [9]. The methanol extract from the leaves of P. canescens was reported tocontain flavonoid glycosides [10], clerodane-type furanoditerpenoid, caffeine acid glycosides, steroid, triterpenoids and flavonoid glycoside [11].

Some flavonoids and steroids are known as analgesic compounds. This study aimed to evaluation the analgesic effectsof P. canescens leaves in rats using the hot plate method and determined the analgesic mechanism of action by examining the muscarinic,

dopamine, and opiate receptors.

MATERIAL AND METHOD

Chemicals and Equipment

Materials used in this study: The leaves of P. canescens, ethanol 96% (Brataco®), Na CMC (Brataco®), diclofenac sodium (Sigma Aldrich®), NaCl (Merck®), atropine sulfate (Ethicaindustrifarmasi®), metoclopramide (Indo Farma®), naloxone hydrochloride (Indo Farma®). Tools used in this study: Rotary evaporator (Yamato®) and hot plate (DLAB®).

Sample preparation

P. canescens leaves (2 kg) were collected from Musi Banyuasin district in South Sumatera Province, Indonesia ($3^0 34' 1.434'' N$ $104^0 77' 18.19''$ E) in November 2021. The sample was identified as Paronema canescens Jack at Herbarium Bogoriense at Research Center for Biology, Indonesian Institute of Science Bogor, with register number B-134/IV/D1-01/1/2021.

Extraction

The fresh P. canescens leaves were dried at room temperature and then ground into a powder. The P. canescen sleaves powder (1 kg) was macerated using ethanol 96% for 3 x 24 hours and then filtration. The maceration was carried out with three repetitions [6]. The pooled filtrated were dried under reduced pressure using a rotary evaporator at a temperature of 70°C to give the ethanol extract at a constant weight of 45 g (4.5%) yield of dried powder plant.

Experimental animals

The animal test used in the experiment is Male albino rats (Wistar strain, aged 2-3 months, weighing 150-200 g) were obtained from the Animal Laboratory centre at Palembang, South Sumatera, Indonesia. Animal experiments in this study were carried out under the Animals in Research: Reporting In Vivo Experiments Guidelines and the Guide for the Care and Use of Laboratory Pharmacology. The Ethics Committee approved the experimental protocol of Ahmad Dahlan University with register No. 022205025. The test animals were acclimatized to the laboratory environment for seven days under adequate lighting (12 h of light) and a room temperature of 22°C. During the acclimatization process, standard food and drinks were provided.

Determination of the Analgesic Effect in the Hot Plate Test

The analgesic effect extract of P. canescens leaves was determined using the hot plate method following the method described by Raveendran et al., (2019) with slight modifications [12]. This study used 25 males Wistar rats. The rats were randomly assigned to five treatment groups: negative control (1% NaCMC), positive control (diclofenac sodium suspension at a dose of 6.6 mg/kg BW), and three treatment groups with oral administration of 0.5 mL of P. canescens ethanol extract at 100, 200, and 400 mg/kgBW. The hot plate test is performed as follow: the animal is placed on the hot plate (50ºC), and the latency to retrieve the feet (response time) is measured in second. First, we pretested the animals to determine the initial response. Immediately after the pretest, the animal was treated with the solution corresponding to its group. Sixty minutes after the treatment administration, the animals were tested in the hot plate test every 60 min for 6 hours. The analgesic effect in the hot plate test was determined based on response time such as jumping, withdrawal of the paws and licking of the claws than the control negative. A stopwatch recorded the latency time.

Mechanism of Analgesic Action

Muscarinic Receptors

For these experiments, rat's other was used to determine the muscarinic receptor system's involvement in the extract's analgesic effect. Twelve rats were divided into two treatment groups. In group 1 (negative), the animals were injected intraperitoneally with 1 ml of physiological NaCl solution (control). In group 2 (positive), the animals were injected intraperitoneally with 1 ml of the muscarinic receptor antagonist atropine sulfate (2mg/kg BW). Ten minutes later, both groups were administered the ethanol extract of P. canescens leaves at the dose with the highest analgesic effect determined by the hot plate test that had been performed before. Both groups conducted a hot plate test 1 hour before administration of muscarinic receptor antagonists and 2 hours after administration of P. canescens leaf extract [13].

Dopamine Receptors

Twelve rats were divided into two treatment groups. In group 1 (negative), the animals were administered 1 ml Na CMC (1%), and in group 2 (positive), animals were orally administered the dopamine receptor antagonist metoclopramide (1.5 mg/kg BW). One hour later, both groups were treated with the ethanol extract of P. canescensat the dose with the highest analgesic effect determined by the hot plate test that had been performed before. All rats have conducted a hot plate test for 1 hour before administration of dopamine receptor antagonist and 2 hours after administered the P. canescens ethanol extract [14].

Opiate Receptors

Twelve rats were randomly divided into two treatment groups. In group 1 (negative), the animals were injected intraperitoneally with 1 ml of physiological NaCl (control), and in group 2 (positive) were injected with 1 ml of the opiate receptor antagonist naloxone hydrochloride (1.5 mg/kg BW). Forty-five minutes later, the two groups were administered the ethanol extract at the dose with the highest analgesic effect, as determined by the hot plate test that had been performed before. All rats have conducted a hot plate test for one hour before administering the opiate receptor antagonist and two h after administering the P. canescens ethanol extract [15].

Statistical Analysis

The data were analysed using data processing software SPSS version 26 and presented as the mean ± standard deviation (SD). The data were tested for normality using the Shapiro–Wilk. If the resulting data are normally distributed (p-value > 0.05), then it can be continued to test the data using the one-way ANOVA test analysis, so differences between experimental groups could be compared and considered significant when $p < 0.05$. If the data are not normally distributed, then the data can be analysed using the Mann–Whitney test.

RESULTS AND DISCUSSION

Analgesic Action of the P. canescens Ethanol Extract

Analgesics effect was determined using the hot plate method based on latency time to heat was carried out for 6hours (Table 1). Responses such as jumping, withdrawing the paws and licking the claws are seen.

Table 1: Latency time to heat stimulation (seconds)

Group	Latency time to heat stimulation: Means ± SD (seconds)						
	Time (minutes)						
	0	60	120	180	240	300	360
control (-)	3.28±1.24	4.45± 0.41	3.79 ± 0.61	3.49±0.63	3.04±0.03	3.39±0.55	3.41±0.64
control (+)[a]	4.64±0.21	7.51± 2.47	8.44 ± 0.98	9.72±0.49	9.43±1.32	7.48 ±0.03	6.27 ± 0.42
Dose 100 mg/kg BW	5.43±0.88	7.84± 1.13	7.39 ± 1.12	7.09±1.47	9.65±3.53	8.00±0.84	6.41 ± 1.04
Dose 200[b] mg/kg BW	4.78±0.55	6.60±1.22	7.78 ± 0.47	8.62±1.35	10.38±0.81	10.06±1.19	8.03 ± 1.88
Dose 400[b] mg/kg BW	4.47±3.28	6.96±1.85	8.65 ± 0.75	8.84±0.23	9.37 ±2.23	8.75±0.85	10.30 ± 2.77

a: significantly different ($p<0.05$) against the control (-)

b: significantly different ($p<0.05$) against the control (+)

Table 1 shows the negative control group; it ranged from 3.28 ± 1.24 to 4.47 ± 3.28 seconds. At minute 60, the negative control group slightly increased the response time to painful stimuli because of the body's natural response when experiencing pain: over time, the body adapts to the presence of a painful stimulus through the action of endogenous analgesics, e.g., endorphins, increasing the body's strength to withstand pain [16]. Endorphins bind to pain receptors in the central nervous system, leading to diminished pain. Here, starting at minute 120, the response time started decreasing [17]. The positive control and treatment groups showed an increase in the latency time. The longest latency occurred at the time observed at minute 180 for the positive control group and minute 240 for the 200 mg/kg BW. Starting at minute 240 for the positive control group and minute 300 for all treatment groups, a decrease in the average latency time (analgesic effect) occurs. This is probably because of drug metabolism, which is a process of modifying the form of the compounds into their inactive state. The decrease in the analgesic effect in the positive control group (minute 240) corresponds to the half-life of sodium diclofenac [18]. Based on each group's average latency time value, the analgesic activity value (%) was determined (Table 2).

Table 2: % analgesic effect

Group	Latency time (Means ± SD)	Analgesic effect (%)
Control (-)	3.60±0.48	-
Control (+)	7.64 ± 0.95	35.44
Dose 100 mg/kg BW	7.73± 1.28	36.22[a]
Dose 200 mg/kg BW	8.04 ± 1.15	38.94[b]
Doses 400 mg/kgBW	8.19 ± 1.28	40.26[b]

a: no significantly different ($p>0.05$) against the control (+)

b: significantly different ($p<0.05$) against the control (+).

Based on each group's average latency time value, the analgesic activity value (%) was determined (Table 2). The activity increased with increasing doses. The results showed that there was a significant difference ($p< 0.05$) between the negative control group and the rest of the groups (i.e., the positive control group and the treatment groups). The comparison between the 100 mg/kg BW group and the positive control showed no significant differences ($p > 0.05$), while the 200 and 400 mg/kg BW groups were significantly different from the positive control ($p < 0.05$). The 200 mg/kg and 400 mg/kg groups revealed also no significant difference ($p > 0.05$). Treatment with the P. canescens extract had higher analgesic activity than the positive control, possibly because the extract includes various active compounds, such as peroneminand diterpenoids of the clerodane type, flavonoid glycoside, steroid, and triterpenoid [11], sitosterol, isopropanol, phytol, and flavonoids that function synergistically to increase the analgesic effect [3]. This is reflected in the analgesic activity of the ethanol extract at a dose of 200 mg/kg BW, reaching an effect of 38.94%, while the positive control was 35.44%. This data revealed the potential of P. canescens leaves as an analgesic medicine. Compounds that provide analgesic effects include flavonoids and steroids [19]. Tragiaplukenetii contained flavonoid compounds that showed significant analgesic activity [20]. Flavonoids play a role in inhibiting lipid peroxidation and the cyclooxygenase enzyme, thereby reducing the biosynthesis of prostaglandins that cause pain [21]. Analgesic activity can also occur through to reducing the biosynthesis of histamine and acetylcholine [22]

Evaluation of the Mechanism of Analgesic Effect

Evaluation of the mechanism of analgesic effect through muscarinic receptors, dopamine receptors, and opiate receptors using the hot plate method base on latency time to heat were shown in Table 3-5.

Table 3: Evaluation of the mechanism of analgesic effect through muscarinic receptors

Group	Rats	Latency time (seconds)	
		Before treatment	After treatment
NaCl Fisiologis + extract (negative)	1	3.73	3.55
	2	4.08	3.80
	3	4.70	3.00
Means ± SD		4.17± 0.49	3.45± 0.41
Atropine Sulfate +extract (positive)	1	3.23	3.30
	2	3.88	6.04
	3	3.85	4.56
Means ± SD		3.65± 0.37	4.63±1.37[ab]

a: significantly different (p<0.05) against after treatment the negative group
b: significantly different (p<0.05) against before treatment the positive group

Table 4: Evaluation of the mechanism of analgesic effect through dopamine receptors

Group	Rats	Latency time (seconds)	
		Before treatment	After treatment
Na CMC 1% + extract(negative)	1	2.75	2.37
	2	4.00	3.36
	3	4.08	3.75
Means ± SD		3.61± 0.75	3.16± 0.71
Metoclopramide + extract (positive)	1	4.40	4.52
	2	3.83	2.90
	3	3.06	3.67
Means ± SD		3.76± 0.67	3.70± 0.81[ab]

a:no significantly different (p> 0,05)) against after treatment the negative group
b: no significantly different (p>0,05) against before treatment, the positive group

Table 5: Evaluation of the mechanism of analgesic effect through opiate receptors

Group	Rats	Latency time (seconds)	
		Before treatment	After treatment
NaCl Fisiologis + extract (negative)	1	4.56	3.43
	2	3.15	3.46
	3	4.23	3.49
Means ± SD		4.01± 0.74	3.46±0.03
Naloxonehydrochloride + extract (positive)	1	4.76	4.09
	2	3.70	3.61
	3	3.40	3.86
Means ± SD		3.95± 0.71	3.85±0.24[ab]

a: no significantly different (p> 0,05)) against after treatment the negative group
b: no significantly different (p>0,05) against before treatment, the positive group

Muscarinic receptors are primarily on the membrane of smooth muscle, cardiac muscle, and exocrine gland cells [23]. To evaluate the muscarinic receptors, atropine sulfate was used as a control (Table 3). Atropine sulfate is an anticholinergic that acts on muscarinic receptors, inhibiting acetylcholine transmission in the cholinergic postganglionic nerves and smooth muscles. The binding to muscarinic receptors prevents actions such as adenylyl cyclase inhibition induced by acetylcholine or other muscarinic antagonists [24].

Atropine reversibly blocks the action of cholinomimetics on muscarinic receptors leading to the elimination of tremors and stimulation of respiration due to bronchial dilatation. Atropine inhibits the enzyme cholinesterase by antagonizing the action of acetylcholine and other choline ester substances [25, 26].Table 3 shows the increase in latency time (3.65 ± 0.37 to 4.63 ± 1.37) for the positive group on the hot plate test after administration of the extract, and statistical analysis shows significant differences ($p < 0.05$).The antinociceptive mechanism of the extract through muscarinic receptors occurs when it shows an increase in latency time [27]. This indicates that the ethanol extract exerts an analgesic effect through a mechanism involving muscarinic receptors.

Table 4 shows the analgesic effect of extract via the dopamine receptor. The using metoclopramide showed a decreased latency time (3.76± 0.67 to 3.70± 0.81) in the positive group, but no significant difference ($p > 0.05$) in the latency time was found before and after the administration of the P. canescens extract. This indicates that the extract no provides a response through a dopamine receptor. Dopamine is a neurotransmitter of the brain that influences emotions, movement, reward, and pain. Dopamine affects bodily functions when at excessive or decreased levels. It also plays an important role in processing pain in the central nervous system and the spinal cord. In sickness, dopamine levels decrease, causing unpleasant feelings [28].

The evaluation of the opiate mechanism (Table 5) using the antagonist naloxone hydrochloride. Table 5 shows the decreased latency time (3.95± 0.71 to 3.85± 0.24) before and after consuming the P. canescensextract in positive groups, and statistical analysis shows no significant differences ($p > 0.05$), meaning that the extract is responsive to opiates. Naloxone hydrochloride is an antagonist of the opioid receptors through which it relieves pain, altering the response to it and producing an analgesic effect. The analgesic efficacy of opioids is based on their ability to bind pain receptors that are not bound by endorphins [29].

The antinociceptive mechanism of the extract through the receptors occurs when it shows an increase in latency time [27]. The data shows an increase in latency time for the muscarinic receptor antagonist mechanism, while the dopamine receptor antagonist mechanism metoclopramide and the opiate receptor antagonist naloxone hydrochloride show a decrease in latency time.

This indicates that the extract action is through the muscarinic receptor antagonist mechanism. The reduction in latency time for the dopamine receptor antagonist mechanism metoclopramide and the opiate receptor antagonist naloxone shows no significant difference ($P > 0.05$). It could be because the test used is from extract, so the secondary metabolites in the extract (flavonoid glycosides, steroid, diterpenoid, phenol, and tannin) [11]. Based on this data, the extracted ethanol of P. canescens leaves shows an antinociceptive effect mechanism as a muscarinic dopamine receptor antagonist.

CONCLUSION

The ethanol extract of P. canescens leaves showed the highest analgesic activity at a 400 mg/kgBW dose with an analgesic effect value of 40.26%. The ethanol extract of P. canescens leaves its analgesic effect through the muscarinic receptors.

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