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The antinociceptive effect of *Chrysophyllum cainito* L. leaves extract and tablet in wistar rats

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Pain and inflammation in the joints from cartilage breakdown characterize osteoarthritis (OA), a degenerative disease linked to low estrogen levels. Because phytoestrogens can perform the same role as estrogen, they may be useful in relieving OA-related pain and inflammation. It is well-documented that some plants, like *Chrysophyllum cainito* L., contain phytoestrogens. To identify the efficacy of a 70% ethanol extract (CLE) and tablet (CLT) formulated from *C. cainito* leaves in reducing pain perception in male Wistar rats. Acute toxicity tests were initially carried out on the CLE in rats. The analysis was carried out for 14 days, and then a probit analysis was performed to determine the LD_{50} value. The antinociceptive activity of CLE and CLT was then tested on rats using the writhing test at doses of 4.05, 8.1, and 16.2 mg/200 g BW rat/day for the CLE, and 24.3, 48.6, and 97.2 mg/200 g BW rat/day for the CLT. After 30 minutes of administration of each sample, the rats were induced intraperitoneally with 1% acetic acid and then observed for their stretch for 30 minutes. The LD_{50} for the CLE was 70.028 g/kg, indicating that it was practically non-toxic. The rats also showed no signs of toxicity qualitatively. Both the CLE and CLT demonstrated antinociceptive activity, with the optimal dose for CLE being 4.05 mg/200 g BW, and the optimal dose for CLT being 48.6 mg/200 g BW, resulting in percentages of writhing inhibition of 80.61 ± 7.3 and 80.62 ± 7.3, respectively. These results indicate that CLE and CLT are safe and have an antinociceptive effect, so they have the potential to be developed as alternative anti-OA drugs.

KEYWORDS

Antinociceptive; *chrysophyllum cainito* L.; extract; tablet.

Introduction

Osteoarthritis (OA) is one of the leading causes of chronic disability-related synovial pain and inflammation, marked by excessive cartilage degeneration and abnormal subchondral bone sclerosis. This disease affects several joints, particularly the knees and hips [1,2]. According to the World Health Organization (WHO), OA is a major public health issue that is growing the fastest and is the second leading cause of disability. In 2018, basic health research in Indonesia revealed that the OA incidence was 8.46% higher in women than in men, whose prevalence was only 6.13% [3]. Compared to

men of the same age, the prevalence and risk of events will increase rapidly from the age of menopause after 50 to 75 years. The correlation between the incidence of osteoarthritis and cartilage loss in postmenopausal women suggests that sex hormones may play an important role in maintaining joint health. Several studies indicate a linear relationship between postmenopausal women's decreased endogenous estrogen levels and their increased risk of OA events [4]. Increased levels of interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-α), and other pro-inflammatory factors can cause joint pain and increase OA risk factors in postmenopausal women due to decreased estrogen function in regulating body functions [5,6].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used to treat pain complaints in OA patients. This drug was chosen because it is the first-line treatment for pain and inflammation in OA patients [7]. However, long-term use of NSAIDs has numerous side effects, particularly in the gastrointestinal tract and kidneys [8]. The existence of numerous side effects caused by the use of synthetic drugs encourages the use of natural-based alternative therapies. Kenitu (*Chrysophyllum cainito* L.) is a plant that has the potential to be alternative anti-OA drugs via an estrogenic mechanism.

The secondary metabolites of *C. cainito* leaves include polyphenols, alkaloids, isoflavones, sterols, tannins, and triterpenoids [9]. Isoflavones, sterols, and triterpenoids are included in phytoestrogen compounds due to their estrogenic activity and structural similarity to 17-estradiol [10]. Indonesians frequently use *C. cainito* leaves as a traditional medicine to treat various conditions, including inflammation of the respiratory tract, fever, and diarrhea [11]. In addition, the phytoestrogen content of *C. cainito* leaves has the potential to be used as an alternative treatment for diseases caused by estrogen deficiency, such as osteoporosis, neurodegenerative disease, and cardiovascular disease [12].

In this study, male Wistar rats were used to evaluate the antinociceptive activity of 70% ethanol extract of *C. cainito* leaves (CLE) and tablets containing 70% ethanol extract of *C. cainito* leaves (CLT). Increased antinociceptive effects may indicate the capacity to alleviate pain in patients with osteoarthritis (OA).

Experimental

Materials

Plants

Chrysophyllum cainito L. leaves were collected in Batu, Indonesia, in June 2022 and identified in UPT. Laboratorium Herbal Materia Medica, Batu, Indonesia with identification letter No. 067/1606/102.20/2023. The leaves were prepared to get dry powder of *C. cainito* leaves.

Animals

Rattus norvegicus was obtained from the experimental animal laboratory of the BioSains Institute, Universitas Brawijaya, Malang, Indonesia, with ethical clearance letter No. 136-KEP-UB-2023.

Tablet

CLT were obtained from PT. Agaricus Sido Makmur Sentosa, Malang, Indonesia. The tablets weigh 900 mg, with the main content of each tablet equivalent to 150 mg of 70% ethanol extract of *C. cainito* leaves. The composition of the tablet excipients is lactose, microcrystalline cellulose, sodium starch glycolate, hydrate silica, magnesium stearate, copovidine, and methylparaben.

Chemical

Ethanol 70%, acetic acid, tween 80, and dimethyl sulfoxide (DMSO) were purchased

from Merck (Darmstadt, Germany). Ibuprofen as a positive control was purchased from PT. Novapharin Pharmaceutical (Gresik, Indonesia). Excipients for tablets were obtained from PT. Agaricus Sido Makmur Sentosa (Malang, Indonesia).

Methods

Extraction of CLE

The dry powder of *C. cainito* leaves was extracted with 70% ethanol using ultrasonic-assisted extraction methods (Sonica 5300P S3). This process was repeated, collecting all the supernatants, which were finally evaporated in a rotary evaporator (Heidolph-VAP G3) to obtain a 70% ethanol extract of *C. cainito* leaves [13].

Acute Toxicity Test for CLE

A total of 48 male Wistar rats were divided into 8 groups, and then each dose group was given 1 ml/kg of CLE orally, once during the test period. The treatment group consisted of doses of 4; 12.8; 40.96; 131.072; 419.42; 1,342.14; and 4,294.848 mg/kg [14]. The use of a given dose of CLE is the result of a modification of the up-and-down method of the Organization for Economic Co-operation and Development (OECD) guidelines 425. The OECD provisions 425 state that the initial dose is 175 mg/kg for conditions where there is no available estimate of the death of the substance. Furthermore, each increase in dose is multiplied by 3.2 [15]. Thereafter, the response of the rats was observed, which included eyes, skin, hair, and behaviour (respiratory frequency, shaking, convulsions, diarrhoea, weakness, and sleep) for 14 days regularly [16,17].

Antinociceptive effect of CLE and CLT

Male Wistar rats were fasted for ± 18 hours before testing. The positive control group was given 7.2 mg/200 gBW of ibuprofen suspension orally, while the negative control group was given 1% tween 80 solution in 0.05% DMSO for as much as 2 ml/200 gBW [18]. The extract group was given CLE at a dose of 4.05, 8.1, and 16.2 mg/200 g BW, while the tablet group was given CLT at a dose of 24.3; 48.6; and 97.2 mg/200 g BW. After 30 minutes, the mice were induced intraperitoneally with 1% acetic acid, as much as 2 ml/200 gBW. Furthermore, the writhing response was observed by recording for 30 minutes with an interval of 5 minutes. Rat's writhing calculations were carried out by three people to avoid subjectivity [5].

Statistical Analysis

Data analysis was performed by calculating the percentage of writhing inhibition, which aims to identify and compare the antinociceptive activity in each group compared to the negative control group [19].

$$\% \text{ writhing inhibition} = 100 - \{(P/K) \times 100\} \times 100\% \quad (1)$$

Where,
P: Cumulative number of stretches for each treatment group, and
K: Cumulative number of stretches in the negative control group.

The results of the research data were tested for normality with the Shapiro-Wilk test. The data is mentioned to be normally distributed if $p > 0.05$. After that, it was proceeded with the homogeneity test (Levene test), where a p-value> 0.05 means that the data obtained is homogeneous, and then statistically analyze it using the analysis of variance method with a 95% confidence level to find out if the activity generated differs significantly from several types of treatment. Furthermore, to find out the significant differences between the tests, the LSD post-hoc test was carried out at p <0.

Results and discussion

Acute toxicity test for CLE

Observation of acute toxicity was carried out after administration of CLE at different doses for 28 days [20]. The results showed that CLE was practically non-toxic to male Wistar rats, with an LD_{50} value of 70.028 g/kg. The extract is practically non-toxic if the LD_{50} value is > 15.00 g/kg. In addition to be proven quantitatively, the safety of CLE was also proven qualitatively by observing the morphology and physiology of rats. The results of the qualitative descriptive test showed that there were no differences in the morphology and physiology of the bodies of the rats in the negative control group and the 4,294.848 mg/kg group after 28 days, so it can be mentioned that the extract is safe.

Antinociceptive effect of CLE and CLT

CLE CLT

FIGURE 1 CLE and CLT

CLE and CLT (Figure 1) antinociceptive activity tests were carried out to compare the amount of writhing in rats between the control group and the treatment groups, in which each rat had been induced first with a 1% acetic acid solution. The average number of rats writhing for 30 minutes is presented in Figure 2 for CLE, and Figure 3 for CLT.

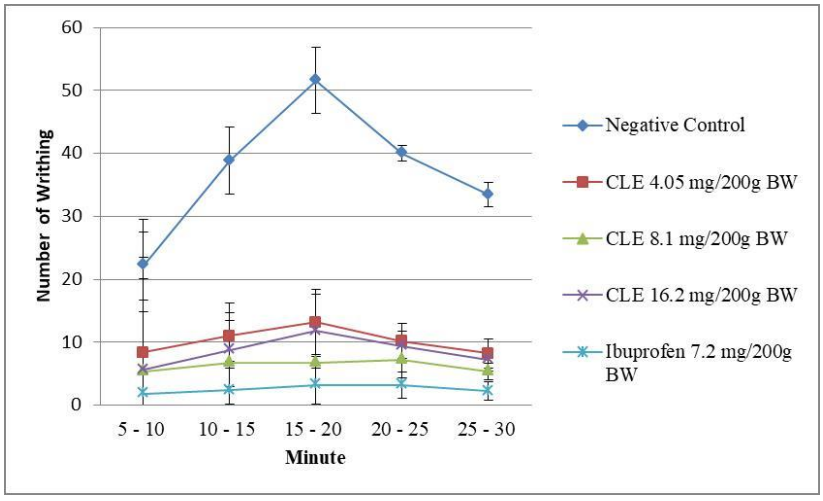

FIGURE 2 The number of writhing in each range of time in each CLE group

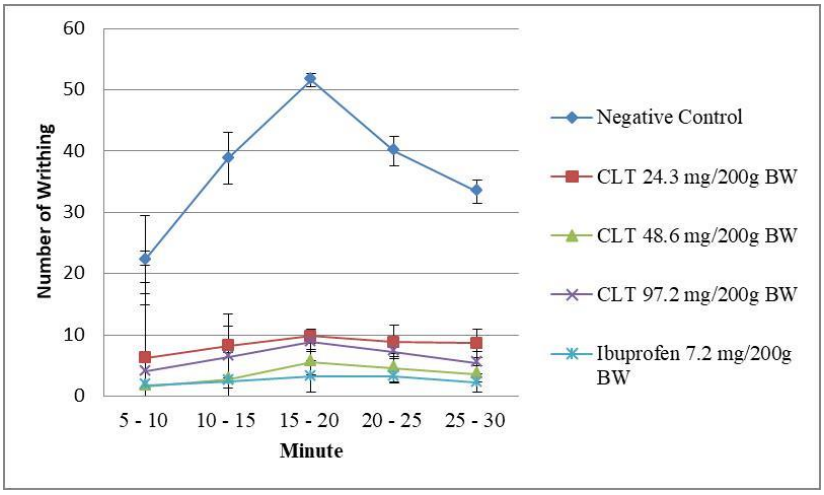

FIGURE 3 The number of writhing in each range of time in each CLT group

The writhing activity in Wistar rats after administration of CLE showed that at 5-10 minutes, there was a significant difference between the negative control group and the CLE 8.1 mg/200 g BW group ($p = 0.042$), CLE 16.2 mg/200 g BW ($p = 0.044$), and ibuprofen ($p = 0.019$). At 10-15 minutes, there was a significant difference between the negative control group's attitude towards the ibuprofen group ($p = 0.036$) and the CLE 16.2 mg/200 g BW group's attitude towards the ibuprofen group ($p = 0.041$). At 15-20 minutes, there was a significant difference between the CLE 16.2 mg/200 g BW group and the ibuprofen group ($p = 0.012$). At 20-25 minutes, there was a significant difference between the negative control group towards the CLE 8.1 mg/200g BW group ($p = 0.041$) and the ibuprofen group ($p = 0.031$) and the CLE 16.2 mg/200 g BW group towards the ibuprofen group ($p = 0.031$). At 25-30 minutes, there was a significant difference between the CLE 16.2 mg/200 g BW group and the ibuprofen group ($p = 0.029$).

The writhing activity in wistar rats after administration of CLT showed that at 5-10 minutes, there was a significant difference between the negative control group and the CLT 48.6 mg/200 g BW ($p = 0.042$), CLT 97.2 mg/200 g BW ($p = 0.044$), and ibuprofen ($p = 0.019$). At 10-15 minutes, there was a significant difference between the negative control group and the ibuprofen group ($p = 0.036$). The CLT 97.2 mg/200g BW group differed significantly from the ibuprofen group ($p = 0.041$). At 15-20 minutes, there was a significant difference between the CLT 97.2 mg/200 g BW group and ibuprofen ($p = 0.012$). At 20-25 minutes, there was a significant difference between the negative control group and the CLT group at 48.6 mg/200 g BW ($p = 0.041$) and Ibuprofen ($p = 0.031$); the CLT group at 97.2 mg/200 g BW was at ibuprofen ($p = 0.024$). At 25-30 minutes, there was a significant difference between the CLT (97.2 mg/200g BW) and ibuprofen groups ($p = 0.029$).

TABLE 1 Percentage of rats writhing inhibition in each CLE group. Each value is expressed as the mean ± SD

Groups	% Writing Inhibition
Negative Control	0
CLE (4.05 mg/200 g BW)	66.03 ± 26.26
CLE (8.1 mg/200 g BW)	80.61 ± 7.3
CLE (16.2 mg/200 g BW)	73.41 ± 10.9
Ibuprofen (7.2 mg/ 200 g BW)	91.79 ± 5.29

TABLE 2 Percentage of rats writhing inhibition in each CTE group. Each value is expressed as the mean ± SD.

Groups	% Writing Inhibition
Negative Control	0
CLT (24.3 mg/200 g BW)	76.69 ± 26.28
CLT (48.6 mg/200 g BW)	80.61 ± 7.3
CLT (97.2mg/200 g BW)	79.6 ± 10.89
Ibuprofen (7.2 mg/200 g BW)	91.79 ± 5.29

Table 1 indicates the percentage of rats writhing in inhibition in each CLE group, while Table 2 presents the percentage of rats writhing in inhibition in each CTE group. Based on the results in both tables and also in Figures 2 and 3, it is known that the best antinociceptive effect for CLE is dose 2, which is 8.1 mg/200 g BW, and for CLT it is also dose 2, namely CLT (48.6 mg/200 g BW).

The research was conducted using the writhing test method on male Wistar rats induced by 1% acetic acid. Acetic acid is used as an irritant to produce localized, acute inflammatory reactions. The mechanism is the release of arachidonic acid through the COX-2 pathway, which then produces prostaglandin E2 and prostaglandin F2-α in the intraperitoneal [21]. These prostaglandins cause an increase in capillary permeability, causing pain. Rats will respond in the form of writhing and are evaluated for the amount of stretching they do for 30 minutes [5]. This observation period is based on the duration of ibuprofen action, which serves as a positive control. Subjective pain response to stretching is observed. The response of writhing movements, which is abdominal contractions, can indicate pain in rats. Both sets of legs are retracted, and the abdomen touches the stand's base. Ibuprofen was used as a positive control because it is a common NSAID that works by inhibiting the formation of prostaglandins, which can inhibit pain responses [22].

In general, the findings of both the CLE and CLT studies revealed antinociceptive activity in all of the treatment groups, which was shown to be significantly different from the control group that did not receive treatment. In point of fact, it was not significantly different from the ibuprofen positive control in some of the treatment groups, and in others, it even exceeded it. The second dose group was the most effective for both CLE and CLT. The best doses for CLE were 8.1 mg/200g BW, and the best doses for CLT were 48.6 mg/200 g BW. When converted into a tablet with a weight of 900 mg, this second dose group has the same effect as giving three tablets to a human being on a daily basis (1 CLT tablet weighing 900 mg is equivalent to 150 mg CLE).

The presence of phytoestrogens in *C. cainito* leaves is the primary contributor to the plant's antinociceptive activity. Phytoestrogen compounds have biological effects that are comparable to estrogen and have the potential to replace estrogen function in estrogen receptor (ER)-dependent as well as ER-independent manners [23]. When it comes to antinociceptive activity, phytoestrogen will act in an ER-dependent manner by binding to ER. This binding will then inhibit proinflammatory transcription factors such as NF-kb, COX-2 expression, and various proinflammatory cytokines and pain mediators such as IL-1, IL-6, and TNF-α. Phytoestrogen will also act in an ER-dependent manner when it comes to antinociceptive activity [24,25]. According to these findings, the leaves of *C. cainito* have the potential to be used as an alternative treatment for diseases such as OA brought on by a lack of estrogen, such as in the body.

Conclusion

The optimal dose for CLE was 4.05 mg/200 g BW, while the optimal dose for CLT was 48.6 mg/200 g BW, resulting in percentages of writhing inhibition of 80.61±7.3 and 80.62±7.3, respectively. These findings indicate that CLE and CLT are safe and have analgesic properties, so they could be developed as alternative anti-OA treatments.

Conflict of interest

All the authors declare that there is no conflict of interest in this article.

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