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ORIGINAL ARTICLE

ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF EXTRACT AND FRACTION OF *ZIZIPHUS JUJUBA* LEAF

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Abstract

Ziziphus jujuba leaves are widely used in traditional medicine across Asia and parts of Europe, largely due to their antioxidant properties and their use in treating inflammatory conditions. This study aimed to validate the antioxidant and anti-inflammatory activities of *Ziziphus jujuba* leaves and to identify potential bioactive compound groups *via* solvent-polarity-based fractionation. Antioxidant activity of the ethanol extract and its fractions was evaluated *in vitro* using the 2,2-diphenyl-1-picrylhydraxyl (DPPH) radical scavenging assay, while the anti-inflammatory activity was assessed using the paw edema model in carrageenan-induced Wistar rats. The ethanol extract contained 43.70 ± 1.78 mg gallic acid equivalents (GAE)/g extract of total phenolics and 19.49 ± 0.88 mg quercetin equivalents (QE)/g extract of flavonoids. The ethanol extract and ethyl acetate fraction showed strong antioxidant activity with IC_{50} values of 89.76 µg/mL and 78.07 µg/mL, respectively. Both samples also demonstrated consistent anti-inflammatory effects between 180 and 360 minutes. These results indicate that bioactive antioxidant and anti-inflammatory compounds are mainly concentrated in the ethyl acetate fraction and, to a lesser extent, in the ethanol fraction.

Rezumat

Frunzele de *Ziziphus jujuba* sunt utilizate în medicina tradițională din Asia și din anumite regiuni ale Europei, în principal datorită proprietăților lor antioxidante și inflamatorii. Scopul acestui studiu a fost validarea acestor activități, precum și identificarea potențialelor grupuri de compuși bioactivi prin fracționare bazată pe polaritatea solvenților. Activitatea antioxidantă a extractului etanolic și a fracțiilor sale a fost evaluată *in vitro* utilizând testul de captare a radicalului liber 2,2-difenil-1-picrilhidrazil (DPPH), în timp ce activitatea antiinflamatorie a fost analizată folosind modelul de edem plantar indus de caragenan la șobolani Wistar. Extractul etanolic a conținut 43,70 ± 1,78 mg echivalenți de acid galic (GAE)/g extract de compuși fenolici totali și 19,49 ± 0,88 mg echivalenți de quercetină (QE)/g extract de flavonoide. Extractul etanolic și fracția de acetat de etil au prezentat o activitate antioxidantă pronunțată, cu valori IC_{50} de 89,76 µg/mL, respectiv 78,07 µg/mL. Ambele probe au demonstrat, de asemenea, efecte antiinflamatorii semnificative în intervalul 180 - 360 de minute. Compușii bioactivi cu proprietăți antioxidante și antiinflamatorii sunt concentrați în principal în fracția de acetat de etil și, într-o măsură mai redusă, în fracția etanolică.

Keywords: anti-inflammatory, antioxidant, DPPH, paw oedema, *Ziziphus jujuba*

Introduction

Ziziphus jujuba, also known as jujube or Chinese date, is a species within the genus Ziziphus that is highly valued and widely recognized in Asian communities (1-3). This plant is extensively cultivated in China, East Asian countries, northern India, and Southern Europe (4,5). It is well known in Traditional Chinese Medicine for its anti-inflammatory and antibacterial properties and is used to treat bleeding as an astringent, a tonic, and an anti-tumor agent (6, 7). In Japan, *Z. jujuba* is traditionally used to treat hepatitis, while in Iran, it is used to manage conditions related to blood pressure, as a laxative, and to treat wounds and pain (8-10).

The potential of plants from the *Ziziphus* genus, including *Z. jujuba*, is often associated with their antioxidant properties (11,12). The antioxidant capacity of natural compounds is frequently correlated with their ability to treat metabolic diseases such as diabetes (13), hyperlipidemia (14), cardiovascular diseases (15), and cancer (16). Additionally, various human diseases, including tendinitis, asthma, inflammatory bowel diseases, and arthritis, are linked to inflammation. Inflammatory conditions also contribute to autoimmune diseases, asthma, allergies, hepatitis, glomerulonephritis, celiac diseases, transplantation rejection, and inflammatory bowel diseases (4).

The antioxidant and anti-inflammatory properties of *Z. jujuba* leaves are crucial for identifying potential

bioactive compounds for therapeutic applications. In this context, the present study aims to evaluate the bioactivities of *Z. jujuba* leaf extract and fractions, facilitating the identification of the most active fraction for subsequent isolation and characterization of its compounds.

Materials and Methods

Materials and instruments

Dried leaves of *Z. jujuba* were obtained from Miaoli, Taiwan (24°33'25"N 120°50'00"E). The plant material had been previously authenticated, and a voucher specimen was deposited at Herbarium Bandungense, Bandung Institute of Technology, Indonesia (voucher specimen No. 74/IT1.C11.2/TA.00/2023). The samples were collected in Taiwan and transported to Indonesia in dried form for further experimental analysis. Because the material was received as predried samples, detailed information on the harvest period, plant developmental stage, and drying conditions was unavailable. Macroscopic and microscopic examinations were not conducted in the present study; however, plant authentication was supported by the herbarium voucher specimen referenced above.

The solvents used in this study included distilled water, ethanol, ethyl acetate, and n-hexane, all of technical and pro-analysis grade. The reagents used for phytochemical screening included Mayer's reagent, Dragendorff's reagent, Bouchardat's reagent, $FeCl_3$, magnesium metal powder, HCl, amyl alcohol, and Liebermann-Burchard reagent. The materials used for determining total phenolic and flavonoid content, as well as antioxidant assays, included $AlCl_3$, Folin-Ciocâlteu reagent, quercetin, gallic acid, DPPH, and ascorbic acid. The materials used for the anti-inflammatory study included sodium carboxymethyl cellulose (CMC-Na), sodium diclofenac (Kimia Farma), and carrageenan.

The equipment used in this study included various laboratory glassware for sample preparation and handling. A drying cabinet or oven was utilized for drying plant materials, while a rotary evaporator (Heidolph VV-300) was employed for solvent evaporation and extract concentration. Additionally, a UV-Vis spectrophotometer (Jasco V-530) was used for spectroscopic analysis, and a plethysmometer was utilized to measure paw oedema in the anti-inflammatory assay.

Animals

The experimental animals used in this study were male Wistar rats (200 - 250 g), which were acclimatized for two weeks in a controlled laboratory environment before the start of the experiments. All animals were housed under standard conditions with ad libitum access to food and water. At the end of the study, the rats were euthanized using CO_2 asphyxiation followed by cervical dislocation to minimize suffering. The study protocol was reviewed and approved by the Animal Research Ethics Committee (AREC), Universitas Sumatera Utara (Approval No. 0306/KEPH-FMIPA/2024), ensuring compliance with ethical guidelines for animal research.

Characterization of dry sample

Prior to extraction, *Z. jujuba* leaves were redried in a drying cabinet at 35 - 40°C for 48 hours to remove moisture while preserving bioactive compounds. The dried leaves were ground into a coarse powder and subjected to physicochemical characterization, including the determination of moisture content, total ash, water-soluble extractive, and ethanol-soluble extractive, to evaluate the quality and consistency of the raw material.

In addition, a preliminary phytochemical analysis of powdered *Z. jujuba* leaves was conducted using qualitative methods to identify key secondary metabolites. This screening aimed to detect the presence of alkaloids, flavonoids, saponins, tannins, glycosides, and steroids/triterpenoids, offering valuable insight into the bioactive constituents of the plant material.

Extraction and fractionation

The extraction was carried out using the maceration method with 96% ethanol as the solvent at a drug-to-solvent ratio of 1:10 (w/v). The maceration process was conducted 3 times for 24 hours in a single extraction cycle at room temperature. After extraction, the macerate was separated from the plant residue by filtration and subsequently concentrated using a rotary evaporator to obtain the crude extract. A portion of the crude extract was reserved for further analysis, while the remaining extract was subjected to liquid-liquid fractionation using a separatory funnel. Before partitioning with n-hexane, the crude extract was diluted with distilled water at a 1:1 ratio. Sequential fractionation was performed using n-hexane followed by ethyl acetate. Each obtained fraction was concentrated under reduced pressure in a rotary evaporator to remove the solvent, yielding the corresponding fractions for further biological evaluation.

Total phenolic content

The total phenolic content (TPC) of *Z. jujuba* leaves was determined using the Folin-Ciocâlteu method. A 50 µL aliquot of the extract of the fraction sample was mixed with 500 µL of 10% Folin-Ciocâlteu reagent and 400 µL of 1 M sodium carbonate. The mixture was incubated at 25°C for 15 minutes, and absorbance was measured at 760 nm using a UV-Vis spectrophotometer. Gallic acid was used as the standard, and the TPC was expressed as milligrams of gallic acid equivalents *per* gram of extract (mg GAE/g extract) (17, 19).

Total flavonoid content

The total flavonoid content (TFC) of *Z. jujuba* leaves was determined using the aluminum chloride colorimetric method. A 100 µL aliquot of the extract or fraction was mixed with 300 µL of pro analysis methanol, 20 µL of 10% aluminium chloride, 20 µL

of sodium acetate, and 560 µL of distilled water. The mixture was incubated at 25°C for 15 minutes, and absorbance was measured at 432 nm using a UV-Vis spectrophotometer. Quercetin was used as the standard, and the TFC was expressed as milligrams of quercetin equivalents *per* gram of extract (mg QE/g extract) (18, 19).

Antioxidant activity

The antioxidant activity of the extract and its fractions was evaluated using the DPPH radical scavenging assay (19-22). Each extract or fraction was dissolved in ethanol to prepare a series of concentrations ranging from 12.5 to 800 µg/mL. Briefly, 1 mL of sample solution was mixed with 1 mL of DPPH solution (0.1 mM in ethanol) and incubated in the dark at room temperature for 30 minutes. The absorbance was measured at 517 nm using a UV-Vis spectrophotometer. To correct for the intrinsic absorbance or turbidity of the samples, extract blanks consisting of the sample solution mixed with ethanol without DPPH were prepared and measured under the same conditions. The antioxidant activity was expressed as the percentage of DPPH radical inhibition relative to the control and calculated using the following equation:

$$\%Inhibition = \frac{A\ DPPH - A\ sample}{A\ DPPH} \times 100$$

All experiments were performed in triplicate. The IC_{50} values were calculated from concentration-inhibition curves using nonlinear regression.

Anti-inflammatory activity

The anti-inflammatory activity was evaluated using the carrageenan-induced paw edema models in Wistar rats (23, 24). In this assay, 0,1 mL of freshly prepared 1% carrageenan suspension was injected sub-plantarly into the right hind paw of all test animals to induce inflammation and edema, while the untreated left hind paw served as a control for measuring changes in paw volume (23). After an adaptation period, the animals were randomly divided into six groups (n = 6 *per* group). Thirty minutes before carrageenan injection, four test groups received the extract and fraction at a dose of 100 mg/kg body weight, administered orally. The selected dose was based on preliminary dose-optimization experiments conducted prior to the main study, in which the extract at 100 mg/kg bw produced a measurable reduction in paw edema. The control group received a CMC-Na suspension (10 mL/kg body weight) as the vehicle (23), while the positive control group received diclofenac sodium (4.5 mg/kg body weight) orally (25). Paw edema progression was measured at 0, 1, 2, 3, 4, 5, and 6 hours after carrageenan injection using a plethysmometer to determine the paw volume (mL). The percentage inhibition of inflammation at each time point was calculated using the following formula:

$$\%Inhibition = \frac{Vx - Vy}{Vx} \times 100$$

Where Vx represents the inflammation volume of the negative control group, and Vy represents the inflammation volume of the treatment group.

Statistical analysis

The data collected in this study were processed and analyzed using Microsoft Excel and SPSS 20 (IBM, USA). IC_{50} values for antioxidant activity were determined by nonlinear regression of concentration-response curves, providing an estimate of the concentration required to inhibit 50% of free radicals. Statistical comparisons between different treatment groups were conducted using one-way analysis of variance (ANOVA), followed by an appropriate Tukey test to assess significant differences.

Results and Discussion

Characteristics and Phytochemicals of Dry Sample of Ziziphus jujuba Leaf

The characteristics of the dried samples were evaluated based on moisture content, ash content, and extractable matter, according to the standards outlined in the Indonesian Herbal Pharmacopoeia (26). Additionally, a phytochemical screening was performed on the dried sample to detect various bioactive compounds. The results of the characterization and phytochemical screening are presented in Figure 1 and Table I.

Table I

Phytochemical screening results

Compound	Result
Alkaloid	+
Flavonoid	+
Glycoside	+
Saponin	+
Tannin	+
Steroid/Triterpenoid	+

The characterization of dried *Z. jujuba* leaf powder demonstrated favourable results, meeting the quality standards for natural materials used in medicinal and traditional remedies in Indonesia (26, 27). One of the primary requirements for storing dried natural materials is maintaining a moisture content below 10% to ensure stability and prevent microbial, mold, or fungal growth. In addition, the acid-insoluble ash content is an important parameter used to evaluate the level of siliceous impurities, such as sand or soil, that may contaminate plant materials during harvesting or handling. Generally, lower acid-insoluble ash values indicate a lower level of such extraneous inorganic matter and reflect better purity and quality of the raw material intended for medicinal use.

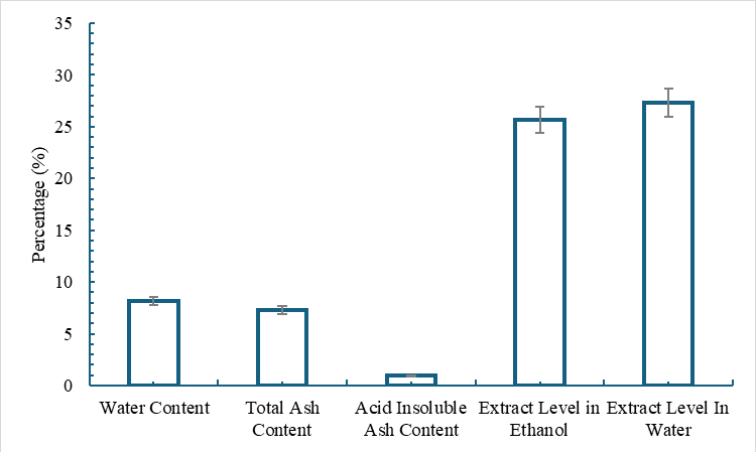

Figure 1.
Characterization of a dried sample of *Z. jujuba* leaves

These findings are consistent with previous studies reporting that *Z. jujuba* leaves contain high concentrations of flavonoid glycosides, alkaloids, saponins, and triterpenoids. Furthermore, metabolite profiling using NMR successfully identified various flavonoids and using UHPLC/PDA/ESI-MS successfully identified various bioactive compounds, including naringenin-6,8-di-c-hexoside, quercetin-3-O-robinoside, quercetin-3-O-rutinoside, quercetin-3-O-hexoside, quercetin-3-O-(2-pentosyl)-rhamnoside, kaempferol-3-O-robinoside, kaempferol-3-O-rutinoside, n-desmethylsativanine a, sativanine a, daechuine, hovenine a, frangulanine, jujuba saponin, ziziphin, ceanothetric acid methyl ester, trihydroxy-urs-12-en-28-oic acid, ceanotic acid, maslinic acid, pomolic acid, 3-O-e-p-coumaroylalphitolic acid, glycerol 1,2-dialkanoates-3-O-hexoside, betulinic acid, and methyl ceanothate (28, 29). These compounds contribute to the pharmacological properties of *Ziziphus jujuba* and highlight its potential as a source of bioactive metabolites.

Total Phenolic and Flavonoid Content

The extract of *Z. jujuba* leaves contains a significant amount of phenolic and flavonoid compounds, which contribute to its potential biological activities. The concentrations of these bioactive compounds are presented in Table II.

Table II
TPC and TFC of *Z. jujuba* leaf extract

Sample	TPC (mg GAE/ g Extract)	TFC (mg QE/ g Extract)
Ziziphus jujuba Leaf Extract	43.70 ± 1.78	19.49 ± 0.88

The TPC and TFC obtained from the *Z. jujuba* leaf extract in this study were relatively high but differed from the values reported by Sakna *et al*., 2019, where the methanol extract of *Z. jujuba* leaves had a TPC of 64.62 ± 2.44 mg GAE/g extract and a TFC of 40.51 ± 1.07 mg QE/g extract (27). These variations in TPC and TFC values may be attributed to several factors, including internal factors such as leaf variety and maturity, as well as external factors such as geographical differences, sample processing methods, and the extraction techniques used in each study.

Several phenolic acid compounds previously reported in *Z. jujuba* include chlorogenic acid, syringoylquinic acid, and trimethoxybenzoylquinic acid. The flavonoids detected in *Z. jujuba* are primarily glycosylated flavonoids, including naringenin-6,8-di-c-hexoside, quercetin-3-O-robinoside, quercetin-3-O-rutinoside, quercetin-3-O-hexoside, quercetin-3-O-(2-pentosyl)-rhamnoside, kaempferol-3-O-robinoside, kaempferol-3-O-rutinoside, caffeic acid-O-hexoside, and myricetin-O-hexose-rhamnose. These findings highlight the presence of glycosylated flavonoids, which are known to enhance the solubility and bioavailability of flavonoid compounds in biological systems (28-31).

Antioxidant of Extract and Fractions

The antioxidant potential of *Z. jujuba* leaf extracts and fractions was assessed using the DPPH radical scavenging assay. The results, summarizing the samples' capacity to inhibit DPPH radicals, are presented in Table III. These findings offer valuable insights into the free radical scavenging properties of *Z. jujuba* leaf extracts and fractions, which may be linked to their phenolic and flavonoid content.

Table III

Antioxidant activity of *Z. jujuba* leaf

Samples	IC_{50} (µg/mL)	Regression Equation	R^2
Ethanol extract	89.76	Y = 61.215X – 69.558	0.9904
n-Hexane fraction	756.61	Y = 0.0633X + 2.1066	0.9968
Ethyl acetate fraction	78.07	Y = 0.6279X + 0.977	0.9986
Residual hydroethanolic fractions	161.05	Y = 0.2816X + 4.6483	0.9898
Ascorbic acid	3.92	Y = 13.1356X – 1.5212	0.9980

The highest antioxidant activity was observed in the ethyl acetate fraction, with an IC_{50} value of 78.07 µg/mL, while the n-hexane fraction exhibited the lowest activity, with an IC_{50} value of 756.61 µg/mL. However, none of the *Z. jujuba* leaf extracts or fractions demonstrated antioxidant activity comparable to that of ascorbic acid, which was used as the positive control.

The antioxidant potential of *Z. jujuba* leaves may be influenced by the presence of flavonoid compounds (32, 33). In natural product extraction, flavonoids are predominantly extracted with ethyl acetate (34-36). A comparative study on three *Ziziphus* species demonstrated a positive correlation between flavonoid content and antioxidant activity (28). However, the relatively moderate antioxidant capacity of *Z. jujuba* leaves may be attributed to the specific type of flavonoid glycosides present. The predominant flavonoids in *Z. jujuba* leaves are glycosylated at the C3 position, where the hydroxyl (-OH) group is replaced by a sugar moiety, leading to a reduction in antioxidant activity (37, 38).

Anti-inflammatory activity of Z. jujuba

The anti-inflammatory activity of *Z. jujuba* leaf extract and its fractions was evaluated *in vivo* by measuring the percentage inhibition of carrageenan-induced paw edema in Wistar rats. The results, presented in Figure 2, show the progressive increase in oedema inhibition from 0 to 360 minutes. The effectiveness of each tested sample was assessed by the stabilization of the inhibition percentage, with a steady increase and low standard deviation indicating consistent anti-inflammatory activity. The stabilization phase, observed between 180 and 360 minutes, is detailed in Table IV.

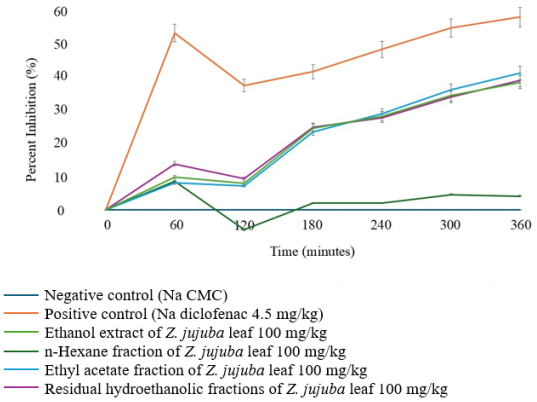

Figure 2.

Anti-inflammatory activity of *Z. jujuba* leaf extract and fractions

Table IV

Anti-inflammatory activity of *Z. jujuba* leaf

Groups	Percent inhibition (%) of edema in time (minutes)			
	180	240	300	360
Negative control	0.00 ± 0.00^{C}	0.00 ± 0.00^{C}	0.00 ± 0.00^{C}	0.00 ± 0.00^{C}
Positive control	40.60 ± 0.07^{A}	47.18 ± 0.11^{A}	53.40 ± 0.21^{A}	56.62 ± 0.08^{A}
Ethanol extract	23.99 ± 0.14^{B}	27.52 ± 0.31^{B}	33.55 ± 0.43^{B}	37.49 ± 0.48^{B}
n-Hexane fraction	2.07 ± 0.09^{C}	1.96 ± 0.23^{C}	4.49 ± 0.27^{C}	4.05 ± 0.23^{C}
Ethyl acetate fraction	22.94 ± 0.54^{B}	$28.25 \pm 0,46^{B}$	35.24 ± 0.37^{B}	40.18 ± 0.27^{B}
Residual hydroethanolic fractions	24.27 ± 0.24^{B}	27.05 ± 0.18^{B}	33.11 ± 0.28^{B}	38.09 ± 0.51^{B}

Data are expressed as mean ± SD (n = 6). Different letters within the same column indicate significant differences among treatment groups at the same time point (one-way ANOVA followed by Tukey's post hoc test, $p < 0.05$).

Data are presented as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by an appropriate post hoc test to determine differences among groups. For the paw oedema experiment, measurements were taken at multiple time points after carrageenan induction. To evaluate the differences among treatment groups, the oedema data at each time point were analysed separately using one-way ANOVA. In this approach, each time point was treated as an independent dataset, allowing comparison of the anti-inflammatory effects of each treatment group at the corresponding time point. A value of $p < 0.05$ was considered statistically significant.

The *in vivo* anti-inflammatory assay demonstrated that all tested samples exhibited consistent activity after 180 minutes, indicating the onset of action of the active compounds. The data further revealed that diclofenac, used as a positive control, exhibited superior oedema inhibition compared to all test samples, with a final inhibition percentage of 56.62 ± 0.08% at 360 minutes. The ethanol extract, ethanol fraction, and ethyl acetate fraction displayed significant anti-inflammatory activity, with no statistically significant differences among them from 180 to 360 minutes. In contrast, the n-hexane fraction at 100 mg/kg did not exhibit significant edema inhibition and did not differ from the negative control. These findings suggest that the ethyl acetate and ethanol fractions possess promising anti-inflammatory potential, warranting further fractionation and isolation of active compounds.

The anti-inflammatory activity of *Ziziphus* species is influenced by the presence of phenolic compounds, flavonoids, saponins, and pentacyclic triterpenoids chlorogenic acid, rutin, and quercetin, which are phenolic and flavonoid compounds found in *Z. jujuba* leaves, have been reported to exhibit anti-inflammatory properties Additionally, saponins and pentacyclic triterpenoids are also suspected to play a significant role in the anti-inflammatory effects of this plant (27, 38, 39). Several pentacyclic triterpenoids from *Z. jujuba*, such as zizyberenalic acid, ceanothenic acid, ursonic acid, betulinic acid, alphitolic acid, oleanolic acid, ceanothic acid, and epiceanothic acid, have been previously reported (40-42).

Limitation of the study

Although the present study demonstrated the antioxidant and anti-inflammatory activities of *Z. jujuba* leaf extract and its fractions, several limitations should be acknowledged. This study represents a preliminary investigation, as the specific bioactive compounds responsible for the observed activities were not isolated or identified. In addition, the anti-inflammatory activity was evaluated only using the carrageenan-induced paw oedema model, and the underlying molecular mechanisms were not explored. Therefore, further studies are necessary to isolate and characterize the active constituents and to elucidate their mechanisms of action.

Conclusions

This study demonstrates that *Z. jujuba* leaves possess antioxidant and anti-inflammatory activities, as indicated by their ability to scavenge DPPH radicals and reduce carrageenan-induced paw oedema in rats. The ethanol extract showed notable biological activity and was further fractionated using solvents of different polarity (*n*-hexane and ethyl acetate), resulting in three fractions. Among these, the ethyl acetate fraction and the residual hydroethanolic fraction showed relatively stronger antioxidant and anti-inflammatory activities compared with the n-hexane fraction. These findings suggest that compounds with potential bioactivity may be present in the semi-polar and polar fractions of the extract.

Overall, these results highlight the potential of *Z. jujuba* leaves as a natural source of antioxidant and anti-inflammatory agents. However, this study should be considered a preliminary investigation, as the specific active compound responsible for the observed activities has not yet been isolated and the underlying mechanisms of action remain to be elucidated. Further studies are therefore required to isolate and identify the active constituents responsible for these activities and to clarify their possible mechanisms of action in the management of inflammation and oxidative stress-related conditions.

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Not applicable.

Availability of data and materials

The data supporting the findings of this study are included in this article. Additional information may be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All experimental procedures involving animals, including housing, treatment administration, and euthanasia, were conducted in accordance with ethical guidelines and were approved by the Animal Research Ethics Committee (AREC), Universitas Sumatera Utara (Approval No. 0306/KEPH-FMIPA/2024).

AI use disclosure

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for translation from

Indonesian to English and for editing assistance language improvement, specifically to improve spelling, grammar, word choice, readability, and clarity. The authors carefully reviewed and revised all outputs generated by this tool and take full responsibility for the final content of the work.

Conflict of interest

The authors declare no conflict of interest.

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