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Phytochemical profile and cytotoxic potential of mulberry (*Morus alba* L.) leaf infusion

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Abstract

Background: Mulberry (*Morus alba* L.) leaves are widely consumed as herbal infusions and have been traditionally associated with various health benefits. However, systematic evaluation of the phytochemical composition and cytotoxic potential of the leaf infusion remains limited. Objective: This study aimed to determine the phytochemical composition and evaluate the anticancer potential of mulberry leaf infusion using the Brine Shrimp Lethality Test (BSLT) method.
Method: Dried mulberry leaves were extracted by infusion using water as the solvent. Dried mulberry leaves were extracted by infusion using water as the solvent. Toxicity evaluation was conducted using *Artemia salina* Leach larvae. Each concentration (10 - 640 µg/mL) was tested in triplicate (n= 3), with twenty larvae used per replicate. Mortality was recorded after 24 and 48 h, and the median inhibitory concentration (IC_{50}) was calculated using probit analysis and a paired t-test analysis was performed to evaluate the significance ($p < 0.05$).
Results: Phytochemical screening revealed the presence of alkaloids, flavonoids, phenolics, and saponins, while terpenoids were absent. The IC_{50} values obtained for the infusion were 169.34 ± 10.79 µg/mL after 24 h and 146.66 ± 17.49 µg/mL after 48 h of exposure. No significant difference was observed between incubation periods ($p > 0.05$).
Conclusion: Mulberry leaf infusion demonstrated moderate cytotoxicity in the BSLT assay, supporting its potential as a natural anticancer candidate.

Keywords: Anticancer; BSLT; Infusion; *Morus alba*; Phytochemical

INTRODUCTION

Cancer remains a major global health burden as one of the leading non-communicable diseases. It is defined by uncontrolled cell proliferation, the ability to invade surrounding tissues, and the potential to metastasize to distant organs (1). The complexity of cancer development involves multiple genetic, molecular, and environmental factors, making its prevention and treatment highly challenging (2,3). According to the Global Cancer Observatory (2024), nearly 20 million new cancer cases were reported worldwide in 2022, including nonmelanoma skin cancers, accompanied by approximately 9.7 million cancer-related deaths. These statistics indicate that about one in five men or women will develop cancer during their lifetime, while roughly one in nine men and one in twelve women will die from the disease (4). Primary Health Research (Riset Kesehatan Dasar) reported that the cancer burden continues to increase. It is estimated that around 400,000 new cancer cases are detected each year in Indonesia, with the highest incidence observed in breast, cervical, lung, colorectal, and liver cancers. This figure aligns with international data for Indonesia, which previously reported approximately 408,661 new cases, indicating that the national cancer incidence remains in the hundreds of thousands annually. In terms of mortality, there are around 240,000 deaths per year, reflecting a significant fatality proportion and emphasizing the urgent need to improve early detection and access to oncology therapy (5). Although surgical resection followed by chemotherapy remains the standard treatment, many chemotherapeutic agents cause severe side effects, including alopecia, anemia, immunosuppression, and hypersensitivity reactions. Therefore, natural products with proven efficacy and reduced toxicity are

being explored as alternative anticancer therapies, such as mulberry (*Morus alba* L.).

Mulberry has gained attention due to its rich phytochemical profile and diverse pharmacological activities. Traditionally used in Asian medicine for its anti-inflammatory, antidiabetic, ultraviolet (UV) protective, and antimicrobial effects, recent studies have begun to explore its cytotoxic potential against various cancer cell lines (6-8). Phytochemical screening is a crucial preliminary step in identifying bioactive constituents responsible for therapeutic effects. Leaves of mulberry are known to contain flavonoids, alkaloids, tannins, saponins, and glycosides, which contribute to its antioxidant and cytotoxic properties (9). The ethanolic extract of mulberry leaves exhibited cytotoxic activity against MCF-7 cells with an IC_{50} value of 75.32 ± 2.78 µg/mL. However, it also demonstrated cytotoxicity toward Vero cells with an IC_{50} value of 71.73 ± 4.39 µg/mL. The extract showed no selectivity toward MCF-7 cells, as indicated by a selectivity index (SI) of 0.95 (10). Not only the leaves but also the fruits showed cytotoxicity. The fruits extracted with 70% (v/v) methanol exhibited the highest cytotoxic activity with an IC_{50} value of 26.83 mg/mL (11). However, scientific evidence regarding the toxicity and biological effects of mulberry leaf infusions prepared using water as the solvent remains limited.

To treat cancer, people generally boil the leaves and consume the infusion regularly. This traditional practice is based on the belief that the bioactive compounds contained in the leaves possess anticancer properties that can inhibit tumor growth and improve overall health. Although such use has been passed down through generations and remains popular in various communities, scientific evidence supporting its efficacy and safety is still limited. Therefore, this study employed an aqueous infusion of mulberry leaves to scientifically validate its claimed anticancer activity using the Brine Shrimp Lethality Test (BSLT). BSLT is a widely accepted rapid screening method for cytotoxic compounds (12,13). The objective was to determine the phytochemical composition and evaluate the anticancer potential of mulberry leaf infusion.

METHOD

Materials

Analytical-grade reagents, including magnesium powder (Mg), hydrochloric acid (HCl), ferric chloride ($FeCl_3$), and aluminum chloride ($AlCl_3$), were obtained from Merck (Indonesia). Distilled water was obtained from OneMed (Surabaya).

Sample collection and preparation

Fresh mulberry leaves were collected in February 2022 from the Wajo District, South Sulawesi. Plant materials were authentically identified in Department of Biological Pharmacy, Sekolah Tinggi Ilmu Farmasi Makassar, a voucher specimen No. A1827888. Mature, undamaged leaves were washed with running water and then oven-dried for 36 h at 40 °C. The dried leaves were ground to a fine powder using a clean mill and then passed through a 40–60 mesh sieve. Store the powder in airtight containers at room temperature until use.

Infusion preparation

The infusion was prepared by heating powdered mulberry leaves in distilled water at 90 °C for 15 min. The resulting mixture was then filtered under vacuum to remove insoluble materials, and the filtrate was subsequently lyophilized to obtain a dry extract for further analysis.

Phytochemical screening

A stock solution was prepared by infusing 100 mg of dried mulberry leaf infusion into 10 mL of distilled water.

Alkaloid test

Two drops of the Dragendorff's reagent were added to the sample solution. The presence of alkaloids was indicated by the formation of an orange to brown precipitate.

Phenolic test

Five drops of 10% $FeCl_3$ solution were added to each sample. Purple, red, or dark blue coloration indicated a positive result for phenolic compounds.

Flavonoid test

The sample was treated with 2 mg of magnesium powder, followed by three drops of concentrated HCl. The formation of a red

or orange color confirmed the presence of flavonoids.

Saponin test

One milliliter of the stock solution was transferred into a test tube and shaken vigorously until froth appeared, followed by the addition of one drop of concentrated HCl. The persistence of froth for at least 15 min indicated a positive result for saponins.

Terpenoid test

The Liebermann-Burchard test was used to detect terpenoids. Three drops of Liebermann-Burchard reagent were added to the sample. The appearance of a red or purple color signified a positive reaction.

Larvae preparation

Approximately 1 g of *Artemia salina* eggs was placed in 500 mL of sterilized seawater, filtered through a 0.4 µm Millipore membrane, and incubated under continuous illumination. The eggs hatched after 48 h, and the nauplii were used for the toxicity assay.

Hatching of brine shrimp

Artificial seawater with a salinity of 35% was prepared or filtered natural seawater was used as the hatching medium. The medium was transferred into a hatching chamber and aerated continuously to ensure proper oxygenation. The temperature was maintained between 25 °C and 28 °C under constant illumination. *A. salina* cysts (approximately 0.1-0.5 g per 500 mL of seawater) were added and incubated for 24 and 48 h until free-swimming nauplii hatched. Only active and healthy nauplii were used in the bioassay.

Preparation of the test concentrations

A series of test concentrations was prepared from the infusion extract stock solution by serial dilution in seawater. The typical concentration range used was 10, 20, 40, 80, 160, 320, and 640 µg/mL. At least seven concentrations covering the expected mortality range (0-100%) were included to ensure the accurate determination of the LC_{50} value.

Toxicity assay

Twenty active *A. salina* were transferred into each 20 mL glass vial containing 10 mL of the test solution. Each concentration was tested in quadruplicate ($n \geq 4$). The vials were incubated at 25 °C till 28 °C under continuous light for 24 h without feeding the nauplii during the exposure period. After 24 h, the number of surviving nauplii in each vial was counted after 24 h using a stereomicroscope or magnifying lens. Nauplii were considered dead if they exhibited no movement when gently probed. Observations were also conducted after 48 h to assess any delayed mortality effects.

Data recording and LC_{50} determination

Record mortality for each concentration and control using the following formula:

$$\text{Mortality (\%)} = \frac{\text{Control - sample}}{\text{Control}} \times 100 \quad \text{.....(1)}$$

The median lethal concentration (LC_{50}), defined as the concentration of the extract that causes 50% mortality in *A. salina*, was determined using probit analysis in Microsoft Excel 365. The mortality percentages at each concentration were first converted into probit values, and the logarithm of the corresponding concentrations was calculated. Then, a linear regression analysis

Table 1. Phytochemical profile of mulberry leaf infusion

Metabolites	Test	Result
Alkaloids	Dragendorff's	+
Flavonoids	Ferri chloride	+
Phenolics	Reaction with magnesium and hydrochloric acid	+
Saponins	Frothing test	+
Terpenoids	Liebermann–Burchard	–

(+): Present; (–): Absent.

Table 2. Toxicity of mulberry leaf infusion against *A. salina* larvae using the BSLT method at various concentrations after 24 h of incubation

Concentration (µg/mL)	Mortality (%)				Mean	SD
	Rep 1	Rep 2	Rep 3	Rep 4		
10	0	0	0	0	0	0.00
20	0	5	5	0	2.5	2.89
40	10	15	10	5	10	4.08
80	25	25	20	20	22.5	2.89
160	50	55	55	55	53.75	2.50
320	75	70	65	80	72.5	6.45
640	100	95	100	95	97.5	2.89

Table 3. Toxicity of mulberry leaf infusion against *A. salina* larvae using the BSLT method at various concentrations after 48 h of incubation

Concentration (µg/mL)	Mortality (%)				Mean	SD
	Rep 1	Rep 2	Rep 3	Rep 4		
10	0	5	5	0	2.5	2.89
20	5	0	0	5	2.5	2.89
40	15	10	15	10	12.5	2.89
80	15	30	30	25	25	7.07
160	60	55	60	70	61.25	6.29
320	85	65	85	80	78.75	9.46
640	100	100	100	95	98.75	2.50

was conducted between the probit values (Y-axis) and the log-transformed concentrations (X-axis). The obtained regression equation was used to estimate the LC_{50} value, corresponding to a probit value of 5, along with the coefficient of determination (R^2) to evaluate the goodness of fit.

Data analysis

Data was presented as the mean ± standard deviation (SD) of three independent replicates. The Shapiro–Wilk test was used to evaluate the normality of the data distribution. Differences between the IC_{50} values obtained after 24 and 48 h of incubation were analyzed using a paired t-test, with a significance level set at $p < 0.05$.

RESULTS

Phytochemical screening

Table 1 presents the phytochemical screening of mulberry leaf infusion, identified using specific group reagents. The infusion tested positive for alkaloids, flavonoids, phenolics, and saponins. In contrast, terpenoids are nonpolar compounds that are poorly soluble in both nonpolar and polar solvents, such as water.

Toxicity after incubation for 24 h

Table 2 presents the toxicity of mulberry leaf infusion against *A. salina* larvae after 24 h of incubation. The BSLT revealed a concentration-dependent increase in larval mortality, where higher extract concentrations resulted in higher mortality rates (Fig. 1A). Initial larval mortality was observed at a concentration of 10 µg/mL, with a mortality rate of 2.5%. The highest mortality rate (97.5%) was recorded at 640 µg/mL. The regression analysis yielded the equation $y = 0.1568x + 8.5129$, with a correlation coefficient (R^2) of 0.8924, indicating a strong positive relationship between the tested variables. These findings indicate that mulberry leaf infusion exhibits notable cytotoxic activity, suggesting its potential as a promising candidate for the development of anticancer drugs.

Toxicity after incubation for 48 h

The toxicity of mulberry leaf infusion increased after 48 h of incubation compared

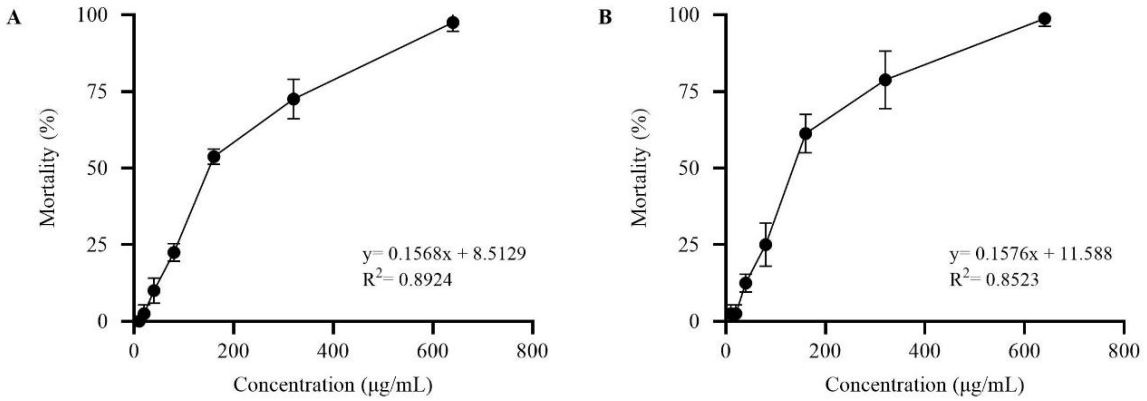

Figure 1. Toxicity of mulberry leaf infusion against *A. salina* larvae using the BSLT method at various concentrations after (A) 24 and (B) 48 h of incubation.

with 24 h (Table 3). A concentration-dependent relationship was observed, where higher extract concentrations resulted in greater larval mortality (Fig. 1B). Similar to the 24-h observation, a mortality rate of 2.5% was recorded at 10 µg/mL. The highest mortality rate of 98.75% was observed at 640 µg/mL. The regression analysis yielded the equation y = 0.1576x + 11.588, with a correlation coefficient (R^2) of 0.8523, indicating a strong positive relationship between the tested variables. These results suggest that prolonged exposure enhances the infusion's cytotoxic effect, further supporting the potential of mulberry leaf infusion as a promising candidate for cancer treatment.

IC_{50} Value

The anticancer potential of a compound can be evaluated based on its IC_{50} value, which represents the concentration required to kill or inhibit 50% of cancer cells. The IC_{50} value was determined using probit analysis by regressing the logarithm of concentration (X-axis) against the percentage of mortality (Y-axis) using Microsoft Office Excel 365. The probit analysis results showed that the IC_{50} value of mulberry leaf infusion against *A. salina* larvae was 169.34 ± 10.79 µg/mL after 24 h of incubation and decreased to 146.66 ± 17.49 µg/mL after 48 h of incubation (Fig. 2). Statistical analysis indicated no significant difference ($p > 0.05$) between the IC_{50} values obtained at 24 and 48 h, suggesting that the increase in toxicity over time was not statistically significant.

DISCUSSION

Considering the persistent global burden of cancer, the results of this study contribute preliminary data to the evaluation of plant-based preparations as potential sources of anticancer agents. Therefore, the discovery of new anticancer agents with higher efficacy and fewer side effects is urgently needed. Various methods, including BSLT, in vitro cancer cell culture assays, and antiproliferative tests using sea urchin embryos, can be employed to evaluate the anticancer potential of natural compounds. In this study, the BSLT method was used because it is considered a practical, cost-effective, and environmentally safe approach. The BSLT employs *A. salina* larvae, which are highly sensitive to the presence of bioactive compounds, making this method a reliable preliminary screening tool for assessing cytotoxic or anticancer potential.

The phytochemical screening of the mulberry leaf infusion revealed alkaloids, flavonoids, phenolics, and saponins, but terpenoids were not detected. The presence of these bioactive compounds suggests that mulberry leaves have diverse pharmacological potential. Alkaloids are known for their wide range of biological activities, including analgesic, antimicrobial, and anticancer properties (14). Flavonoids and phenolic compounds are potent

antioxidants that play a crucial role in free radical scavenging, thereby contributing to the prevention of oxidative stress–related diseases (15). Saponins have membrane-permeabilizing effects, cholesterol-lowering properties, and potential cytotoxic activity against certain cell types (16). The absence of terpenoids may indicate that the infusion process or the solvent used was inefficient in extracting these compounds. Overall, the phytochemical profile of mulberry leaf infusion supports its potential therapeutic value, particularly in terms of antioxidant and cytoprotective applications.

Rahmadi *et al*. (2021) classified compounds' anticancer potential based on their IC_{50} values. A compound is considered nontoxic if it has an IC_{50} value greater than 1,000 µg/mL, slightly toxic if the IC_{50} ranges from 500 to 1,000 µg/mL, toxic when the IC_{50} value is between 100 and 500 µg/mL, and highly toxic if the IC_{50} is less than 100 µg/mL (17). The results of this study demonstrated that mulberry leaf infusion possesses notable cytotoxic activity against *A. salina* larvae, as indicated by the concentration-dependent increase in mortality. The BSLT revealed that higher extract concentrations resulted in greater lethality, consistent with the findings of other studies that employed this method for preliminary toxicity screening of plant-derived compounds. The LC_{50} values obtained after 24 and 48 h of incubation were 169.34±10.79 and 146.66 ± 17.49 µg/mL, respectively. Based on this classification, the mulberry infusion, which exhibited an IC_{50} value within the toxic range, can be considered cytotoxic toward *A. salina* larvae and thus shows potential for further development as a candidate for anticancer therapy.

The cytotoxic potential of mulberry observed in this study is consistent with previous reports on the anticancer effects of its extracts and isolated compounds. Mulberry leaf polyphenol extract is a potential anticancer agent that targets autophagy and apoptosis in cells with p53 status, as demonstrated in human hepatoma HepG2 cells, HCC Hep3B cells, and human breast carcinoma cells MCF-7 (18). Kwak *et al.* (2023) isolated moracin E and M from mulberry, which can induce skeletal muscle cell proliferation via the PI3K-Akt-mTOR signaling pathway (19). The PI3K-Akt-mTOR signaling pathway plays a crucial role in regulating key cellular processes, including growth, proliferation, metabolism, and survival. This pathway is frequently hyperactivated in a wide range of human cancers, leading to uncontrolled cell growth and resistance to apoptosis. Dysregulation of the PI3K-Akt-mTOR signaling pathway has been recognized as a hallmark of tumorigenesis and is often associated with a poor prognosis and therapeutic resistance. Due to its central involvement in cancer development and progression, this pathway has become a significant focus of targeted therapy (20,21).

Moreover, mulberry leaf extract, along with the flavonoids isoquercetin and rutin, is toxic to the gastric cancer cell line. Mulberry also demonstrated a synergistic cytotoxic effect with cisplatin (22). Mulberry hydromethanolic extracts induce apoptosis in lung carcinoma cells A549 with IC_{50} 18.4 ± 3.01 to 29.41 ±3.6 µg/mL. Moreover, the extracts effectively inhibited cell migration, making them suitable for cancer metastasis treatment. This study also reported that mulberry induces programed cell death in lung cancer cells via a ROS-dependent apoptotic pathway (23). Although the BSLT is a general bioassay that does not specify the mechanism of toxicity, the strong correlation between brine shrimp lethality and cytotoxicity in mammalian cells supports its reliability as an initial screening tool for anticancer potential.

Overall, the findings of this study indicate that mulberry infusion exhibits moderate cytotoxic activity, suggesting its potential as a natural source of anticancer agents. However, further research is necessary to isolate and characterize the active constituents responsible for this activity and to confirm their efficacy through in vitro assays on specific cancer cell lines and in vivo models. Additionally, toxicity and safety evaluations in mammalian systems are crucial for determining the therapeutic

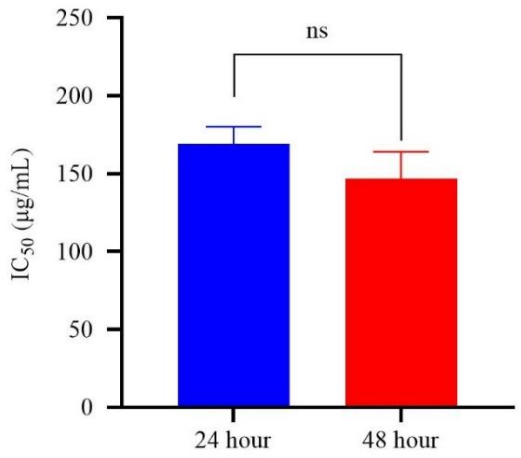

Figure 2. IC_{50} values of mulberry leaf infusion against A. salina larvae in the BSLT assay after 24 and 48 h of incubation. NS: not significant at a 95% confidence level ($p > 0.05$).

potential and clinical relevance of mulberry as a candidate for anticancer drug development.

CONCLUSIONS

This study conducted a preliminary toxicity screening of mulberry leaf infusion using the BSLT. The infusion exhibited measurable toxicity, with IC_{50} values of 169.34 ± 10.79 µg/mL at 24 h and 146.66 ± 17.49 µg/mL at 48 h. These findings provide initial evidence that supports further evaluation using more specific in vitro and in vivo models.

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