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Original Research Article

Phytochemical Profiling and Cytotoxicity Evaluation against HeLa Cell Line of the Extract of *Artocarpus elasticus* Stem Bark

Andi Adi A M Naneng[1,2], Alfi H Karomah[3] Mohamad Rafi[4] Pinus Jumaryatno[1*]

[1]*Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Yogyakarta 55584, Indonesia*
[2]*Faculty of Health Sciences, Almarisah Madani University, Makassar 90242, Indonesia*
[3]*Advanced Research Laboratory, IPB University, Bogor 16680, Indonesia*
[4]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, IPB University, Bogor 16880, Indonesia*

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ABSTRACT

Cervical cancer is the second most common cancer affecting Indonesian women and is becoming a major health issue in Indonesia because of its high prevalence. The challenges associated with cancer treatment, such as adverse side effects and drug resistance, highlight the urgent need for new therapeutic options. *Artocarpus* is known for its diverse secondary metabolites, including flavonoids, which have shown potential anticancer properties. However, no research has examined the potential of *Artocarpus elasticus* as an anticervical cancer agent and the compounds responsible for anticervical cancer activity. Therefore, the objectives of this study were to evaluate the cytotoxic activity of the *A. elasticus* stem bark extract against the HeLa cell line and to identify the secondary metabolites of the active extract. The extract was obtained by the ultrasound-assisted extraction method using 96% ethanol. The cytotoxicity of the extract was evaluated by the PrestoBlue assay, and the data were analyzed by the linear regression method using Microsoft Excel 2016. The secondary metabolites contained in the extract were identified using UHPLC-Q-Orbitrap HRMS analysis. Results showed that the extract exhibited moderate cytotoxic activity against the HeLa cell line with an IC_{50} of 193.30 µg/mL. A total of 13 metabolites were identified in the extract, including prenylated flavonoids, such as artonin E and artocarpin. Thus, the *A. elasticus* stem bark extract has moderate cytotoxic activity against the HeLa cell line and contains a bioactive compound that has the potential to be further investigated as a candidate anticervical cancer agent.

Keywords: *Artocarpus elasticus*, cervical cancer, HeLa cell line, cytotoxic, PrestoBlue assay

Introduction

Cervical cancer is the fourth most prevalent cancer among women worldwide.[1] In Indonesia, cervical cancer significantly impacts women and their families, with over 103 million women aged 15 years and older at risk of developing this disease and approximately 36,000 women diagnosed with this disease each year. Furthermore, approximately 70% of all diagnosed women are in the advanced stages of the disease, resulting in a high mortality rate, with approximately 21,000 deaths reported in 2020.[2] Consequently, cervical cancer represents a serious public health issue in Indonesia and has become a priority for government intervention. Chemotherapy is one of the treatment modalities for cancer; however, its side effects can be burdensome for patients, often eliciting feelings of anxiety and fear regarding the threat of death.[3] Initially, chemotherapy was thought to exclusively target cancer cells; however, it also damaged normal cells, leading to side effects, such as fatigue, nausea, hair loss, vomiting, and even death.[4] The current options for cancer treatment are constrained by drug resistance and adverse side effects, underscoring the need for alternative or adjunct therapies.[5] This situation highlights the urgency for the discovery of new therapeutic agents as alternative options for cancer treatment.

*Corresponding author. E mail: pinus.jumaryatno@uii.ac.id
Tel +6285643728457

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Several studies are currently underway to explore the potential of natural products as adjuncts to chemotherapy, aiming to enhance the sensitivity of cancer cells and mitigate the side effects of chemotherapy.[6] Plants represent a promising source of natural compounds that can be developed into pharmaceuticals because of their diverse chemical constituents, which exhibit various pharmacological activities beneficial for disease prevention and treatment,[7] including cancer.[8]

The *Artocarpus* genus contains a variety of secondary metabolites, including flavonoids, tannins, polyphenols, steroids, and triterpenoids.[9] Flavonoids found in plants of the *Artocarpus* genus have been reported to possess anticancer effects by inhibiting the growth of cancer cells. Previous research has indicated that artonin E, isolated from the bark of *A. elasticus*, can inhibit the proliferation of MDA-MB 231 breast cancer cells, making it a potential agent in breast cancer therapy.[10] Rahman *et al*. reported that artonin E, isolated from the bark of *A. elasticus*, can induce apoptosis in SKOV-3 ovarian cancer cells through the regulation of pro-survival and proapoptotic Bcl-2 expression.[11] Furthermore, artonin E has been shown to inhibit the growth of MDA-MB 231 breast cancer cells.[10] Studies of the bark of *A. elasticus* detected significant antioxidant activity in DPPH, oxygen radical absorbance capacity, and thiobarbituric acid reactive substance assays.[12] Various flavonoid derivatives have been identified and isolated from *A. elasticus* in previous studies. However, despite the potential of *A. elasticus* as an anticancer agent, to date, no investigation into its potential as a candidate for cervical cancer treatment has been conducted. Therefore, the aims of this study were to evaluate the cytotoxic activity of the stem bark of *A. elasticus* from Luwu, South Sulawesi, using PrestoBlue assay against HeLa cell line and identify the metabolites that may have the potential to inhibit HeLa cell growth using UHPLC-Q-Orbitrap HRMS analysis.

Materials and Methods

Equipment

The equipment used in this research included glassware, freezers (4°C and −86°C), analytical scale (OHAUS 214), sonicator (Branson 2510), volumetric flask, separatory funnel, Büchner funnel, rotary evaporator (Heidolph Hei-VAP Precision, Germany), blender, tube rack, micropipette, hemocytometer, CO_2 incubator, liquid nitrogen tank, centrifuge, biological safety cabinet (BSC) Class II, EVOS XL Core microscope, multimode reader (TECAN Infinite M200 Pro, Switzerland), and Thermo Scientific Vanquish Flex UHPLC Tandem Q Exactive Plus Orbitrap High-Resolution Mass Spectrometer (Thermo Scientific, Waltham, MA, USA).

Materials

The materials used in this research were *A. elasticus* stem bark, 96% ethanol (technical grade), acetonitrile (LC-MS grade; Merck, Darmstadt, Germany), water (LC-MS grade; Merck, Darmstadt, Germany), HeLa cell, fetal bovine serum (FBS), phosphate-buffered saline (PBS), dimethyl sulfoxide (DMSO), aluminum foil, plastic wrap, filter paper, Roswell Park Memorial Institute Medium 1640 (RPMI 1640) growth media, PrestoBlue™ cell viability reagent, trypsin–EDTA, penicillin–streptomycin, 96-well microplate, blue-tip and yellow-tip serological pipettes, conical tube, culture dish, cryotube, microtube, cisplatin, and Trypan blue.

Plant Collection and Determination

The *A. elasticus* stem bark was collected in Je'ne Maeja village (3°15′48.2″ S, 120°23′22.0″ E), Luwu District, South Sulawesi, Indonesia, in January 2024. Plant determination was conducted at the Plant Determination Unit, Laboratory of Pharmacognosy–Phytochemistry, Faculty of Pharmacy, Universitas Muslim Indonesia, and identified as *A. elasticus* Reinw ex Blume, which belongs to the *Artocarpus* genus and Moraceae family. A voucher specimen (No. 0104) was deposited at the Faculty of Pharmacy, Universitas Muslim Indonesia.

Extraction

A total of 10 g of *A. elasticus* stem bark powder was extracted by the ultrasound-assisted extraction method using 96% ethanol with a ratio of 1:10 (weight/volume) in 30 minutes at 42 KHz and a temperature of 30°C. Then, the extract was filtered and evaporated using a rotary evaporator (Heidolph Hei-VAP Precision, Germany) to obtain the viscous extract.

Cytotoxic Activity Evaluation Against the HeLa Cell Line

The evaluation of the cytotoxic activity of the *A. elasticus* stem bark extract followed the work protocol of the Central Laboratory of Padjadjaran University, Jatinangor, West Java, Indonesia, Division of Biological Activities (Cell Culture). All cytotoxic testing procedures were conducted aseptically in a BSC Class II at the Central Laboratory of Padjadjaran University, Jatinangor, West Java, Indonesia.

The HeLa cell lines were obtained from a collection of the Biological Activities Division at the Central Laboratory of Padjadjaran University, Indonesia. The culture medium used was complete RPMI 1640 containing 10% FBS and 1% penicillin–streptomycin. Cisplatin was used as the positive control. The cell culture was performed using 96-well microplates. The *A. elasticus* stem bark extract was prepared in a concentration series of 1,000, 500, 250, 125, 62.5, 31.25, 15.63, and 7.81 µg/mL, with a 2% DMSO solvent. The cells used should reach 70% to 80% confluency. The cell cultures in the 96-well microplates were incubated for 24 hours at 37°C and 5% CO_2. Exposure to HeLa cells was performed by removing the 96-well microplates containing the cells from the CO_2 incubator, followed by observation of the cell morphology under the EVOS XL Core microscope. Once the cells were ready for treatment, the culture medium was discarded, and the microplate was washed with 100 µL of PBS in each well. Then, 100 µL of each sample concentration series, blank control (PBS), media control, solvent control (2% DMSO), and positive control (cisplatin) were added to the respective wells. Subsequently, the 96-well microplate was incubated in a 5% CO_2 incubator at 37°C for 24 and 48 hours. At the end of the incubation period, each well in the 96-well microplate that contained the cultured cells was labeled and supplemented with 100 µL of the sample concentration series (treatment), positive control (cisplatin), solvent control (2% DMSO), media control (RPMI 1640), and blank (PBS). Subsequently, the 96-well microplate was incubated in a 5% CO_2 incubator at 37°C and observed at intervals of 24 and 48 hours.

Cytotoxicity evaluation was performed using the PrestoBlue assay method after the incubation period for the positive control, treatment concentration series, solvent control, media control, and blank. The process started by removing the medium from each well and washing it with 50 µL PBS. A mixed solution of 9.9 mL medium and 1.1 mL PrestoBlue reagent was prepared in a 50 mL conical tube. Then, 100 µL of the prepared mixed solution was added to each well of the 96-well microplate and incubated for 2 hours in the CO_2 incubator until a color change occurred. Absorbance was measured at 570 nm (reference = 600 nm) using a multimode reader (TECAN Infinite M200 Pro, Switzerland) after 2 hours of incubation.

Data Analysis of the Cytotoxic Evaluation

The qualitative analysis was conducted by observing the morphology of HeLa cells in each concentration series and control groups (i.e., positive control, solvent, medium, and blank) at 24 and 48 hours, both before and after treatment. The quantitative analysis involved determining the IC_{50} value. Absorbance data obtained from measurements using a multimode reader were used to calculate the percentage of viable HeLa cells, which were then used to calculate the IC_{50} value by the linear regression method using Microsoft Excel 2016. The IC_{50} analysis was performed to determine the concentration of the sample that inhibits 50% of cell growth. Equation **1** was used to calculate the percentage of cell viability:

$$(\%)\ \text{Cell Viability} = \frac{(\text{Absorbance of Treatment} - \text{Absorbance of Media Control})}{(\text{Absorbance of Cell Control} - \text{Absorbance of Media Control})} \times 100\% \quad (\mathbf{1})$$

Identification of Metabolites in A. elasticus *Stem Bark Extract Using UHPLC-Q-Orbitrap HRMS Analysis*

A total of 5 mg of the extract was dissolved in 1 mL of LC-MS grade methanol. Then, the solution was filtered with a 0.22 µm filter membrane, and 2.5 µL of the filtrate was injected in LC-MS/MS. Samples were analyzed using the optimized mobile phase of 0.1% formic acid in water (Solvent A) and acetonitrile (Solvent B) with a flow rate of 0.2 mL/min. The elution system used is a gradient. The column used was Accucore™ C18 (100 × 2.1 mm; 1.5 µm). The MS ionization source was ESI with a Q-Orbitrap mass analyzer. The *m/z* range is from 150 to 2,000, with ionization energies of 18, 35, and 53 eV. The MS^2 spectra of the detected compounds were validated using the ChemSpider and mzCloud databases to identify the compounds.

Results and Discussion

Metabolite Profile of the A. elasticus *Stem Bark Extract*

Artocarpus is an important genus in the Moraceae family, which is known as a prolific source of bioactive metabolites, especially flavonoids with a variety of diverse structures, such as flavones, flavonones, flavanones, isoflavones, xanthones, chalcones, and arylbenzofurans.[13–15] The uniqueness of flavonoids in *Artocarpus* is the presence of the prenyl group in their skeleton commonly at position C3 (Ring C) and Ring B oxygenated at positions C-4′ or C-2′ and C-4′ or C-2′, C-4′, and C-5′.[16] Other positions of the prenyl group can also occur at C6, C8, and C3′.[17,18] These patterns are distinctive to *Artocarpus* and generate a wide range of biological activities, such as antitumor and anticancer.[19,20] The *Artocarpus* genus comprises 50 species that are indigenous to South and Southeast Asia, New Guinea, and the Pacific region.[21] One species that is widely spread in Southeast Asia but less known is *A. elasticus*. This species has been reported to be a source of diverse prenylated flavonoids, which are found abundantly in the bark and roots,[22] such as artelasticin and artocarpesin,[23] artelastocarpin and carpelastofuran,[24] artonin E and elastixanthone,[25] and artobiloxanthone.[14] Although *A. elasticus* can be found across several regions of Indonesia, including Java, Kalimantan, and Sulawesi, the chemistry of this species is still underexplored. Based on the literature search, limited prenylated flavonoids have been reported from a previous study of *A. elasticus* from Indonesia. Musthapa *et al*.[19] reported the isolation of artoindonesianin E1, artocarpin, cycloartocarpin,

and cudraflavones A and C from the wood of *A. elasticus*. Artoindonesianin A-3 was isolated by Kurang and Ersam[26] from the bark of *A. elasticus* collected in Alor Island, East Nusa Tenggara, Indonesia. A study of *A. elasticus* leaves from the Mekongga Forest, Southeast Sulawesi, Indonesia isolated a 6-prenyl apigenin along with the well-known flavonoid, apigenin.[27]

Table 1. Putative Identification of Metabolites in *Artocarpus elasticus* Stem Bark Extract

No	Retention Time (Minute)	Molecular Formula	Compound
1	6.254	$C_{16}H_{18}O_9$	Chlorogenic acid
2	7.235	$C_{27}H_{30}O_{15}$	Nictoflorin
3	9.166	$C_{15}H_{12}O_7$	Taxifolin
4	11.544	$C_{15}H_{10}O_6$	Kaempferol
5	12.558	$C_{20}H_{20}O_7$	Tangeritin
6	15.841	$C_{25}H_{26}O_7$	Morusinol
7	18.28	$C_{25}H_{22}O_7$	6,10,11,13-Tetrahydroxy-9-isopropenyl-3,3-dimethyl-8,9-dihydro-3H,7H-benzo[c]pyrano[3,2-h]xanthen-7-one
8	18.747	$C_{25}H_{24}O_7$	Artonin E
9	20.255	$C_{25}H_{26}O_6$	Kuwanon C
10	20.757	$C_{26}H_{28}O_7$	2-[2,5-Dihydroxy-4-methoxy-3-(3-methyl-2-buten-1-yl)phenyl]-5,7-dihydroxy-3-(3-methyl-2-buten-1-yl)-4H-chromen-4-one
11	21.016	$C_{25}H_{24}O_6$	Morusin
12	23.064	$C_{26}H_{28}O_6$	Artocarpin
13	23.192	$C_{30}H_{30}O_7$	Cycloheterophyllin

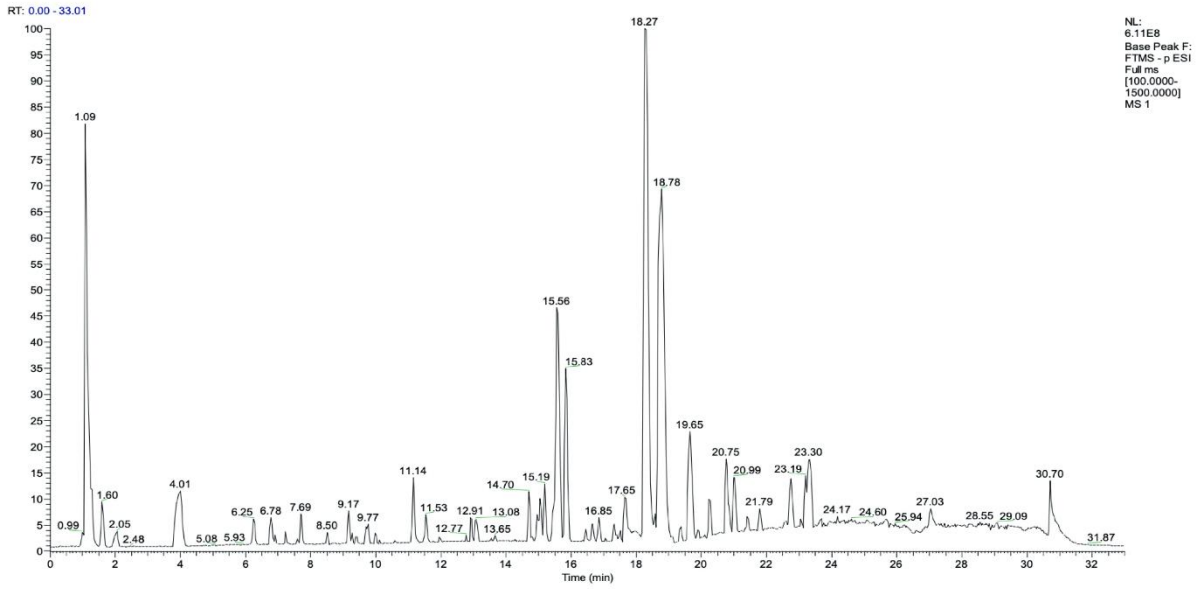

Figure 1. LC-HRMS chromatogram of *Artocarpus elasticus* stem bark extract

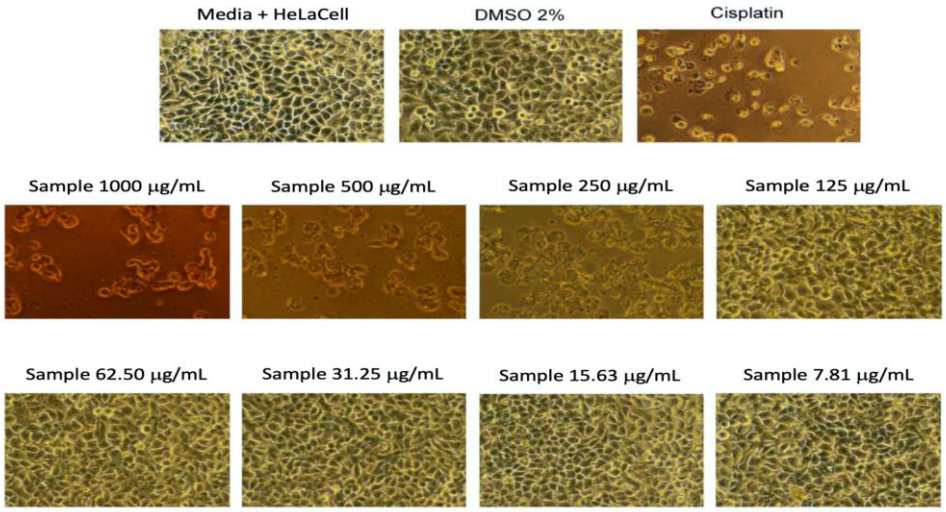

Figure 2. HeLa cell morphology after treatment with *Artocarpus elasticus* stem bark extract after 48 hours

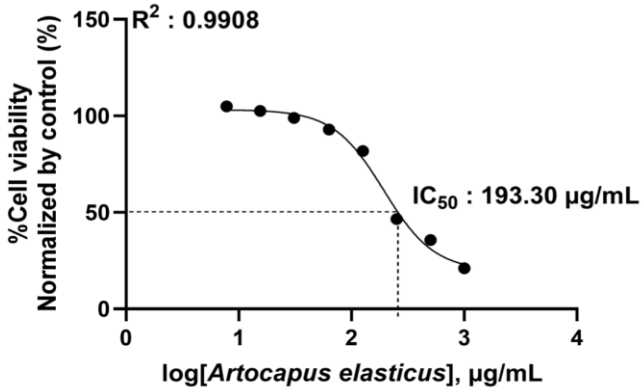

Figure 3. %Cell viability vs concentration of *Artocarpus elasticus* stem bark extract

In the present study, the *A. elasticus* stem bark collected from Luwu, South Sulawesi, Indonesia, known locally as Tarra' was chemically investigated using UHPLC-Q-Orbitrap HRMS analysis. **Figure 1** depicts the LC-HRMS chromatogram of the *A. elasticus* stem bark extract. A total of 13 compounds were identified from the *A. elasticus* stem bark extract (**Table 1**). The identified metabolites in the extract were mainly prenylated flavonoids, comprising artonin E, artocarpin, morusin, morusinol, kuwanon C, cycloheterophyllin, 6,10,11,13-tetrahydroxy-9-isopropenyl-3,3-dimethyl-8,9-dihydro-3*H*,7*H*-benzo[c]pyrano[3,2-h]xanthen-7-one (known as artobiloxanthone), and 2-[2,5-dihydroxy-4-methoxy-3-(3-methyl-2-buten-1-yl)phenyl]-5,7-dihydroxy-3-(3-methyl-2-buten-1-yl)-4*H*-chromen-4-one (known as heteroartonin A). The presence of prenylated flavonoids in the investigated *A. elasticus* stem bark extract, as shown in **Table 1**, is consistent with the characteristics of compounds found in the *Artocarpus* genus. Interestingly, except for artocarpin,[19] artonin E,[25] and artobiloxanthone,[25] none of those identified prenylated flavonoid compounds have been previously reported in *A. elasticus*. This finding highlighted the potential of *A. elasticus* from Luwu, South Sulawesi as a new source of prenylated flavonoid compounds.

Cytotoxic Evaluation against the HeLa Cell Line

The cytotoxic evaluation of the *A. elasticus* stem bark extract against the HeLa cell line was conducted *in vitro* using PrestoBlue assay method. The evaluation in this research used the extract in the form of 96% ethanol extract with a concentration series of 1,000, 500, 250, 125, 62.5, 31.25, 15.63, and 7.81 µg/mL.

The observation of the cell morphology of HeLa cells after incubation for 48 hours (**Figure 2**) indicated that cell death was caused by exposure to cisplatin and ethyl acetate extract of *A. elasticus* at a concentration of 250 µg/mL, whereas the other treatment wells did not change the cell morphology. The morphological change is characterized by the shrinkage of cells, the decrease in cell density, and the release of cells from the bottom of the microplate well/floating, as shown in **Figure 2**. Based on the observation of the morphological HeLa cells, the ethyl acetate extract of *A. elasticus* exhibited a cytotoxic effect on HeLa cells, which was characterized by the change in cell morphology that led to cell death characteristics.

The data presented in **Figure 3**, which plots cell viability against extract concentration, indicate that the concentration of the 96% ethanol extract of the *A. elasticus* stem bark affects the growth of HeLa cells. Specifically, higher concentrations of the extract lead to an increase in cell death, whereas lower concentrations resulted in a higher percentage of viable cells. The cytotoxicity of the extract was further assessed by calculating the IC_{50} value, which represents the concentration required to inhibit 50% of cell viability. The IC_{50} value was determined using the linear regression analysis of the relationship between the corrected absorbance and the extract concentration. The resulting IC_{50} value was 193.30 µg/mL, classifying the extract as exhibiting moderate cytotoxicity.[28] The R^2 value of 0.9908 indicates a robust fit of the dose–response curve to the data, explaining over 99% of the variability in cell viability based on the changes in the extract concentration. To the best of our knowledge, this study is the first to document and report the cytotoxic effects of *A. elasticus* stem bark extract on HeLa cells, making a valuable contribution to the expanding body of literature on the potential medicinal properties of *A. elasticus*. The observed cytotoxicity of the extract, sourced from Luwu, South Sulawesi, Indonesia, may be attributed to the presence of prenylated flavonoids, such as artonin E and artocarpin, as identified through UHPLC-Q-Orbitrap HRMS analysis. Further studies are required to identify the specific metabolites responsible for the cytotoxic activity of *A. elasticus* stem bark extract against the HeLa cell line.

Conclusion

This study showed that the 96% ethanol extract of the *A. elasticus* stem bark exhibits moderate cytotoxic activity against the HeLa cell line, as evidenced by the PrestoBlue assay. The extract was determined to contain prenylated flavonoids, along with other flavonoid compounds, which may contribute to its anticancer properties. These findings highlight the potential of *A. elasticus* stem bark as a promising source of bioactive compounds for cancer therapy. Future investigations should focus on identifying the specific flavonoids responsible for the observed cytotoxic effects, exploring their mechanisms of action, and conducting *in vivo* studies to assess the safety and therapeutic potential of the extract, particularly as an adjunct to existing cancer treatments.

Conflict of Interest

The authors declare there is no conflict of interest

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