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Cytotoxic Effect, Antibacterial Activity, and in Silico Evaluation of Berberine Compound from Methanolic Extract of *Arcangelisia flava* Merr Stems

Fitriyanti Jumaetri Sami*, Syamsu Nur

Department of Pharmaceutical Chemistry, Health Faculty, Almarisah Madani University, Makassar, South Sulawesi, Indonesia

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*Corresponding author.
E-mail: fitriyantisami@gmail.com

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ABSTRACT

The Menispermaceae family has 72 genera and more than 400 species, geographically distributed in Asia, Africa, America, and Oceania. The plants of this family are known to have high alkaloid content. One genus of this family is Arcangelisia, with only one species known as *Arcangelisia flava* Merr. This plant is used as traditional medicine for ailments such as diarrhea, jaundice, and malaria. Therefore, this study was to isolate the alkaloid compounds and test the antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, as well as their toxicity to the shrimp larvae. The isolated compound was confirmed for in silico activity against the target proteins 1UAG (*E. coli*) and 7RM7 (*S. aureus*). Based on the analysis of spectroscopic data, UV VIS, FT IR, and NMR, one alkaloid compound was successfully isolated and determined to be a berberine compound. Methanol extract and berberine test against *Artemia salina* shrimp larvae exhibit active toxicities with LC_{50} values of 89.13 µg/mL and 75.86 µg/mL, respectively. Antibacterial test result shows that methanol extract and berberine are more active against *E. coli* than *S. aureus*. The in-silico activity of the berberine compound supports the result of in vitro antibacterial evaluation. *A. flava* plant extract has biological capabilities as an anti-microbial and cytotoxic effect, so further development can be carried out in utilizing *A. flava* plant extract as an effective natural medicine candidate.

***Keywords*:** Antibacterials; *Arcangelisia flava*; Alkaloid; Berberine; Cytotoxic; Molecular docking

INTRODUCTION

Nowadays, health costs are increasing along with the development of diseases, especially infectious diseases caused by pathogenic bacteria. Handling infectious diseases requires antibiotic therapy, especially those caused by *E. coli* and *S. aureus* bacteria.[1,2] However, both types of bacteria have strong adaptation abilities, resulting in bacterial resistance to various antibiotics (Multiple Drug Resistance/MDR). Antibiotics can kill or inhibit susceptible bacteria. This can lead to the selection of resistant strains, and ultimately, the use of antibiotics becomes ineffective.[1,3]

Antibiotic resistance has been proven by several studies of 12 types of bacteria, such as Carbapene-resistant Enterobacteriaceae. *S. aureus* is resistant to Methicilline. Other studies show that *E. coli* resists Ceftriaxone, Levofloxacin, Doxycycline, and Ciprofloxacin.[4–6] The study's results reported that *S. aureus* infection had a mortality rate of 31%.[7] This

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problem requires alternative efforts to be found, namely by using natural medicines made from plants or what are usually called herbal medicines.

Indonesia is a country that has abundant wealth and its tropical forests are rich with various types of plants. Our ancestors have long carried out the use of Indonesian plants in terms of pesticides and medicines.[8] However, the use of these plants is still done traditionally. This needs to be developed along with developments in science and technology. From a chemical perspective, biological natural resources are sources of chemical compounds that have different amounts and types. Bioactive compounds from Indonesian plants have the potential to be used for human needs, namely medicines and pesticides, and can even be developed industrially.[9,10]

The Manispermaceae family belongs to the dicotyledon group, which has a high alkaloid content. Manispermaceae plants have around 72 genera and 400 species spread across Asian countries, including Indonesia.[11,12] One of the genera of this family is Arcangelisia. This genus only has one species, namely *Arcangelisia flava* Merr, known by the regional names of yellow wood, yellow rope, thrush, and moon leaf.[13]

According to the previous study, *Arcangelisia flava* contains alkaloids that can be derived from benzylisoquinoline alkaloids. These alkaloids include protoberberine, berberine, palmatine, and bis-benzylisoquinoline.[14,15] This group of alkaloids has physiological activity, for example, as a medicine for diabetes, malaria, liver, diarrhea, antioxidants, cancer, mouth ulcer medicine, etc.[16–19] This plant produces various potential uses and biological activities, so it is fascinating to study its chemical content. This research aims to determine the antibacterial activity and toxicity of the active compounds contained in *Arcangelisia flava*. Thus, it is hoped that this research can contribute to the development of natural product chemistry and other fields of science regarding *Arcangelisia flava*.

METHODS

Instruments and Materials

The tools and instruments used in this research include laboratory glassware, micropipette, analytical balance, liquid vacuum chromatography (KVC), rotary evaporator, Fourier Transform Infra Red (FTIR, Shimadzu Prestige-21) spectrophotometer, UV-Visible spectrophotometer (Hewlett Packard 8543 Agilent technologies), ^{1}H NMR 400 MHz spectrophotometer, ^{13}C NMR 125 MHz (JEOL software), laminar airflow, petri dish, incubator, oven, petri disk, vernier caliper, micropipette (effendorf), and autoclave.

The samples of *Arcangelisia flava* stems were obtained from the Bremi subdistrict, West Papua (0°47'40.5"S 133°57'50.4"E) and were determined in the Biology Laboratory, Science Department, Makassar State University, with specimen code 087/SKAP/LAB. The materials used were methanol (Merck, Germany), ethyl acetate (Merck, Germany), anhydrous MgSO4 99.6% (Merck, Germany), distilled water, silica gel 60 GF254 (Merck, Germany), TLC plates (Merck, Germany), and Dragendorff reagent. The BSLT test uses seawater and *Artemia salina* L shrimp larvae. The antibacterial test uses the agar diffusion method using disc paper. It uses the test bacteria *E. coli* and *S. aureus* as well as chloramphenicol as a positive control and dimethylsulfoxide (DMSO) as a negative control.

Sample Preparation and Extraction

The stems of *Arcangelisa flava* were washed and cut into small pieces, then dried in the oven at 40 ^{0}C for five times 24 hours. Dried samples were sorted and powdered. Extraction of compounds from *Arcangelisia flava* stems was carried out by maceration. A total of 1 kg of stem powder was macerated with methanol for 1 x 24 hours while stirring occasionally and then filtered. The filtered residue was then macerated again with the same solvent and method twice. The maceration results are evaporated with a rotary evaporator to

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produce total methanol extract. This study used the solvent methanol to attract both polar and nonpolar compounds. This is based on the molecular structure of methanol, which has an alcohol OH group, which is polar, and an aliphatic chain, which is non-polar, so it is likely to be able to attract chemical components from the compound.[20]

Separation and Purification of Compounds

A total of 30 grams of methanol extract was dissolved in methanol and water with a ratio of 1:1 and left for 24 hours to remove chlorophyll. The filtrate was filtered to obtain a dark orange colored filtrate and acidified by adding 5% citric acid until the filtrate was acidified (pH 3). The filtrate was partitioned and extracted with ethyl acetate three times to obtain the ethyl acetate fraction and the water fraction. The water phase was taken, and ammonia was added until the filtrate was alkali (pH 9). The filtrate was extracted with ethyl acetate three times. The ethyl acetate fraction was dried with anhydrous MgSO4 and evaporated using a rotary evaporator to produce the total alkaloid fraction.[21,22]

A total alkaloid fraction of 8 grams was fractionated using vacuum liquid chromatography (VLC) using the eluent ethyl acetate: methanol, whose polarity was gradually increased. Purification was continued by gravity chromatography until a single compound was obtained.[23]

Cytotoxic Profile of Extract by *Brine Shrimp Lethality Test* (BSLT)

Fertilized *Artemia salina* Leach eggs of ± 50-100 mg are placed in a vessel containing seawater. The egg was covered with aluminum foil, and the light was turned on for 48 hours. After that, the eggs will hatch into larvae that are ready to be used as test animals. A total of 10 mg of sample was dissolved in 10 µL of dimethyl sulfoxide (DMSO). Seawater was added to make 5 ml of the extract/isolate solution to obtain a concentration of 2,000 µg/mL of the stock solution. From the stock solution, concentrations of 1000, 500, 200, 100, 10 µg/mL were made, after which seawater was added to 1 ml. The control was carried out without adding a sample. Each variation of solution concentration was put into a test container, and ten shrimp larvae as test animals were put into each variation of solution concentration in the test container.[24]

For each concentration, three repetitions (triplicate) were carried out. Shrimp larvae were left in the test solution for 1 x 24 hours under 18-watt fluorescent lamps. After 24 hours, the dead and living shrimp larvae were counted (equation 1).

Equation 1:

$$Mortality\ (\%)\frac{Dead\ larvae\ -control\ larvae}{Larva\ total}x100\%$$

Antibacterial Activity

A total of 100 µl of bacterial suspension was put into a petri dish. Then, pour in 15 ml of liquid nutrients, make it homogeneous, and let it solidify. After that, the antibiotic disc paper and empty disc paper were placed, then dripped the empty paper disc with isolate at a concentration of 2%, 5%, and 10%, ten µL each. It was then incubated at 30 C for 18-24 hours. The clear zone that forms around the disc indicates an area of bacterial resistance.[25,26]

Molecular Docking Evaluation

In silico evaluation of the berberine compound was performed using the molecular docking method using Autodock Tools v4.2.6 software.[25,27] The berberine compound was docked against the bacterial target protein *E. coli* (PDB 1UAG) and *S. aureus* (PDB 7RM7), which is involved in the Inhibition of cell wall synthesis, which was downloaded at https://www.rcsb.org/. Visualization of docking results was carried out using Biovia Discovery Studio 2021.

Data Analysis

The results of antibacterial activity and toxicity testing of samples were expressed as mean ± SD using Microsoft Excel 19 Version.

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RESULTS AND DISCUSSION

The stem of *Arcangelisia flava* is an endemic plant in the Papua region, and until now, its use in communities outside Papua has not been optimal. Therefore, in this research, an exploration of the chemical content of *Arcangelisia flava* stems was carried out so that in the future, it can provide information related to data on chemical compounds and their bioactivity as antibacterials. The results of the research that has been carried out identified the presence of alkaloid compounds.

One compound was successfully isolated from the stem of *Arcangelisia flava*, namely a berberine compound in the form of a yellow solid with a melting point of 203-205^{0}C. The UV spectrum shows a maximum absorption of λ (MeOH) 230 nm, 266 nm, and 348 nm (Figure 1). This spectrum indicates the presence of a conjugated system in an increasingly long molecule (involving more π-bonded atoms).[14] The existence of the aromatic group, as seen in the UV spectrum, is confirmed by the absorption at 1479, 1505, and 1567 cm^{-1} in the FT IR (Figure 2).[28]

The ^{1}H NMR data showed that there were two singlet signals at chemical shear of 7.79 and 7.08 ppm. These two signals indicate the presence of two protons in the aromatic region, which is suitable for ring A. The ^{1}H spectrum also shows the presence of two singlet signals at chemical shifts of 9.88 and 8.93 ppm because this shift is more deshielding and suitable for ring C, where the protons are directly bonded to N+ will shift more towards deshielding. The singlet signal integrated as 2 protons at a chemical shift of 6.17 ppm is the methylenedioxide group (-OCH$_2$O-) found on ring A. The chemical shift of 3.20 ppm is coupled to 4.92 ppm with triplet multiplicity, and this

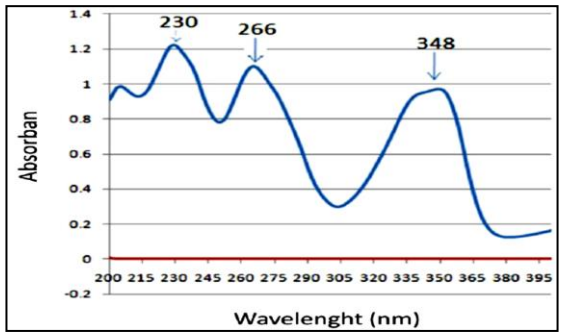


Figure 1. UV spectrum (MeOH) of berberine compounds

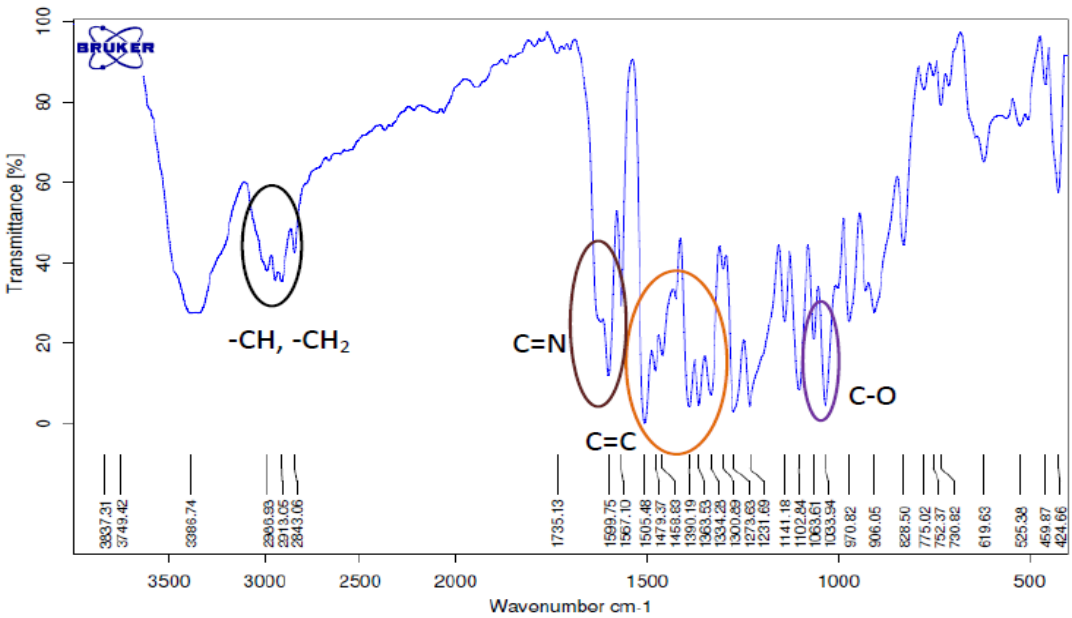


Figure 2. FT IR (KBr) spectrum of berberine compounds

is probably suitable for ring B, where the protons that bind N+ will shift more towards deshielding. The doublet signal at chemical shear is 7.99 and 8.19 ppm with a coupling constant of 9.0 Hz, indicating that the aromatic region has ortho coupling, so it is suitable for the D ring. The -OCH_3 (C-9) group is more downfield compared to –OCH_3 (C- 10) due to the influence of the N+ group, which is an electron withdrawer, allowing –OCH_3 (C-9) to be slightly more downfield on the D ring, which can be seen more clearly in Figure 3.

The ^{13}C NMR spectrum shows that this compound has 22 carbon atoms consisting of two –CH_3 (methyl) atoms bonded to oxygen atoms at 57.3 and 62.1 ppm, three –CH_2 (methylene) carbon atoms consisting of two methylene atoms at 55.4, 26.5 ppm and one methylene 102.2 ppm. Six -CH (methine) atoms, namely 105.6, 108.6, 120.4, 121.6, 123.7, 127.0, 133.2, 145.6 ppm. Nine quaternary C atoms 120.6, 121.6, 130.9, 133.2, 137.7, 143.9, 147.9, 150.0, and 150.6 ppm (Figure 4).[29]

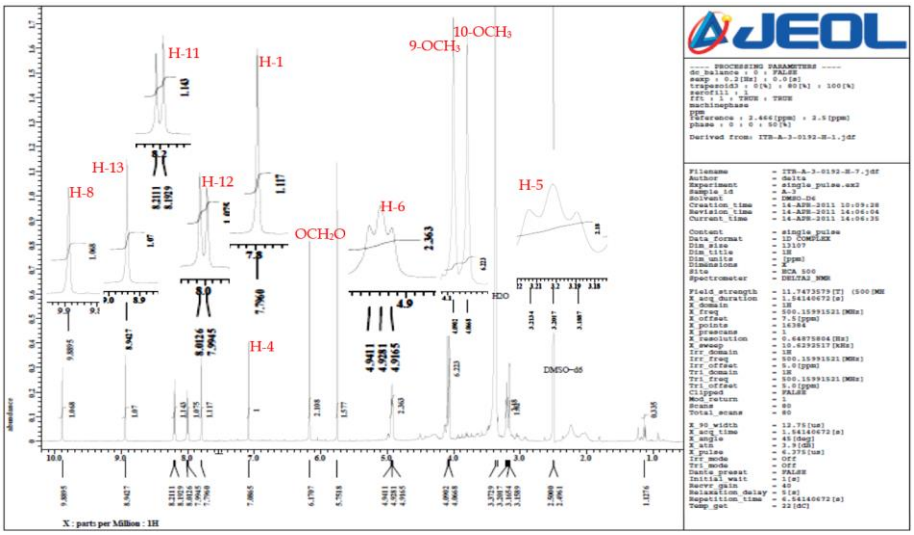


Figure 3. ^{1}H NMR spectrum of Berberine compounds

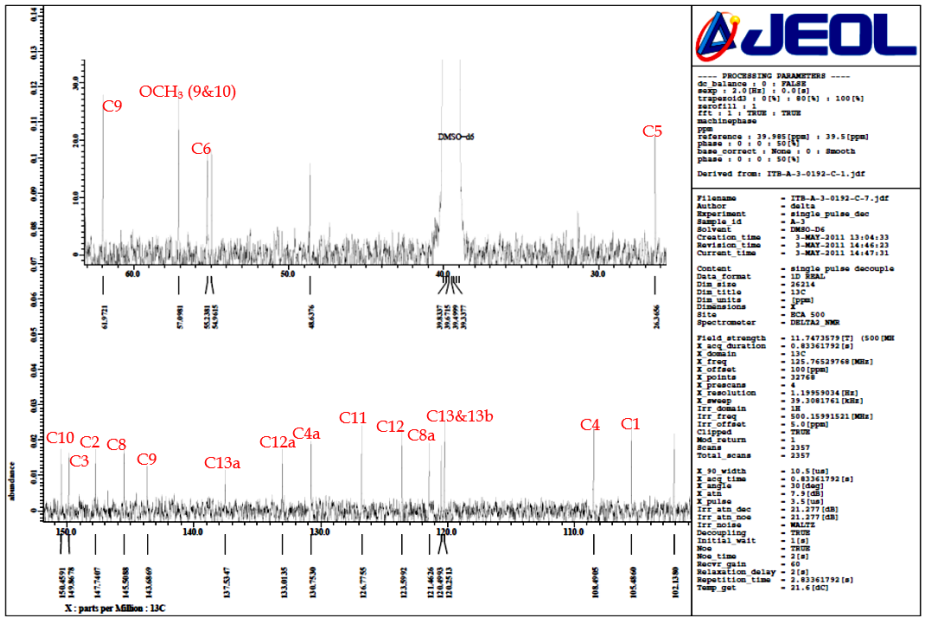


Figure 4. ^{13}C NMR spectrum of Berberine compounds

Based on the spectroscopic data, the structure of berberine can be put together and shown in Figure 5. The ^{1}H NMR and ^{13}C NMR spectrum data were compared to the data of barberine from the literature (Table 1).[30] These data strengthen the assumption that the isolated compound is berberine.

Characterization of compounds isolated from the methanol extract by spectroscopy of *Arcangelisia flava* identified compounds derived from alkaloids of the berberine type. The identified berberine compounds were then evaluated for their

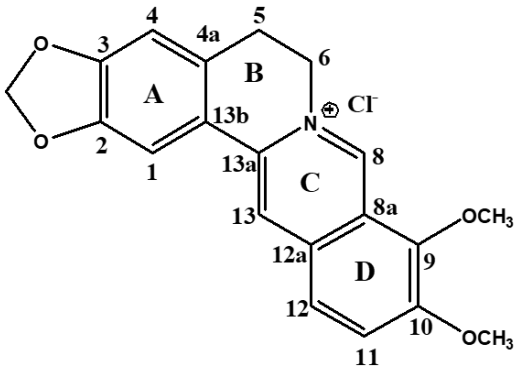


Figure 5. Structure of the berberine compound

Table 1. Table ^{1}H and ^{13}C NMR of isolated berberine compounds and literature results

Position (C)	Chemical shift ^{13}C δ (ppm)		Chemical shift ^{1}H δ (ppm) *J, Hz*	
	References [29]	Isolate	References [29]	Isolate
	(DMSO)	(DMSO)	(DMSO)	(DMSO)
1	105.6	105.5	7.79 (1H. s)	7.79 (1H. s)
2	147.9	147.7	-	-
3	150	149.9	-	-
4	108.6	108.5	7.08 (1H.s)	7.08 (1H.s)
4a	130.9	130.8	-	-
5	26.5	26.4	3.20 (2H. t. J = 6.4 Hz)	3.20 (2H. t. J = 6.5 Hz)
	55.4	55.2	4.92 (2H. t. J = 6.4 Hz)	4.92 (2H. t. J = 6.5 Hz)
6				
7	-	-	-	-
8	145.6	145.5	9.88 (1H. s)	9.88 (1H. s)
8a	121.6	121.5	-	-
9	143.9	143.7	-	-
10	150.6	150.5	-	-
11	127	126.8	8.19 (1H. d. J= 9.0 Hz)	8.19 (1H. d. J= 9.0 Hz)
12	123.7	123.6	8.00 (1H. d. J= 9.0 Hz)	8.01 (1H. d. J= 9.0 Hz)
12a	133.2	133	-	-
13	120.4	120.3	8.93 (1H. s)	8.94 (1H. s)
13a	137.7	137.5	-	-
13b	120.6	120.5	-	-
OCH_2O	102.2	102.1	6.17	6.17
9 OCH_3	62.1	61.9	4.09 (3H. s. -OCH3)	4.09 (3H. s. -OCH3)
10 OCH_3	57.3	57.1	4.06 (3H. s. -OCH3)	4.06 (3H. s. -OCH3)

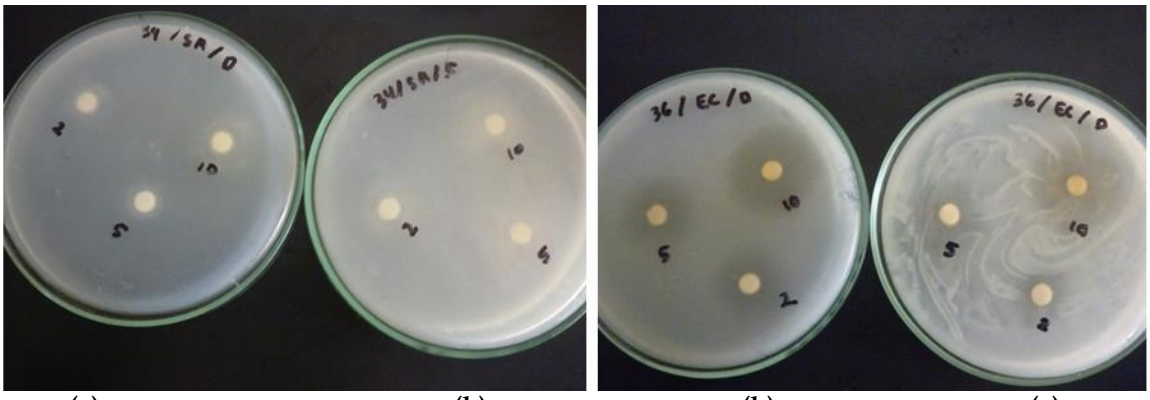
toxicity and antibacterial activity compared to the methanol extract of *Arcangelisia flava*. Toxicity testing was carried out using the Brine Shrimp Lethality Test (BSLT) method, which is one of the initial methods for estimating the level of toxicity of an active compound in a natural substance using *Artemia salina* shrimp larvae.[24,31] Toxic components contained in the extract if given to *A. salina*, can cause the death of the animal. *A. salina* is an eater of organic materials, so the components of the extract will accumulate continuously in the body of *A. salina*.[32] The LC_{50} value is the concentration that can cause the death of 50% of the *A. salina* population. This value can be obtained from the relationship between log concentration and % mortality through a linear regression equation so that the LC_{50} value of the compound and methanol extract can be calculated. The calculation results show that the berberine compound has an LC_{50} value of 75.86 ppm and the methanol extract 89.13 ppm. An extract is considered toxic if it has an LC_{50} value < 1000 ppm, while a pure compound is said to be toxic if the LC_{50} < 200 ppm.[17]

Antibacterial activity was carried out using the disc method. Inhibitory effectiveness is one of the criteria for selecting an antibacterial compound to be applied as a natural medicine.[25] The activity of bacterial isolates was determined at concentrations of 2%, 5%, and 10% against gram-negative and gram-positive bacteria *Escherichia coli* and *Staphylococcus aureus.* Data on antimicrobial test results for isolates are in Table 2.

It can be seen that the treatment of methanol and berberine extracts formed an inhibitory zone for *E. coli* and *S. aureus* bacteria. At a concentration of 2%, both the extract and berberine provided inhibition against *E. coli* (Table 2). However, the extract inhibited *S. aureus* bacteria at a concentration of 5% and berberine at 10%. This shows that methanol and berberine extracts are more active in inhibiting the growth of *E. coli* bacteria than *S. aureus* but less so than chloramphenicol as a positive control (Figure 6).

Table 2. Data on the inhibitory activity of isolates and extracts against *E. coli* and *S. aureus* bacteria using the disc method

Concentration (%)	**Diameter (mm) in *E. coli* bacteria**		
	Berberine (Isolate)	**Methanolic Extract**	**Positive control (Chloramphenicol)**
10	12.34 ± 0.37	29.34 ± 1.11	36.38 ± 1.82
5	10.61 ± 0.92	16.68 ± 0.89	27.23 ± 2.01
2	9.63 ± 0.64	15.18 ± 1.02	16.32 ± 0.57
Concentration (%)	**Diameter (mm) *S. aureus* bacteria**		
	Berberine (Isolate)	**Methanolic Extract**	**Positive control (Chloramphenicol)**
10	9.23 ± 0.66	11.44 ± 0.98	20.65 ± 1.67
5	0	9.08 ± 0.52	16.43 ± 0.44
2	0	0	12.48 ± 1.01



(a) (b) (b) (a)

Figure 6. Inhibition (mm) zone berberine (a) and methanol extract (b)

Chloramphenicol, as a control antibacterial, can inhibit all test bacteria with a larger zone of inhibition than the isolated compound. This antibacterial has a broad spectrum that is active against gram-positive and gram-negative bacteria.[33] Chloramphenicol is an aminoglycoside antibacterial, a bacteriostatic antibacterial, which does not kill bacteria but only inhibits protein synthesis, which is necessary for the multiplication and division of bacterial cells.[2] Chloramphenicol is also an antibacterial that is quickly absorbed by the digestive tract. The inhibition zone formed around the well-treated yellow root extract shows that the content contained in the yellow root stem was able to inhibit the growth of *S. aureus* and *E. coli*.

In silico testing through molecular docking simulations of the berberine compound aims to evaluate the inhibitory mechanism on the bacterial target proteins *E. coli* (1UAG) and S. aureus (7RM7).[27] These two target proteins both have inhibitory mechanisms against bacterial cell wall synthesis [25]. Based on the results of the simulations that have been carried out, information is obtained that the berberine compound has a binding free energy value (ΔG) that is more negative than the native ligand, namely -5.13 and 7.03 kcal/mol, respectively, in inhibiting *E. coli* bacterial proteins. The strong in silico activity of the berberine compound against *E. coli* protein is due to covalent interactions in the form of phi-alkyl bond interactions and hydrogen interactions at the 1UAG amino acid residue. This aligns with in vitro results, which show strong inhibition at 5 and 10% concentrations.

Meanwhile, the in-silico activity of the berberine compound against the *S. aureus* target protein shows that the binding free energy of berberine (ΔG -7.30 kcal/mol) is no more negative than the native ligand (ΔG -10.87 kcal/mol). The binding affinity of the native ligand on the 7RM7 protein is more negative due to intramolecular and intermolecular interactions (unfavorable donor-donor and donor-acceptor as well as hydrogen interactions) that occur between the native ligand and the 7RM7 amino acid residue. In vitro results also support that the inhibitory diameter of the berberine compound against *S. aureus* bacteria only occurs at a concentration of 10%. In contrast, at low concentrations, there is no inhibition.

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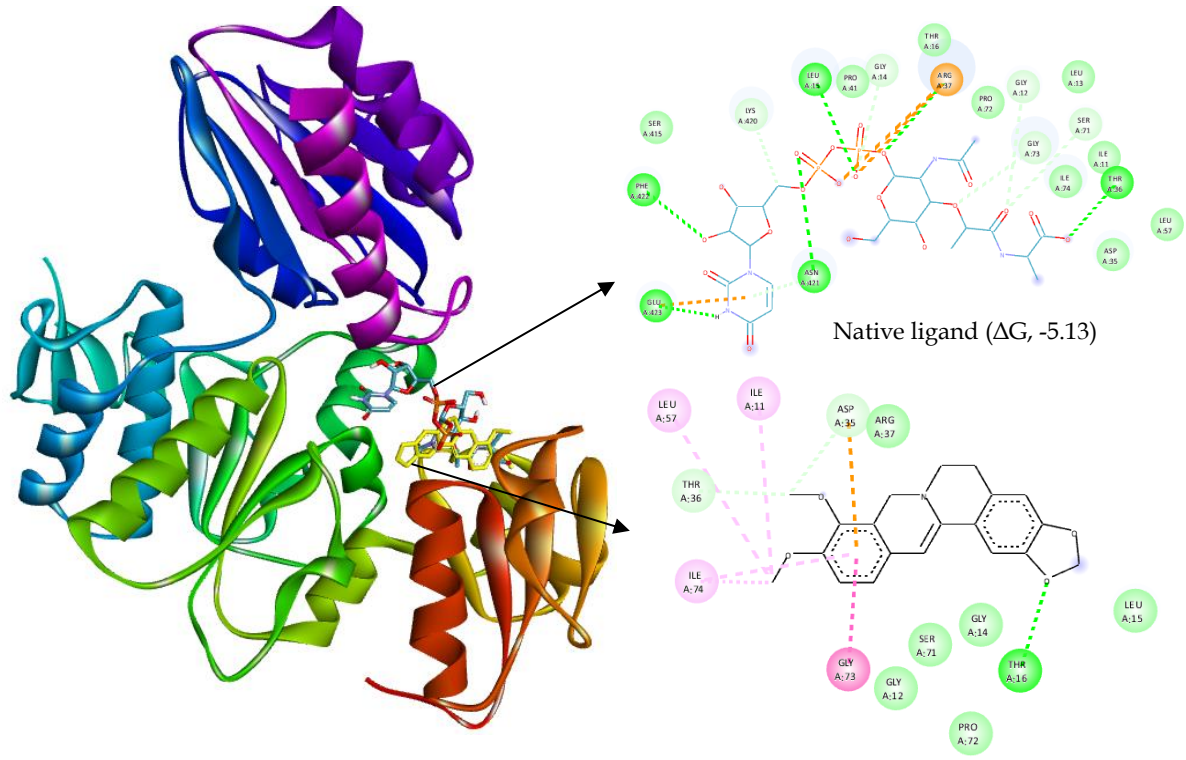
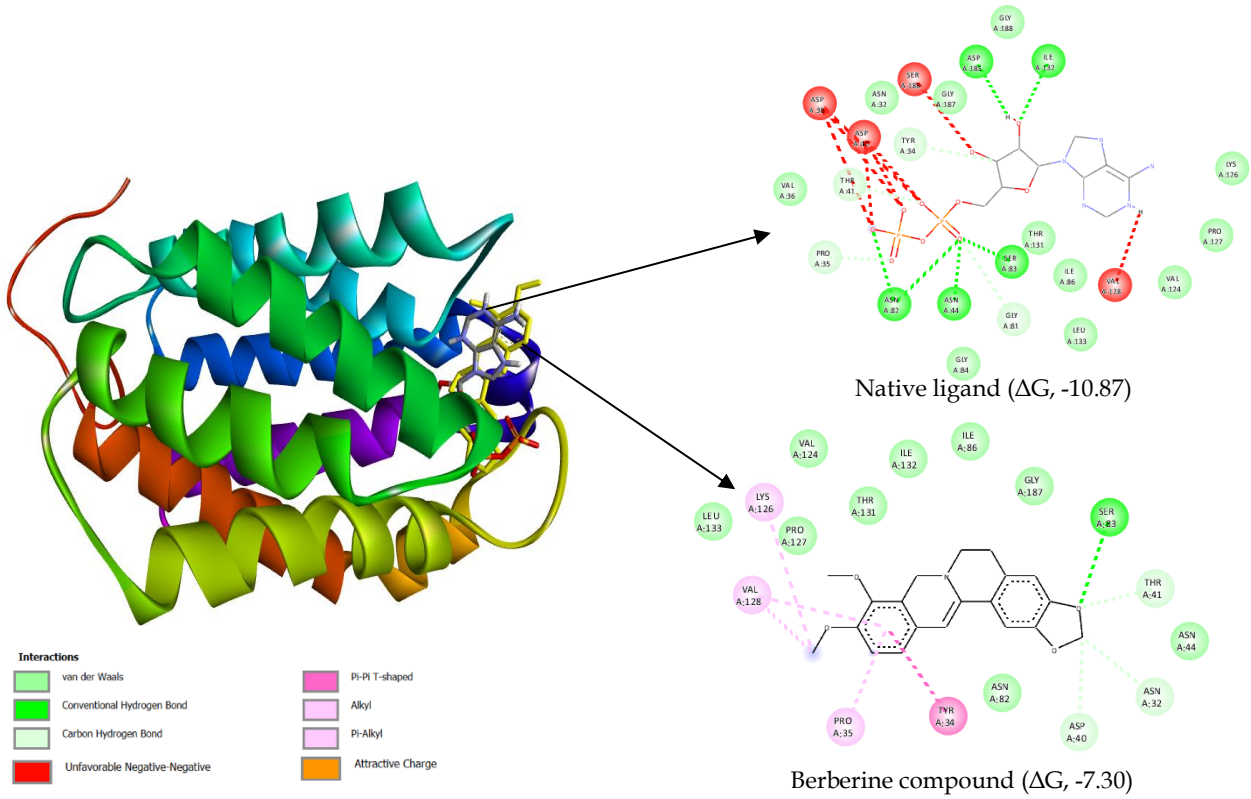


(a)



(b)

Figure 7. Molecular docking simulations of the berberine compound compared with the native ligands of the 1UAG (a) and 7RM7 (b) proteins.

CONCLUSION

Berberine is an alkaloid derivative compound successfully characterized as being found in the methanol extract of the stem of the *A. flava* plant. Berberine compounds show strong cytotoxic activity and tend to have the ability to inhibit *E. coli* bacteria compared to *S. aureus*. In silico evaluation of berberine compounds support the resulting in vitro data. This research provides scientific information that the methanol extract of *A. flava* contains the main compound of Berberine and has toxic and antibacterial effects, with a strong category that can be developed in further research.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that they will bear any liability for claims relating to the content of this article.

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