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Article

Alkaloid Profiling of Kadamba (*Mitragyna speciosa* Korth. Havil.) Leaves through Chromatographic Separation and UV–Vis Spectrophotometery Analysis

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Abstract

Mitragyna speciosa Korth. belongs to the Rubiaceae family and is commonly found in Southeast Asian countries. This plant, known as Kratom, is also referred to as "Kadamba" in East Kalimantan. Kadamba has been used for generations as a traditional medicine and contains a majority of alkaloid compounds that generally function as analgesics, antitussives, antidiarrheals, adrenergics, antimalarials, antibacterials, and antinociceptives. The aim of this study is to investigate the isolation and identification of alkaloid compounds in Kadamba leaves. In this study, extraction was carried out using methanol solvent, followed by fractionation using Vacuum Liquid Chromatography (VLC) and Column Chromatography (CC) with a stepwise elution system consisting of a combination of solvents: n-hexane, ethyl acetate, and methanol. The fractionation results were monitored using Thin Layer Chromatography (TLC) under UV light at 254nm and 366nm, and the Dragendorff reagent was sprayed, which turns orange when alkaloid compounds are detected. The results showed that alkaloid compounds were successfully isolated and identified using UV-Vis spectroscopy at wavelengths of 288nm and 294nm.

Keywords: Alkaloid; *Mitragyna speciosa* Korth.; Isolation; Chromatography

1. INTRODUCTION

From an ecological perspective, alkaloids play an important role in plant defense mechanisms. Alkaloids often act as a deterrent to herbivores and pathogens due to their toxicity and bitter taste. Alkaloids have also attracted significant attention because of their pharmacological properties. For example, neferine, a benzylisoquinoline alkaloid derived from lotus seed embryos, has been shown to induce autophagy and apoptosis in cervical cancer cells, making it a potential anticancer agent. Additionally, the compound berberine, an isoquinoline alkaloid, has been used in traditional medicine as an antidiabetic and antioxidant. The exploration of such compounds has led to the identification of various pharmacological effects, including antimicrobial, anti-inflammatory, and anticancer activities (1–4).

Among the well-known plants rich in alkaloid compounds is Kadamba or Kratom (Mitragyna speciosa Korth.), which has been used since ancient times as medicine. People in Southeast Asia have traditionally used Kadamba leaves to address various health issues. In traditional medicine practices, Kadamba is often used to alleviate pain, boost energy, aid digestion, and reduce anxiety (5–7). Kadamba is known to contain various alkaloid compounds, including mitragynine and 7-hydroxymitragynine, which have been shown to possess pharmacological activities similar to opioids, including analgesic, antidepressant, and anti-inflammatory effects (5–10).

Research on the isolation of compounds from Kadamba leaves is still very limited, including the search for alkaloid compounds, which are the major constituents of Kadamba plants (11). Furthermore, the TLC profile of alkaloid compounds is crucial for the identification of alkaloids that can lead to the isolation of these compounds. Given the importance of alkaloid activity in Kadamba, research into the isolation and characterization of alkaloid compounds from Kadamba is necessary and could serve as a foundation for testing pharmacological activities, contributing to the development of new drugs.

2. MATERIALS AND METHODS

2.1. Material

The materials used in this study included Kadamba leaves as the sample, which were collected from the Tenggarong Seberang area. The leaves were then identified at the Dendrology Laboratory, Faculty of Forestry, Mulawarman University, and processed into dry simplicia at the Research and Development Laboratory of "FARMAKA TROPIS" Pharmaceutical Sciences, Faculty of Pharmacy, Mulawarman University, Samarinda, East Kalimantan. In addition, other materials used included methanol, ethyl acetate, n-hexane, Dragendorff's reagent (Bismuth (III) Nitrate, Potassium iodide, Glacial Acetic Acid 30%), Glacial NH_4OH 25%, Silica Gel 60, Silica Gel 60 H, Silica Gel F_{254}, Filter paper and aluminum foil.

2.2. Instrument

The tools used in the study include Thin Layer Chromatography (TLC) equipment, Pyrex vacuum liquid chromatography (VLC) column equipment (height of 20 cm and a diameter of 8 cm), Pyrex conventional column chromatography (CC) equipment (height of 30 cm and a diameter of 2 cm), UV lamps at 254 and 366 nm, rotary evaporator (Buchi R210), Thermo Scientific Genesys 10S UV-VIS Spectrophotometer, analytical balance (Ohaus PX224), beakers (Pyrex), Erlenmeyer flasks (Pyrex), volumetric flasks (Pyrex), dropper pipettes, vials, glass jars, volumetric pipettes, chambers, glass funnels, mortars, and pestles.

2.3. Method

2.3.1. Sample Preparation

Leaf samples of Kadamba were collected from the Tenggarong Seberang district. The leaves were then sorted and cut into small pieces until the desired size was achieved, after which they were dried in an oven at 50°C for several days until fully dried. The dried plant material was weighed for the next process, which was extraction.

2.3.2 Extraction Process

The dried samples (2 Kg) was weighed for extraction using the maceration method with 15 L of methanol solvent for 9 days at room temperature, with solvent changes every 3 x 24 hours until the solvent became clear. The extract was then filtered using a funnel lined with filter paper to avoid contamination and residuals that could be carried over into the container. The extract was concentrated using a rotary evaporator at 40°C to obtain a thick methanol extract, which was then weighed.

2.3.4 Vacuum Liquid Chromatography

The thick Kadamba leaf extract (10 g) was dissolved with ethyl acetate solvent and then mixed with 10 g of silica gel 60H, which was ground in a mortar to form a dry powder. The powder was then placed into a prepared column under vacuum and sealed with filter paper shaped to fit the column (circle). The column was eluted with a gradient eluent, which was done sequentially until completion, and the fractionated result was evaporated until dry. The eluents used are listed in Table 1. The VLC I fraction was spotted on a TLC plate with an eluent of n-hexane:ethyl acetate:NH_4OH 25% (6.5:3:0.5) v/v, which was observed under UV light at 254 nm and 366 nm and sprayed with Dragendorff reagent.

Table 1. VLC I Eluent from Kadamba Leaf Methanol Extract

No.	Eluents	Ratio	Volume (mL)
1.	*n*-hexane	100%	725
2.	*n*-hexane: Ethyl Acetate	5:1	1560
3.	*n*-hexane: Ethyl Acetate	1:1	300
4.	*n*-hexane: Ethyl Acetate	1:5	360
5.	Ethyl Acetate	1	300
6.	Ethyl Acetate: Methanol	1:1	400
7.	Ethyl Acetate: Methanol	1:5	300
8.	Methanol	100%	400

The result of the VLC I fractionation yielded 18 fractions, which were combined into fraction B (fractions 10-16) and further fractionated using VLC (VLC II) with an eluent prepared sequentially based on polarity. The eluents used are listed in Table 2. The result of the VLC I fraction was spotted on a TLC plate with an eluent of n-Hexane:Ethyl acetate:NH_4OH 25% (6.5:3:0.5), observed under UV light at 254 nm and 366 nm, and sprayed with Dragendorff reagent.

Table 2. VLC II Eluent from Fraction B

No.	Eluents	Ratio	Volume (mL)	Fraction
1.	*n*-hexane	100%	300	1-2
2.	*n*-hexane: Ethyl Acetate	7:1	1040	3-9
3.	*n*-hexane: Ethyl Acetate	5:1	420	10
4.	*n*-hexane: Ethyl Acetate	3:1	400	11
5.	Ethyl Acetate	1:1	800	12-13
6.	Ethyl Acetate: Methanol	1:5	300	14
7.	Ethyl Acetate	100%	150	14
8.	Methanol	100%	150	15

2.3.5 Column Chromatography (CC)

The result of the VLC II fractionation from fraction B yielded 15 fractions, and based on the positive results with Dragendorff reagent on the TLC plate, fraction 6 was identified as alkaloid-positive. Fraction B6 was then further

fractionated using the Column Chromatography (CC) method with a stepwise polarity eluent, which is shown in Table 3.

Table 3. CC Eluents for Fraction B6

No.	Eluents	Ratio	Volume (mL)
1.	*n*-hexane	100%	100
2.	*n*-hexane: Ethyl Acetate	7:1	960
3.	*n*-hexane: Ethyl Acetate	5:1	120
4.	*n*-hexane: Ethyl Acetate	1:1	240
5.	Ethyl Acetate	1:5	240
6.	Ethyl Acetate	100%	200
7.	Ethyl Acetate: Methanol	1:1	20
8.	Ethyl Acetate: Methanol	1:5	80
9.	Methanol	100%	60

2.3.6 Preparative Thin Layer Chromatography (PTLC)

The subfraction obtained, namely fraction B6-B, was further processed using Preparative Thin Layer Chromatography (PTLC) with an eluent of n-hexane:ethyl acetate:NH_4OH 25% (6.5:3:0.5) v/v in 100 mL. A spot band was obtained, separated, and dissolved with ethyl acetate solvent. The compounds contained in the ethyl acetate solvent were then extracted and evaporated to obtain the alkaloid isolate B6-B.

2.3.7 Two-Dimensional Chromatography (2D)

The alkaloid isolate B6-B was spotted onto a TLC plate and eluted in two different directions using the first eluent, n-hexane:ethyl acetate (10:1), and the second eluent, n-hexane:ethyl acetate (5:1). The TLC profile was checked under UV light at 254 nm and 366 nm, and Dragendorff reagent was sprayed, which turned orange if alkaloids were present.

2.3.8 UV-Vis Spectrophotometry Analysis

The isolate B6-B was then analyzed for its maximum wavelength, which was detected using a UV-Vis spectrophotometer.

3. RESULT AND DISCUSSION

3.1. Extraction Process

The sample used was Kadamba leaves, which were dried and ground into powder to facilitate the extraction process. A total of 2 kg was macerated with 15 L of methanol solvent for 9 days, with solvent changes every 3 x 24 hours. The filtrate obtained was dark green, and the extract was concentrated using a rotary evaporator under vacuum. The extraction process was repeated several times until a clear solvent filtrate was obtained.

3.2. Fractionation I (VLC I)

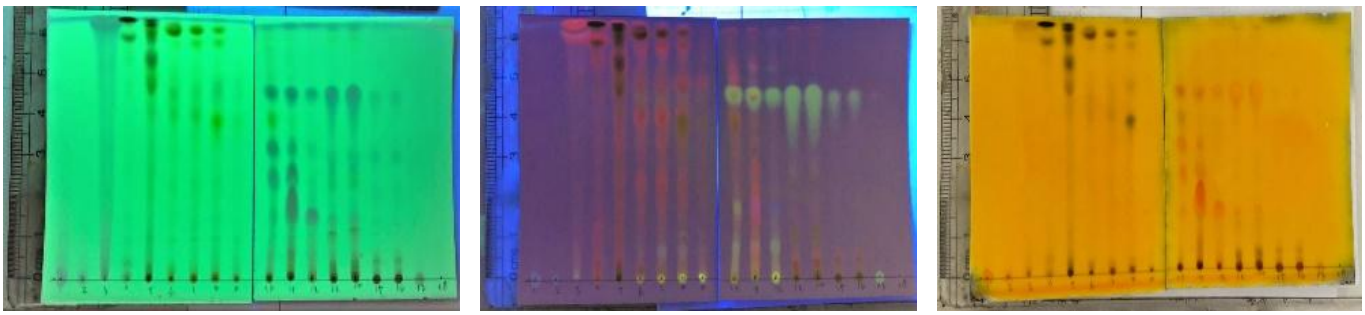
This stage used the Vacuum Liquid Chromatography (VLC) method, which is a separation technique to divide the extract into several fractions based on their polarity, aided by vacuum, which accelerates the separation process according to the polarity of the eluent. The VLC method used three solvents with different polarities: n-hexane (nonpolar), ethyl acetate (semi-polar), and methanol (polar), each combined in the elution ratio shown in Table 1.

This separation process using the VLC method has the advantage of accelerating the separation of compounds in the extract with the aid of vacuum equipment, allowing the separation duration in the column to be very fast. The eluents were used sequentially as per Table 1, starting with the nonpolar solvent and then gradually increasing the polarity. The results of the VLC process can be seen in Table 2.

Table 4. VLC Results from Kadamba Leaf Methanol Extract

No.	Eluents	Ratio	Volume (mL)
1.	*n*-hexane	100%	725
2.	*n*-hexane: Ethyl Acetate	5:1	1560
3.	*n*-hexane: Ethyl Acetate	1:1	300
4.	*n*-hexane: Ethyl Acetate	1:5	360
5.	Ethyl Acetate	1	300
6.	Ethyl Acetate: Methanol	1:1	400
7.	Ethyl Acetate: Methanol	1:5	300
8.	Methanol	100%	400

The VLC of the thick methanol extract (Table 4), with a mass of 10 grams each, resulted in 18 fractions. These were then analyzed using a TLC profile with an eluent of n-hexane:ethyl acetate:NH_4OH 25% (6.5:3:0.5) v/v, followed by spraying with Dragendorff reagent. The fractions with the same Rf value and positive Dragendorff spray results (orange color) were combined. Based on the TLC chromatogram analysis in Figure 1, the fractions were grouped into three categories: A (1-9), B (10-16), and C (17-18).



a. b. c.

Figure 1. TLC Chromatogram of the VLC results. a) UV light 254 nm appearance; b) UV light 366 nm appearance; c) After spraying with Dragendorff's reagent

Fraction A (1-9) did not show positive alkaloid spots on the TLC. Fraction B (10-16) exhibited six spots containing alkaloid compounds, with distinct Rf values of 0.938, 0.69, 0.538, 0.41, 0.307, and 0.216. Fractions 17-18 showed a positive alkaloid spot at the lower edge of the TLC plate due to the alkaloid spot being more polar than the eluent used. Fraction B contains a higher proportion of alkaloid compounds compared to the other fractions, as the semi-polar eluent used facilitates the elution of less polar (semi-polar) alkaloid compounds more than the polar ones. Fraction B (10-16) will be further processed in the next VLC to separate the detected alkaloid compounds.

3.3. Fractionation II (VLC II)

Fraction B, with a weight of 5.2091 g, was then re-separated using VLC (VLC II) to obtain a purer alkaloid fraction. The separation yielded 15 fractions, with fraction 6 (B6) showing two dominant positive alkaloid spots with Rf values of 0.938 and 0.69 (TLC profile shown in Figure 2).

Table 5. TLC Identification of VLC II Results from Fraction B

Fraction	Rf Value (Positive for Alkaloids)
1	0,938
2	0,938
3	0,938

4	0; 0,938
5	0; 0,938
6	0; 0,69; 0,938
7	0,69; 0,938
8	0,41; 0,69; 0,938;
9	0,307; 0,41; 0,538;
10	0,307
11	0,216; 0,307; 0,41;
12	0,41; 0,216
13	0,216; 0,307
14	0; 0,307
15	0; 0,307

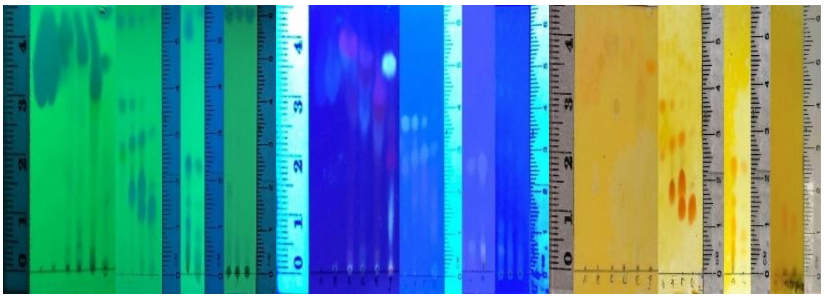


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Figure 2. TLC Chromatogram of the CC results. a) UV light 254 nm appearance b) UV light 366 nm appearance c) After spraying with Dragendorff's reagent

3.4. Fractionation III (CC)

The result of Fraction B6 was separated using the Column Chromatography (CC) method to obtain a more specific separation, although a large number of fractions (vial fractions) were obtained, which required detection of alkaloid compounds by spraying with Dragendorff reagent on the TLC profile of the various fractions obtained. Fractions with the same spot and Rf values for alkaloids were combined into a single fraction.

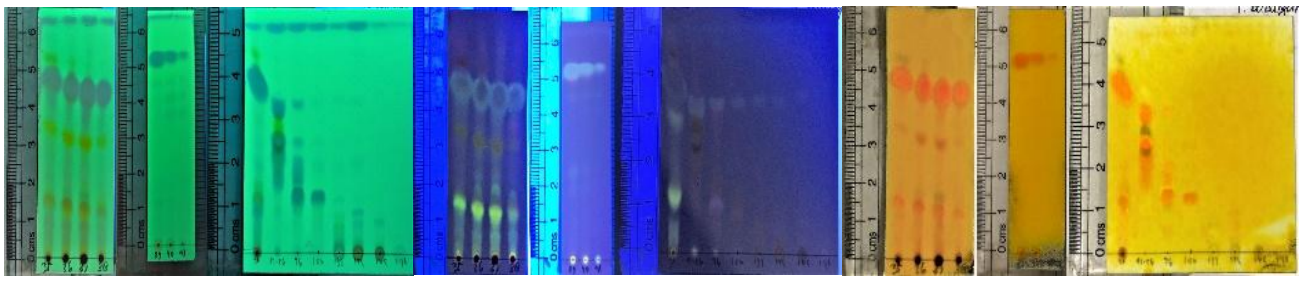

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Figure 3. VLC II Chromatogram of Fraction B with eluent n-Hexane: Ethyl acetate: NH4OH 25% (6.5:3:0.5). a) UV light 254 nm appearance; b) UV light 366 nm appearance; c) After spraying with Dragendorff's reagent

The eluents used in this stage are shown in Table 6, and the result yielded 183 fractions. The large number of fractions was then spotted, selected randomly based on the difference in the color of the solution before combining the fractions. This was done to ensure that the fraction combination was based not only on the color similarity of the fraction solutions but also on the TLC profile, where alkaloid compounds were detected with the same Rf values. Spotting was done using an eluent of n-Hexane:Ethyl acetate:NH_4OH 25% (6.5:3:0.5).

Table 6. Spotting Results of Several Fraction B6

Fraction	Alkaloid Results (Dragendroff's Reagent)	R_f
35	(+) X1, X2, X3, X4, X6	X1 = 0,69
36	(+) X1, X2, X3, X4, X6	X2 = 0,538
37	(+) X1, X2, X3, X4, X6	X3 = 0,41
38	(+) X1, X2, X3, X4, X6	X4 = 0,3
39	(+) X1, X6	X5 = 0,23
40	(+) X1, X6	X6 = 0
41	(+) X1, X6	
42-56	(+) X2, X3	
76	(+) X3, X4	
106	(+) X4, X5	
133	(+) X5, X6	
155	(+) X5, X6	
165	(+) X5, X6	
178	(+) X6	

Based on the results, Fraction B6 was divided into Fraction A (1-34), Fraction B (35-38), Fraction C (39-41), Fraction D (42-56), Fraction E (57-75), Fraction F (76-106), Fraction G (107-132), and Fraction H (133-183). Each of these combined fractions was spotted using an eluent of n-hexane:ethyl acetate:NH_4OH 25% (6.5:3:0.5) v/v, followed by spraying with Dragendorff reagent. The TLC profile results are shown in Figure 4 below.

Table 7. TLC Results from the CC Process

	Fraction	Alkaloid Results (Dragendroff's Reagent)	R_f
A	1-34	(-)	X1 = 0,69
B	35-38	(+) X1, X4, X5, X6	X2 = 0,538
C	39-41	(+) X1, X6	X3 = 0,41
D	42-56	(+) X2, X3, X4, X6	X4 = 0,3
E	57-75	(+) X4, X5, X6	X5 = 0,23
F	76-106	(+) X5, X6	X6 = 0
G	107-132	(+) X5, X6	
H	133-183	(+)X6	

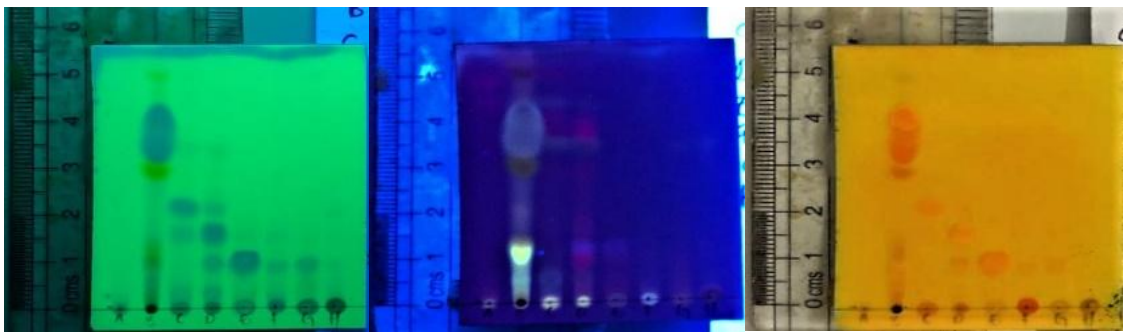

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Figure 4. TLC Chromatogram of the combined CC fractions. a) UV light 254 nm appearance; b) UV light 366 nm appearance; c) After spraying with Dragendorff's reagent

Based on the TLC profile of Fraction B6, in Fraction B (B6-B), alkaloid compounds were detected (with some contamination from other spots) with an Rf of 0.69, and they predominantly turned orange when sprayed with Dragendorff reagent. Spotting of Fraction B6-B was also performed using the eluent n-Hexane:Ethyl acetate:NH_4OH 25% (6.5:3:0.5), which gave an Rf = 0.938, and n-Hexane:Ethyl acetate (10:1), which gave an Rf of 0.6 (as shown in Figures 5 and 6).

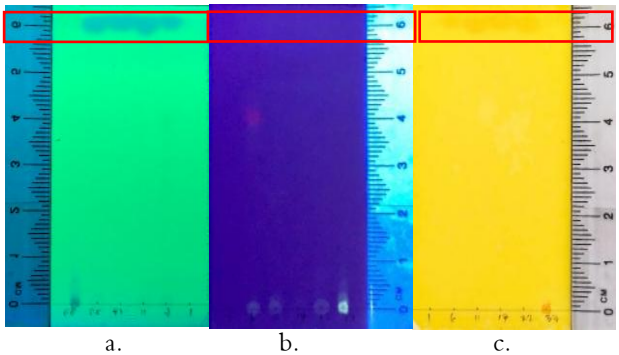

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Figure 5. TLC Chromatogram of Fraction B6 Identification with eluent n-Hexane: Ethyl acetate: NH_4OH 25% (6.5:3:0.5). a) UV light 254 nm appearance; b) UV light 366 nm appearance; c) After spraying with Dragendorff's reagent

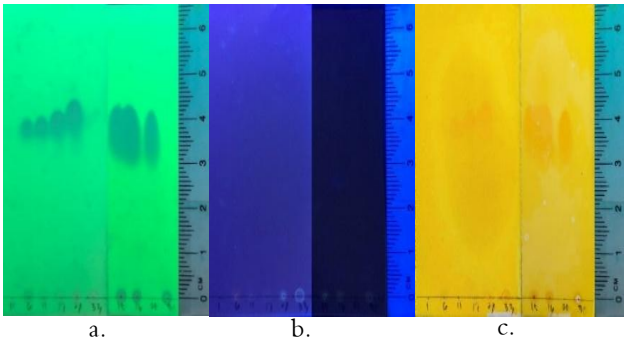

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Figure 6. TLC Chromatogram of Fraction B6 Identification with eluent n-Hexane: Ethyl acetate (10:1). a) UV light 254 nm appearance; b) UV light 366 nm appearance; c) After spraying with Dragendorff's reagent

3.5. Preparative Thin Layer Chromatography (PTLC)

Subfraction B6-B was further processed in PTLC, resulting in a B6-B band that produced a single spot forming a line or band, identified as an alkaloid upon spraying with Dragendorff reagent. Using an eluent of n-Hexane:Ethyl acetate (10:1), an Rf of 0.6 was obtained. The result was then separated to confirm its purity using 2D TLC.

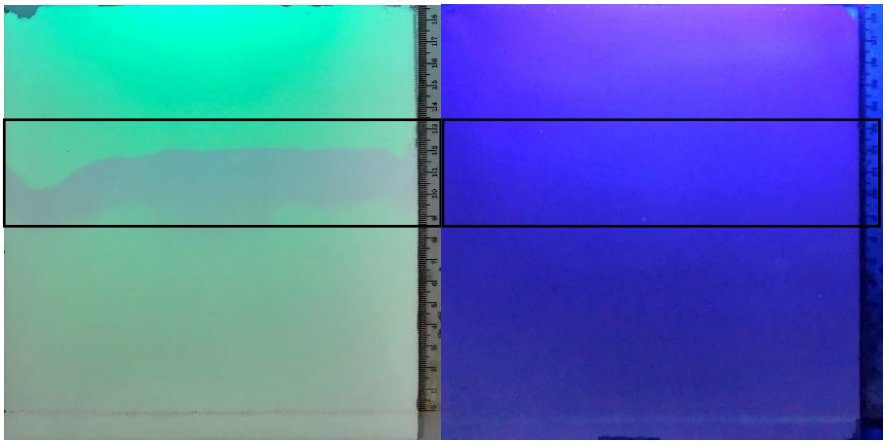

Figure 4. PTLC Profile of the Subfractions from the Conventional Column B6-B

3.6. Two-Dimensional Chromatography (2D)

This method is used to confirm that the obtained isolate is detected as a single spot (pure) by using eluents with different polarities and eluting in two different directions on the same TLC plate, allowing for the assessment of the isolate's purity. The 2D TLC results using the first eluent, n-hexane:ethyl acetate (10:1), and the second eluent, n-hexane:ethyl acetate (5:1), showed that only one spot was produced, which reacted positively and appeared orange when sprayed with Dragendorff reagent.

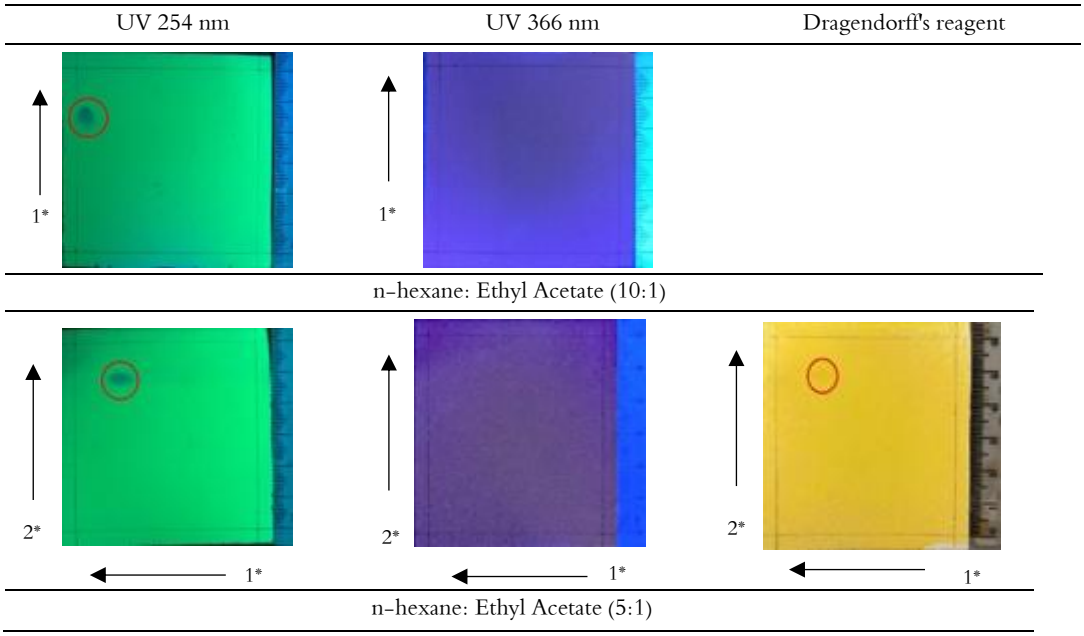

Figure 5. 2D TLC Chromatogram of the Pure Isolate B6-B

3.7. UV-Vis Spectrophotometric Analysis

The UV-Vis spectrophotometry results of the B6-B isolate show two peaks at wavelengths of 288 nm and 294 nm. In the context of UV-Vis spectroscopy analysis, absorption at wavelengths around 288 nm to 294 nm is often associated with electronic transitions involving C=O and N-H bonds, reflecting the compound's ability to absorb UV radiation and providing insight into its electronic structure. Research by John et al. indicates that the n-π* transition for the C=O and N-H groups can be observed at these wavelengths, which highlights the relevance of UV absorption in the characterization of organic compounds, especially in the context of bio-pharmaceutical applications (12,13).

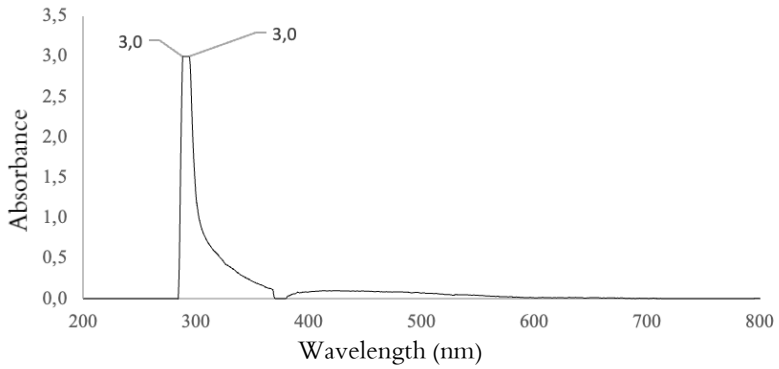

Figure 6.UV-Vis Spectrophotometry Results of Isolate B6-b

As a comparison, the alkaloid extract from betel fruit (Piper betle L.) shows an absorption peak at 282 nm using UV-Vis spectrophotometry. This peak indicates the presence of alkaloid compounds and is related to the compound's ability to interact with UV radiation. A characteristic feature of alkaloids is the presence of nitrogen atoms with lone pairs of electrons. These nitrogen atoms absorb UV light at wavelengths >270 nm (14).

Additionally, the UV-Vis spectroscopy results of the alkaloid isolate from Peperomia pellucida show a maximum absorption at a wavelength of 206 nm. Absorption at this wavelength indicates an $n \rightarrow \sigma^*$ transition occurring in compounds such as nitrogen (C-N). This transition is commonly found in alkaloids, particularly those with a piperidine structure, as suspected in this alkaloid isolate. As a comparison, other piperidine-type alkaloids, such as Nigramide L and Nigramide N, also show similar wavelengths at 209 nm and 208 nm (15).

4. CONCLUSION

Based on the results of this study using the Vacuum Liquid Chromatography (VLC) and Column Chromatography (CC) separation methods, a pure alkaloid compound was obtained, which was detected by UV-Vis spectrophotometry with absorption at wavelengths of 288 nm and 294 nm.

AUTHOR CONTRIBUTION: Conceptualization, M. Arifuddin, Fathur Rahman Azmi, Herman; methodology, formal analysis and validation, M. Arifuddin, Fathur Rahman Azmi, Iswahyudi, Mahfuzun Bone, Maria Almeida, Arman Rusman, Erwin Samsul, Riki, Hifdzur Rashif Rija'i; writing—preparation of original draft, M. Arifuddin, Baso Didik Hikmawan, Harra Ismi Farah, Hanggara Arifian, Junaidin, Lizma Febrina, Rolan Rusli,; writing—reviewing and editing, M. Arifuddin, Arsyik Ibrahim, Islamudin Ahmad, Herman.

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CONFLICT OF INTEREST: The author declares no conflict of interest.

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