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
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
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
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
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
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# Metabolite profile and *in vitro* cholinesterase inhibitory activity of extract and fractions of *Aaptos suberitoides*

[Perfil de metabolitos y actividad inhibidora de la colinesterasa *in vitro* del extracto y fracciones de *Aaptos suberitoides*]

Hanifa R. Putri<sup>1</sup>, Rhesi Kristiana<sup>2</sup>, I Wayan Mudianta<sup>3</sup>, Edwin Setiawan<sup>4</sup>, Aty Widyawaruyanti<sup>5,6</sup>, Nitra Nuengchamnong<sup>7</sup>, Nungruthai Suphrom<sup>8</sup>, Suciati Suciati<sup>5,6\*</sup>

<sup>1</sup>Master Program in Pharmaceutical Sciences, Faculty of Pharmacy Universitas Airlangga, Surabaya 60115, East Java, Indonesia.

<sup>2</sup>Indonesian Marine Education & Research Organisation (MERO) Foundation, Desa Tulamben, Karangasem 80853, Bali, Indonesia.

<sup>3</sup>Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Pendidikan Ganesha, Singaraja 81116, Bali, Indonesia.

<sup>4</sup>Department of Biology, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya 60115, East Java, Indonesia.

<sup>5</sup>Department of Pharmaceutical Sciences, Faculty of Pharmacy Universitas Airlangga, Surabaya 60115, East Java, Indonesia.

<sup>6</sup>Center for Natural Product Medicine Research and Development, Institute of Tropical Diseases, Universitas Airlangga, Surabaya 60115, East Java, Indonesia.

<sup>7</sup>Science Laboratory Center, Faculty of Science, Naresuan University, Phitsanulok 65000, Thailand.

<sup>8</sup>Department of Chemistry, Faculty of Science and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok 65000, Thailand.

\*E-mail: [suciati@ff.unair.ac.id](mailto:suciati@ff.unair.ac.id)

## Abstract

**Context:** Marine sources such as sponges have shown a significant impact on the drug development from nature. Metabolites isolated from sponges show diversity in terms of structural features and pharmacological properties. Several sponges have been reported to have potency as cholinesterase inhibitors as one of the target therapies for Alzheimer's disease.

**Aims:** To investigate the potency of marine sponge *Aaptos suberitoides* as cholinesterase inhibitors and to explore the chemistry of the sponge.

**Methods:** The cholinesterase inhibitory assay was carried out against two enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), based on the modified Ellman's method. The chemistry of the active fractions was studied by LC-MS/MS method, followed by molecular networking using GNPS.

**Results:** The results suggested that the extract and fractions inhibited both AChE and BChE enzymes. All samples demonstrated more potent inhibition against AChE compared to BChE enzymes. The n-hexane fraction gave the strongest inhibition against both AChE and BChE, with IC<sub>50</sub> values of 4.76 µg/mL and 6.79 µg/mL, respectively. Based on the LC-MS/MS analysis, alkaloids were detected in the n-hexane and ethyl acetate fractions. Four alkaloids were identified in the ethyl acetate fraction, namely demethylaaptamine, aaptamine, iso-aaptamine, and 8,9,9-trimethoxy-9H-benzo[de][1,6]naphthyridine at RT 1.52, 1.67, 2.92, and 3.22 mins, respectively. Aaptamine was also identified in the n-hexane fraction together with demethyloxyaaptamine.

**Conclusions:** The extract, n-hexane, and ethyl acetate fractions of *A. suberitoides* have shown promising cholinesterase inhibitory properties against both AChE and BChE enzymes. The alkaloids present in the active fractions may be responsible for the bioactivity.

**Keywords:** *Aaptos suberitoides*; alkaloid; Alzheimer's disease; cholinesterase inhibitor.

## Resumen

**Contexto:** Las fuentes marinas como las esponjas han mostrado un impacto significativo en el desarrollo de fármacos a partir de la naturaleza. Los metabolitos aislados a partir de esponjas muestran diversidad en cuanto a características estructurales y propiedades farmacológicas. Se ha informado que varias esponjas tienen potencia como inhibidores de la colinesterasa como una de las terapias diana para la enfermedad de Alzheimer.

**Objetivos:** Investigar la potencia de la esponja marina *Aaptos suberitoides* como inhibidor de la colinesterasa y explorar la química de la esponja.

**Métodos:** El ensayo de inhibición de la colinesterasa se llevó a cabo contra dos enzimas, la acetilcolinesterasa (AChE) y la butirilcolinesterasa (BChE), basándose en el método de Ellman modificado. La química de las fracciones activas se estudió por el método LC-MS/MS, seguido de la creación de redes moleculares mediante GNPS.

**Resultados:** Los resultados sugirieron que el extracto y las fracciones inhibían las enzimas AChE y BChE. Todas las muestras demostraron una inhibición más potente contra las enzimas AChE en comparación con las BChE. La fracción de n-hexano produjo la mayor inhibición tanto contra la AChE como contra la BChE, con valores de IC<sub>50</sub> de 4,76 µg/mL y 6,79 µg/mL, respectivamente. Según el análisis LC-MS/MS, se detectaron alcaloides en las fracciones de n-hexano y acetato de etilo. Se identificaron cuatro alcaloides en la fracción de acetato de etilo, a saber, desmetilaaptamina, aaptamina, iso-aaptamina y 8,9,9-trimetoxi-9H-benzo[de][1,6]naftiridina a RT 1,52; 1,67; 2,92 y 3,22 minutos, respectivamente. También se identificó aaptamina en la fracción n-hexano junto con desmetiloxyaaptamina.

**Conclusiones:** Las fracciones de extracto, n-hexano y acetato de etilo de *A. suberitoides* han mostrado prometedoras propiedades inhibidoras de la colinesterasa frente a las enzimas AChE y BChE. Los alcaloides presentes en las fracciones activas pueden ser los responsables de la bioactividad.

**Palabras Clave:** *Aaptos suberitoides*; alcaloide; enfermedad de Alzheimer; inhibidor de la colinesterasa.

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### AUTHOR INFO

ORCID: [0000-0003-2436-4119](https://orcid.org/0000-0003-2436-4119) (SS)

## INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disease that accounts for 60-80% of dementia cases in the elderly. AD symptoms include memory loss, cognitive deficit, and behavioral disturbances. Today more than 43 million people are affected by AD, and the majority are elderly population. This number is predicted to increase 60% by 2030 and 180% by 2050. AD is characterized by the presence of amyloid-beta plaques, neurofibrillary tangles, and a low level of the neurotransmitter acetylcholine due to the loss of cholinergic nerves in the brain. Pathogenesis of this disease is complicated, but several factors, including A $\beta$  aggregations, cholinesterase enzyme activity, and oxidants, are recognized in this brain dysfunction (Hafez Ghoran and Kijjoo, 2021; Silva et al., 2021).

Cholinesterase is an enzyme in the central nervous system of humans and plays a role in the hydrolysis of acetylcholine into choline and acetate. There are two types of cholinesterase enzymes: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). AChE is an enzyme that regulates neurotransmission in the cholinergic pathways of the vertebrate, and BChE is an enzyme that assists and regulates cholinergic transmission when AChE activity is compromised (Moodie et al., 2019). Since AD patients have decreased levels of acetylcholine, cholinesterase inhibitors have become a strategy for treating this disease.

Alkaloids from natural products are known to have good activity as a cholinesterase inhibitor. Several alkaloid compounds have been clinically used for the treatment of AD, such as galantamine, rivastigmine, and donepezil (Moodie et al., 2019). Marine sponges have been known as the source of various bioactive metabolites, including alkaloids. Several alkaloids isolated from marine sponges have been reported as cholinesterase inhibitors (Lima and Medeiros, 2022), such as pyridinium alkaloids from *Reniera sarai* and a genus *Plakortis* (Alonso et al., 2005; Kubota et al., 2010; Turk et al., 2007), a steroidal alkaloid from *Corticium* sp. (Langjae et al., 2007), pyridocridine alkaloid petrosamine, isolated from *Petrosia* sp., which was predicted to bind to the TcAChE enzyme (Nukoolkarn et al., 2008), a bis-indole alkaloid from *Fascaplysinopsis* sp. (Bharate et al., 2012), a bromopyrrole alkaloid isolated from *Agelas oroides* (Erdogan-Orhan et al., 2012), and discorhabdin alkaloids from *Latrunculia* spp. (Botić et al., 2017). Previously we have investigated the potency of several marine sponges collected from Tabuhan Island, Banyuwangi, Indonesia, as cholinesterase inhibitors, from which we found that *Agelas nakamurai*, *Callyspongia* sp., and

*Niphates olemda* showed significant cholinesterase inhibitory activity (Suciati et al., 2019). Subsequent research on *Agelas nakamurai* obtained iso-agelastine C that inhibits the AChE enzyme (Aristyawan et al., 2022). Following these findings, the current study investigates the cholinesterase inhibitory activity of *Aaptos suberitoides* (Brøndsted, 1934), family *Suberitidae* and its chemical profile.

## MATERIAL AND METHODS

### Reagents

Acetylcholinesterase from electric eel (AChE type VI-S, EeAChE), horse-serum butyrylcholinesterase (BChE), acetylthiocholine iodide (ATCI), butyrylthiocholine iodide (BTCI), 5,5'-dithiobis [2-nitrobenzoic acid] (DTNB), bovine serum albumin (BSA), and trisma base-HCl buffer (Tris-buffer) were obtained from Sigma-Aldrich.

### Biological material

The sponge was collected from the coast of Tulamben, Bali, Indonesia, in December 2020 by using SCUBA at a depth of 5-20 m (Lat. -8.29526; Long. 115.61224). The sponge specimen was immediately frozen at -20°C until extraction and deposited as a voucher (SPT-11) at the Department of Biology, ITS, Surabaya, Indonesia. The sponge identification was carried out by Dr. Edwin Setiawan. For species identification, the specimen was subsampled approximately  $\pm 2$  cm<sup>3</sup> and divided into two approximately equal parts for macroscopic observation of morphological character, e.g., lifeform, consistency, color, and microscopic examination of skeleton and spicules analysis. The first  $\pm 1$  cm<sup>3</sup> tissue was cross-sectioned and longitudinally cut with a hand-cutting knife, and tissues were mounted on the object glass and covered with a cover slip. The second  $\pm 1$  cm<sup>3</sup> tissue was immersed in bleach. After the bleach was completely removed, the spicules were allowed to settle. Subsequently, the spicules were rinsed three times with distilled water to completely remove bleach from the spicules and were finally preserved in 70% ethanol. The spicules were mounted on the object glass and covered with a cover slip. Entellan® | 107960 - Merck Millipore for adhesive substance for the skeleton and spicules slides. Analysis was carried out following the identification manual from World Porifera Database (WPD) (de Voogd et al., 2023), using an Olympus CX 31 light microscope device.

### Extraction and fractionation

The frozen sponge (380 g) was thawed, diced then soaked in a mixture of methanol and dichloro-

methane (1:1, 200 mL) for an hour before being filtered. The procedure was repeated twice, and the filtrates were combined and concentrated using a rotary evaporator to give black gummy crude extract (15 g). Subsequently, the extract was partitioned exhaustively between water (50 mL) and n-hexane (75 mL). The collected n-hexane layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to yield 68.6 mg of brown gum. Finally, the remaining water fraction was partitioned exhaustively with ethyl acetate (75 mL) to give a deep brown fraction (83.0 mg).

### Cholinesterase inhibitory assay

The assay was carried out according to the modified Ellman's method (Aristyawan et al., 2022; Ellman et al., 1961; Sirimangkalakitti et al., 2015). The extract and fractions were dissolved in methanol to make 10 mg/mL and diluted with water to get 1 mg/mL solutions. These samples were serially diluted to obtain a range of sample concentrations of 0.01–300 µg/mL. Sample solutions were added to a 96-well microplate (25 µL), followed by the addition of 1.5 mM ATCI (25 µL) as a substrate for the AChE enzyme and BTCl (25 µL) as a substrate for the BChE enzyme. Then 3 mM DTNB (125 µL), Tris-buffer (50 µL), and AChE or BChE enzymes (25 µL) 0.22 U/mL were added. Before measurement, The solutions were shaken for 30 s in a microplate reader (Thermo Scientific Multiskan FC). The yellow color from the product, 5-thio-2-nitrobenzoate, was measured at 405 nm every 5 s for 2 min. Every experiment was carried out in triplicates. Methanol 10% was used as a control. The enzyme activity was calculated as a percentage of the velocity of the sample compared with the negative control. The inhibitory activity was calculated based on the equation [1].

$$\text{Inhibition (\%)} = \frac{(V_{\text{control}} - V_{\text{sample}})}{V_{\text{control}}} \times 100 \quad [1]$$

Where V: Velocity.

### LC-MS/MS and Global Natural Product Social (GNPS) molecular networking

The samples were dissolved in methanol (10 mg/mL), sonicated, and 0.45 µm filtered. Chromatographic separation was performed using a Luna C18(2), 150 × 4.6 mm, 5 µm column (Phenomenex, USA). The analysis used an Agilent HPLC 1260 consisting of a vacuum degasser, a binary pump, an autosampler, and a column thermostat equipped with QTOF 6540 UHD accurate mass (Agilent Technologies, USA). A 10 µL sample was injected into the LC system with a solvent flow rate of 0.5 mL/min. The mobile phase consisted of a gradient elution between

water (solvent A) and methanol (solvent B), both containing 0.1% v/v formic acid. The isocratic elution was initially held at 70% of solvent B for 20 min, then the linear gradient started from 70% to 100% of solvent B for 10 min and finally held for 5 min. The column temperature was controlled at 35°C. The mass analysis was performed using a QTOF 6540 UHD accurate mass spectrometer. Analysis parameters were set using both negative and positive modes with spectra acquired over a mass of *m/z* 100–1,000 amu. The ESI-MS condition parameters were as follows: capillary voltage +3,500 V; drying gas (N<sub>2</sub>) 7 L/min; dry gas temperature at 350°C; and nebulizer pressure at 30 psig. Fragmentations were performed using auto MS/MS experiments with collision energies at 10 V, 20 V, and 40 V. The MS data, MS/MS fragmentation profiles, and molecular formula proposed by the Agilent MassHunter were compared with the literature data and some databases, such as Human Metabome and Metfrag, to annotate the phytochemicals analyzed from the samples, and a maximum error of 5 ppm was accepted. A GNPS analysis of the n-hexane and ethyl acetate fractions was carried out on the LC-MS/MS data. The LC-QTOF-MS/MS data from Agilent MassHunter data files (.d) were converted to mzXML file format using MSConvert software. The data were then transferred to the GNPS server (gnps.ucsd.edu) to generate the chemical networking map (ID = 1f87661d4fdf42d2a316e55b1312a10d) (Wang et al., 2016). The GNPS analysis workflow using the spectral clustering algorithm with a cosine score of 0.7 and a minimum of 4 matched peaks in the fragmentation spectrum. The molecular networking data were visualized with Cytoscape software version 3.9.1. A ball-and-stick layout where nodes represent parent mass and cosine score was reflected by edge thickness (Nothias et al., 2020; Wu et al., 2021).

### Statistical analysis

One-way ANOVA analyses were carried out to compare the inhibition data between the samples, followed by Tukey's multiple comparison tests. The IC<sub>50</sub> values were determined based on the data obtained from three independent experiments, each done in triplicates, and analyzed using GraphPad Prism 8.0 (GraphPad Software, USA) with *r*<sup>2</sup>>0.95. The data were considered significantly different if the *p*-value<0.05.

## RESULTS AND DISCUSSION

### Cholinesterase inhibitory assay

Cholinesterase is an enzyme that can hydrolyze choline esters, including the naturally occurring substrate acetylcholine (Moodie et al., 2019). As one of

the main features of AD is the deficiency of the neurotransmitter acetylcholine, inhibition of cholinesterase enzymes becomes one of the targets in the treatment of AD. In this research, the extract and fractions of a marine sponge *A. suberitoides* were screened against AChE and BChE enzymes. The results presented in Table 1 showed that the extract and fractions inhibited both AChE and BChE enzymes. All samples demonstrated stronger inhibition against AChE compared to BChE enzymes, which was reflected in the lower IC<sub>50</sub> values against AChE enzymes. The n-hexane fraction gave the strongest inhibition against both AChE and BChE, with IC<sub>50</sub> values of 4.76 µg/mL and 6.79 µg/mL, respectively. According to Dos Santos et al. (2018), the potency of cholinesterase inhibitors can be classified into three categories, high potency, IC<sub>50</sub><20 µg/mL; moderate potency, 20<IC<sub>50</sub><200 µg/mL; and low potency, 200<IC<sub>50</sub><1,000 µg/mL. Based on these, the extract, n-hexane, and ethyl acetate fractions of *A. suberitoides* are highly potent against the AChE enzyme. The n-hexane fraction also demonstrated high potency against BChE, while the extract and ethyl acetate fraction showed moderate potency against BChE. From Table 1 can be seen that the IC<sub>50</sub> values of the extract and fractions were higher than the standard drug, galantamine, with IC<sub>50</sub> values of 0.20 µg/mL and 1.33 µg/mL against AChE and BChE, respectively. The one-way ANOVA analysis suggested significant differences between all samples tested with p<0.0001 for all groups, except for the n-hexane and galantamine BChE groups, with p=0.0074.

**Table 1.** The IC<sub>50</sub> values of *A. suberitoides* extract and fractions.

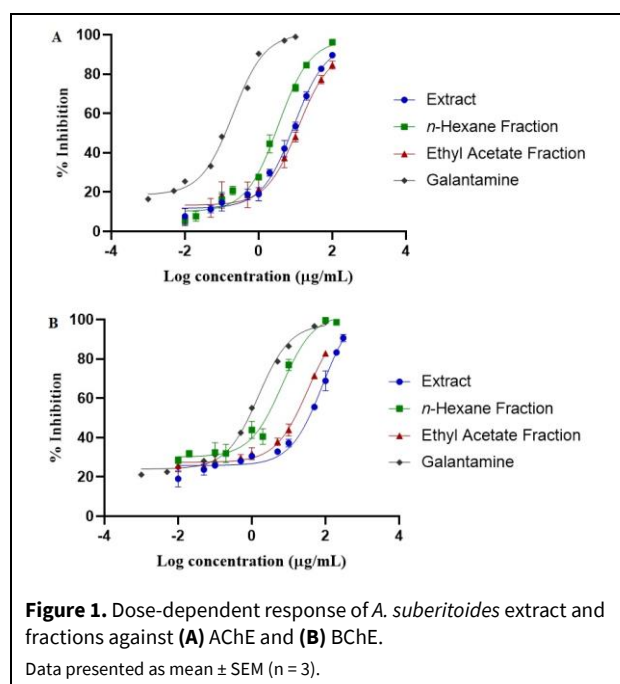
Samples	IC <sub>50</sub> (µg/mL)	
	AChE	BChE
Extract	9.12 ± 0.19	90.28 ± 0.28
n-Hexane fraction	4.76 ± 0.29	6.79 ± 0.32
Ethyl acetate fraction	13.42 ± 0.39	30.91 ± 1.55
Galantamine	0.20 ± 0.01	1.33 ± 0.02

Data presented as mean ± SEM of three independent experiments, each done in triplicates.

Fig. 1 represents the inhibition of the extract and fractions at various concentrations against AChE and BChE enzymes. It was found that the extract and fractions tested inhibited the enzymes in a dose-dependent manner. The same trend was observed for the reference drug, galantamine, in agreement with the previous reports (Dalai et al., 2014; Voskressensky et al., 2013).

## Identification of metabolites by LC-MS/MS

The chemistry of the n-hexane and the ethyl acetate fractions of *A. suberitoides* were studied by LC-MS/MS instrument. The total ion chromatograms (TIC) of the two fractions were compared (Fig. 2), which showed a slightly different TIC profile. In the n-hexane fraction, several major peaks at RT, approximately 1-5 min and 28-35 min, were detected, whereas, in the ethyl acetate fraction, the major peaks were observed at 1-4 min and minor peaks at a range of 30-37 min. The GNPS molecular networking (Fig. 3) shows the cluster of compounds present in the n-hexane and ethyl acetate fractions. The blue dots represent compounds identified in the n-hexane fraction, the green dots for compounds present in the ethyl acetate fraction, and the red dots for compounds identified in both n-hexane and ethyl acetate fractions. Nearly half of the compounds were identified in both fractions, including two major ions at *m/z* 229 and *m/z* 117.



**Figure 1.** Dose-dependent response of *A. suberitoides* extract and fractions against (A) AChE and (B) BChE.

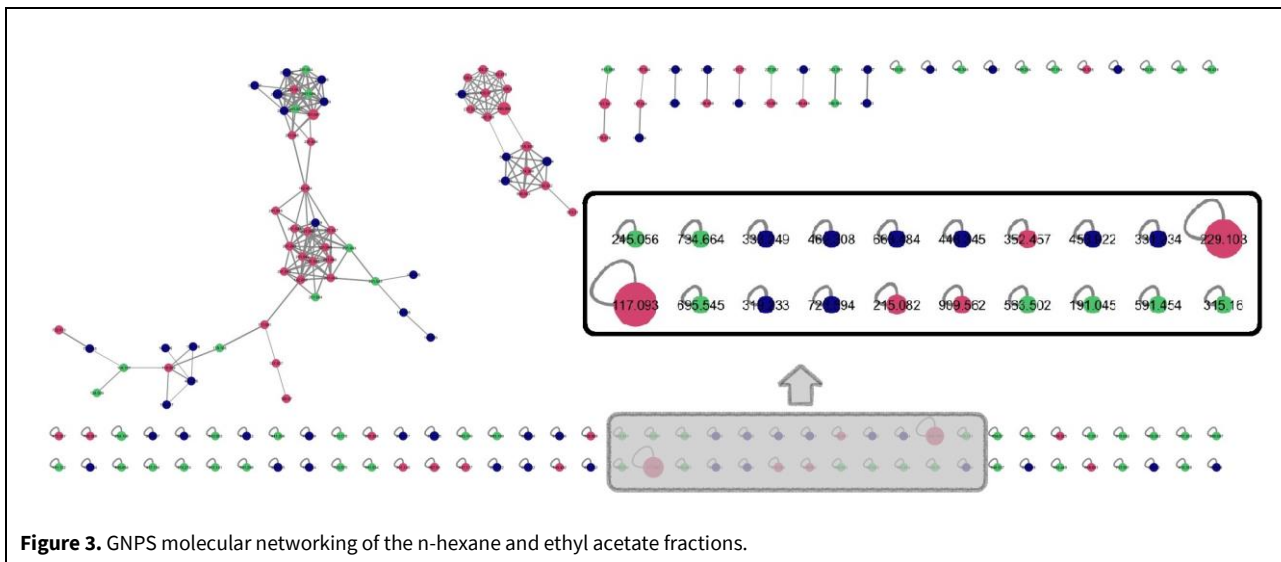
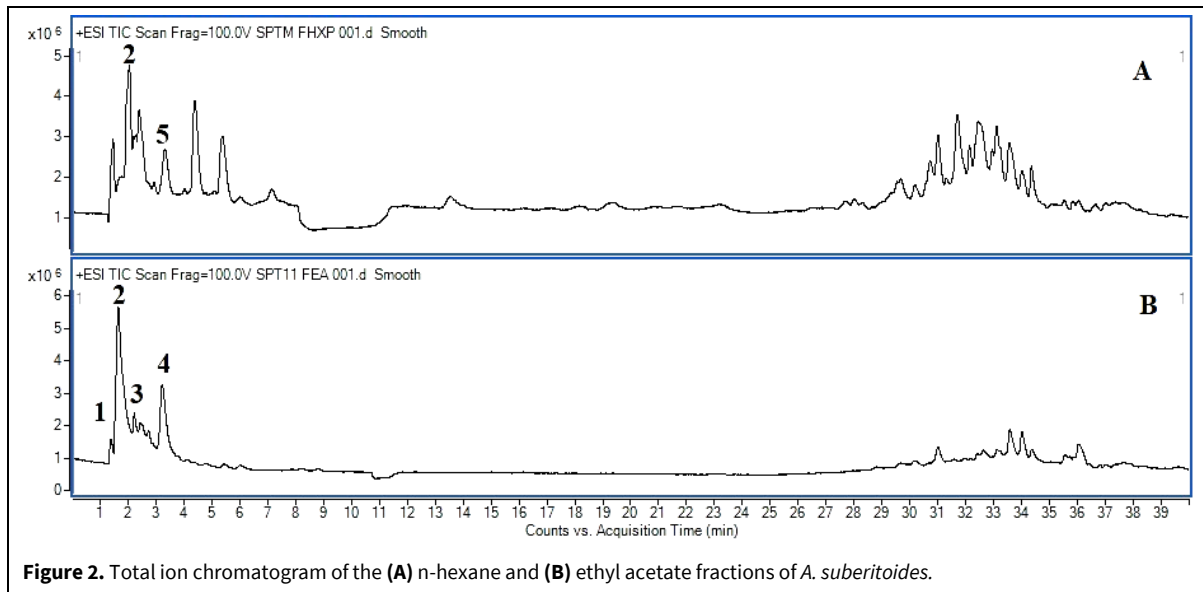
Data presented as mean ± SEM (n = 3).

The search for cholinesterase inhibitor from natural sources has discovered a wide range of compounds; however, alkaloids is reported as the main class of compounds showing a promising potency as cholinesterase inhibitor (Dos Santos et al., 2018; Moodie et al., 2019; Ng et al., 2015; Tamfu et al., 2021). This is also supported by the fact that cholinesterase inhibitors clinically used are alkaloids. *Aaptos suberitoides* is a marine sponge rich in alkaloids (He et al., 2020). Therefore, the identification of alkaloids becomes the main target of the current study. Alkaloids identified in the samples are presented in Table 2, which shows the presence of five known alkaloids.

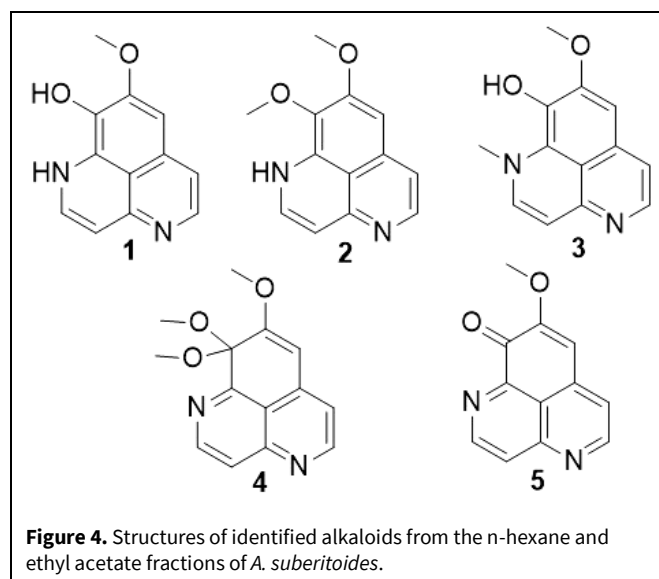
Four alkaloids were detected in the ethyl acetate fraction, namely demethylaaptamine (1), aaptamine (2), iso-aaptamine (3), and 8,9,9-trimethoxy-9H-benzo[de][1,6]naphthyridine (4) at RT 1.52, 1.67, 2.92 and 3.22 mins, respectively. Aaptamine (2) was also identified in the n-hexane fraction together with demethyl-oxyaaptamine (5) (Fig. 4).

Aaptamine and its derivatives are well-known alkaloids isolated from the marine sponge of the genus

*Aaptos*, such as *A. aaptos*, *A. suberitoides*, *A. nigra*, and *Aaptos* sp. This class of compounds has shown significant biological activities such as antioxidant, anti-cancer, antiviral, antifouling, antimicrobial, antiatherosclerotic, and antileishmanial activities (He et al., 2020). To the best of our knowledge, there is no report on the cholinesterase inhibitory potential of the alkaloid aaptamines and derivatives. Isolation of aaptamine and related compounds from the active fraction should be carried out followed by bioactivity analysis.





**Table 2.** LC-MS/MS data for identified alkaloids from the n-hexane and ethyl acetate fractions of *A. suberitoides*.

Compounds	RT <sup>a</sup> (mins)	[M+H] <sup>+</sup>	Product ions m/z (relative abundance) <sup>b</sup>	Formula	Exact mass	Mass error (ppm)
1	1.52	215.0814	200.0579 (100), 171.0553 (81.05), 154.0524 (70.96), 144.0678 (19.18), 127.0415 (15.38), 117.0570 (11.46)	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	215.0815	0.48
2	1.67	229.0971	196.0632 (21.89), 184.0630 (14.63), 168.0682 (100), 155.0604 (9.03), 143.0603 (7.65), 128.0494 (4.78)	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	229.0972	0.24
3	2.92	229.0970	196.0628 (25.29), 186.0424 (31.75), 168.0680 (100), 158.0467 (15.29), 143.0599 (12.91), 130.0519 (16.09)	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	229.0972	0.67
4	3.22	259.1075	211.0500 (24.59), 199.0863 (16.69), 184.0631 (71.9), 168.0679 (40.53), 156.0680 (100), 129.0570 (12.08)	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	259.1077	0.84
5	3.37	213.0656	183.0598 (13.92), 170.0517 (71.25), 155.0641 (25.43), 142.0561 (100), 128.0525 (19.45), 115.0445 (26.38)	C <sub>12</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	213.0659	1.19

<sup>a</sup>RT: Retention Time, <sup>b</sup>Product ions at collision energy 40 eV.

## CONCLUSION

The extract, n-hexane, and ethyl acetate fractions of *A. suberitoides* have shown promising cholinesterase inhibitory properties against both AChE and BChE enzymes. The presence of alkaloid compounds, such as aaptamine and its derivatives, may be responsible for the cholinesterase inhibitory activity.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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**AUTHOR CONTRIBUTION:**

Contribution	Putri HR	Kristiana R	Mudianta IW	Setiawan E	Widyawaruyanti A	Nuengchamnong N	Suphrom N	Suciati S
Concepts or ideas					x			x
Design					x			x
Definition of intellectual content								x
Literature search	x	x	x	x	x	x	x	x
Experimental studies	x	x	x	x		x	x	x
Data acquisition	x	x	x			x		
Data analysis				x		x	x	x
Statistical analysis								x
Manuscript preparation	x							x
Manuscript editing	x							x
Manuscript review	x	x	x	x	x	x	x	x

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