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## Evaluation of Indonesian selected macroalgae for their antitumor and cytoprotective activity

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### ABSTRACT

**Context:** Macroalgae are known to exhibit secondary metabolites with interesting bioactive properties, including antibacterial, antioxidant, antitumor, and anti-UV effects. Indonesia is endowed with an abundance of macroalgae, yet information regarding their pharmaceutical properties remains largely unexplored.

**Objective:** This study evaluates the antitumor and cytoprotective effects of Indonesian selected seaweeds *Acanthophora spicifera* (ASE), *Acanthophora muscoides* (AME), *Sargassum polycystum* (SPE), and *Sargassum crassifolium* (SCE) crude ethanol extracts.

**Materials and Methods:** Preliminary phytochemical screening was used to determine chemical constituents in macroalgae ethanol extracts. Cytotoxicity and antiproliferative activity of macroalgae extracts were evaluated with Methyl Thiazolyl Tetrazolium (MTT) assay from 5 to 200 µg/ml concentration in human cervical cancer (HeLa) and human umbilical vein endothelium (HUVEC) cells for 72 hours. UV absorbing capabilities of macroalgae extracts were determined with UV-VIS (240–340 nm). Cytoprotective effects were evaluated by fluorescence microscopy observation of cells irradiated with UV-B for 3 minutes.

**Results:** AME appeared to exhibit most diverse chemical constituents. Only ASE and AME demonstrated moderate cytotoxicity (ASE-IC<sub>50</sub> = 190 ± 24 µg/ml; AME-IC<sub>50</sub> = 180 ± 14 µg/ml) against HeLa cells in 72 hours incubation. Furthermore, the cytotoxicity effects of all macroalgae extracts could not be detected in HUVEC cells at tested concentrations. In addition, SPE and SCE potentially reduced nuclear DNA damage induced by UV-B radiation.

**Conclusion:** Current results show Indonesian macroalgae possesses a broad range of possible therapeutic applications. Therefore, further advanced studies relating to the isolation of specific bioactive compounds and molecular mechanisms would be reasonable to fully utilize macroalgae potential uses in the pharmaceutical industries.

### INTRODUCTION

The recent studies demonstrated the importance of natural products, both plant extracts and isolated compounds which have shown appreciable biological activities (Butler, 2004; Cragg *et al.*, 2006). There are some terrestrial plant-derived oncology drugs which are already approved by

the United States Food and Drug Administration (FDA) such as vepesid, vumon, hymecatin, and Camptosar (Kintzios, 2006). However, the marine environment has provided various bioactive products that continue to show unique biological activities. Until now, the marine environment consists of three FDA approved drugs, 1 EU registered drug, 13 natural products, and a large number of marine chemicals in the pre-clinical category (Mayer *et al.*, 2010). Another analysis showed that by the end of 2013, 307 natural products and 15 natural product derivatives from the plant, bacteria, fungi, and marine sources had been approved by the FDA or 21% of all approved new chemical entities (Patridge *et al.*, 2015).

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Macroalgae or seaweeds have attracted the attention of the pharmaceutical industry, due to the great diversity of species that are available and the ability to produce secondary metabolites with various pharmacological activities such as cytotoxic activity, antiproliferative, antimicrobial, cytoprotective, anticoagulant, and antioxidant activities (Bouhhal *et al.*, 2011; Heo and Jeon, 2009; Kang *et al.*, 2012; Kim *et al.*, 2011; 2015; Na *et al.*, 2005; Shi *et al.*, 2010). In addition, as a mechanism to protect themselves against other organisms in their environment, macroalgae produce a wide variety of bioactive metabolites as a potential source of novel compounds for various purposes (Kawaguchi and Hayashizaki, 2011). Some of these metabolites such as iodine, carotene, glycerol, alginates, and carrageenan have been evaluated for its pharmaceutical properties (Barbosa *et al.*, 2014; Luo *et al.*, 2015; Prasedya *et al.*, 2016).

Despite such advantages of natural products and a proven track record of succeeding discoveries, most pharmaceutical companies have been discouraged from pursuing natural product-based drug discovery due to perceived disadvantages of the natural products. These include challenges in ensuring access and adequate supply of potential natural product resources. Indonesia tropical warm waters are well-known as a suitable place for the macroalgae growth. Hence, it is endowed with an abundance of macroalgae (Tarman *et al.*, 2011). However, there remains little information regarding Indonesian macroalgae pharmaceutical properties. The present study was, therefore, to evaluate pharmaceutical properties of selected macroalgae from Indonesian coastal areas; *Acanthophora spicifera* (ASE), *Acanthophora muscoides* (AME), *Sargassum polycystum* (SPE), and *Sargassum crassifolium* (SCE) crude ethanol extracts. We discovered that only ASE and AME provided selective cytotoxic activity in the human cells. However, SPE and SCE shown effectivity in the reduction of nuclear DNA damage induced by UVB radiation in human cervical cancer (HeLa) cells.

Our current results would provide preliminary information of potential pharmaceutical properties of Indonesian macroalgae for potential utilization in various medicinal applications. In addition, further advanced research regarding bioactive compound mechanisms would be reasonable for further development of macroalgae-based natural pharmaceutical products.

## MATERIALS AND METHODS

### Sample collection and extraction

Macroalgae samples were collected from North West Lombok area, Mentigi beach (8°24'11.7396"S, 116°4'1.9056"E), West Nusa Tenggara Province, Indonesia at the end of 2017. Macroalgae specimens were identified according to Sulistijo (2009) and Guiry and Guiry (2018). The seaweed samples were washed with fresh water to remove adhering debris. The collected samples were then dried and powdered. Powdered samples were mixed with absolute ethanol solvent with 5 × volume of sample weight (w/v). Suspensions were then macerated by incubation in room temperature for 48 hours. For every 24 hours, suspensions were filtered with Whatman number 1 filter papers. Filtrates were evaporated with rotary evaporators until concentrated ethanol extracts were obtained. These filtrates were then used for seaweed ethanol extracts.

### Chemicals and reagents

Methyl Thiazolyl Tetrazolium (MTT) assay were purchased from Dojindo Laboratories (Kumamoto, Japan), nicotinamide adenine dinucleotide was obtained from Oriental Yeast Ltd. (Tokyo, Japan). General reagents including lithium lactate were purchased from Wako Pure Chemicals (Osaka, Japan).

### Preparation of macroalgae extract for analysis

Macroalgae extraction with ethanol solvent was conducted according to methods by Cho *et al.* (2007) with small modifications. Powdered seaweed (50 g) was extracted successively using Soxhlet extractor sequentially with different solvents of increasing polarity of ethanol until the extract was clear. The resulting pasty extracts were stored in a refrigerator at 4°C for further use. The extraction was centrifuged at 2,000 × g for 10 minutes. The supernatant was collected, dried, and stored at 4°C until for future use. The dried macroalgae extract was resolved in dimethyl sulfoxide (DMSO) and centrifuged at 15,000 × g for 15 minutes, and then clear macroalgae extract sample was obtained.

### Phytochemical profiling

Gas chromatography-mass spectrometry (GC-MS) analysis of the ethanol extract of macroalgae extracts was performed using a Perkin-Elmer GC Clarus 500 system comprising an AOC-20i auto-sampler and a gas chromatograph interfaced to a mass spectrometer (GC-MS) equipped with an Elite-5MS (5% diphenyl/95% dimethyl polysiloxane) fused a capillary column (30 × 0.25 μm ID × 0.25 μm df). Macroalgae extracts were also subjected to phytochemical screening following the methodology of Harborne (1998).

#### Test for alkaloids

One gram powder of macroalgae samples was taken in a conical flask and added ammonia solution (3 ml). It was allowed to stand for few minutes to evaluate free alkaloids. Chloroform (10 ml) was added to the conical flask shaken by hand and then filtered. The chloroform was evaporated from the crude extract by water bath and added Mayer's reagent (3 ml). A cream color precipitation was obtained that showed the presence of alkaloids.

#### Test for flavonoids

The stock solution (1 ml) was taken in a test tube and added a few drops of dilute NaOH solution. An intense yellow color appeared in the test tube. It became colorless when on the addition of few drops of dilute acid that indicated the presence of flavonoids.

#### Test for saponins

The stock solution (1 ml) was taken in a test tube and diluted with 20 ml of distilled water. It was shaken by hand for 15 minutes. A foam layer was obtained on the top of the test tube. This foam layer indicated the presence of saponins.

#### Test for steroids

The crude plant extract (1 mg) was taken in a test tube and dissolved with chloroform (10 ml), then added an equal volume of concentrated sulfuric acid to the test tube by sides. The



upper layer in the test tube turns into red and sulfuric acid layer showed yellow with green fluorescence. It showed the presence of steroids.

#### Test for tannins

The stock solution (3 ml) was taken in a test tube and diluted with chloroform and added acetic anhydride (1 ml). Finally, sulfuric acid (1 ml) was added carefully by the side of the test tube to the solution. A green color was formed which showed the presence of tannins.

#### Test for triterpenoids

The dry crude plant extract (5 mg) was dissolved in chloroform (2 ml) and then acetic anhydride (1 ml) was added to it. Concentrated sulfuric acid (1 ml) was added to the solution. Formation of reddish-violet color shows the presence of triterpenoids.

#### Cell culture

HeLa cell lines were routinely cultivated in Dulbecco's modified Eagle medium (DMEM, Wako) supplemented with 10% fetal bovine serum at 37°C in a 5% CO<sub>2</sub> humidified incubator. HUVEC cells were cultured in MCDB131 medium supplemented with 10 ng/ml epidermal growth factor, 10 µg/ml heparin, and 10% FBS. For all experiments, cells were plated in medium, incubated overnight, and incubated in specific medium supplemented with various concentrations (5–200 µg/ml) of macroalgae extracts. Cell images were obtained from phase-contrast microscopy by BZ-9000 microscope (Keyence, Osaka, Japan).

#### Cytotoxicity assay

Cytotoxicity activity of macroalgae samples was estimated by methyl thiazolyl tetrazolium (MTT) assay. Cells were cultured in 96-well culture plate over-night, then the culture mediums were discarded and changed with new medium containing several concentrations of macroalgae ethanol extracts (5–200 µg/ml). Cell counting was performed with FlexStation 3 multi mode microplate reader at an absorbance of 450 nm. Cytotoxicity was calculated by the following equation:

$$\text{Cytotoxicity (\%)} = \frac{(A_{450 \text{ treatment}} - A_{450 \text{ min}})}{(A_{450 \text{ max}} - A_{450 \text{ min}})} \times 100\%$$

#### Absorption of UV-B by macroalgae extracts

For UV-VIS spectrophotometer analysis, the extracts were centrifuged at 3,000 rpm for 10 minutes and filtered through Whatman No. 1 filter paper by using a high-pressure vacuum pump. The sample is diluted to 1:10 with the same solvent. The crude extracts containing the bioactive compound were analyzed spectroscopically for further confirmation. To detect the UV-VIS spectrum profile of the crude macroalgae ethanol extracts, the extracts were scanned in the wavelength ranging from 200 to 1,100 nm by using NanoDrop 2000c spectrophotometer, Thermo Scientific, and the characteristic peaks were detected.

#### HeLa cell exposure to UV-B irradiation

HeLa cells were cultured in DMEM while the cells adhered to the dish, and thereafter, the medium was changed to DMEM with 20 µg/ml of macroalgae extracts. Followed by subsequent ultraviolet radiation (302 nm) for 3 minutes by using UV trans-illuminator (ChemiDoc XRS+, Bio-Rad Laboratories, Inc., Hercules). After the radiation treatment, the cells were incubated at 37°C for an additional 24 hours. Double staining with 1 µg/ml propidium iodide (PI) and 1 µM Hoechst 33342 was conducted to differentiate live and dead cells. Cell image was obtained from red fluorescence (PI-staining as a dead cell) and blue fluorescence (Hoechst 33342-staining as a total cell) view by BZ-9000. UV-damage was estimated as the ratio of dead cells to total cells.

#### Statistical analysis

The results were expressed as means ± standard error of the mean (SEM), and experiments were conducted at least in triplicate ( $n=3$ ). Significant differences were assessed with analysis of variance followed by *post-hoc* test LSD and Tukey-HSD,  $p < 0.05$  was considered as statistically significant, and SPSS statistical package for Windows (release 15.0, SPSS Inc., Chicago, IL) was used.

## RESULTS

#### Phytochemical profile of macroalgae ethanol extracts

Investigation of the ethanol macroalgae extracts with GC-MS analysis led to the identification of potential bioactive compounds. Seven main compounds were seen in AS and AM ethanol extracts. The main compounds identified in ASE were palmitic acid (9.24%) and Heptadecene-(8)-carbonic acid (9.77%). Whereas, AME shown the more diverse presence of main compounds, such as β-copaen-4.α-ol (3.47%), 1-Naphthalenamine, 4-bromo (9.77%), valeranal (11.48%), palmitic acid (12.01%), and 2,3,5-Tribomo-N-methylindole (12.91%). SPE and SCE shown similar chemical constituents, the dominant compounds were palmitic acid and stearic acid. This result was also confirmed by a phytochemical screening of macroalgae ethanol extracts which shown the presence of alkaloids, terpenoids, steroids, tannins, and saponins. However, the existence of these compounds varies between the macroalgae species. All macroalgae ethanol extracts exhibited the presence of steroids. However, flavonoids were absent in all macroalgae ethanol extracts. Alkaloid constituents were present in all macroalgae ethanol extracts except in SPE. Overall, AME and SCE revealed the most promising profile of phytochemical constituents.

#### Cytotoxicity assay

Cytotoxicity effects of macroalgae ethanol extracts were investigated via MTT assay against HeLa cell line and HUVEC cell line. After 72 hours treatment, only ASE and AME shown cytotoxic effects against HeLa cell line with IC<sub>50</sub> of 190 ± 24 µg/ml and 180 ± 14 µg/ml, respectively. Furthermore, the cytotoxicity effects of all macroalgae ethanol extracts could not be detected in HUVEC cells in all tested concentrations. Treatment with macroalgae ethanol extracts of concentration over 200 µg/ml resulted in some debris which appeared in the culture medium; therefore, we could not perform higher concentration in this study.

### Cell morphology

To assess the alterations of cell morphology, subsequent to treatments of macroalgae ethanol extracts, cells were grown on 35-mm glass bottom culture dish for microscopy observation. Untreated HeLa cells were homogeneously distributed, exhibit an elongated shape, observed by phase-contrast microscopy (Fig. 3). However, ASE and AME treated cells resulted in cell morphology changes. Cells were seen to lose cell membrane integrity which could potentially lead to cell death. The alterations induced by the treatment included reduction of cell size, cell shrinkage, and the formation of blebs on cell surface resulted in the generation of apoptotic bodies. These cytotoxicity features were not detected in HeLa cells treated with SPE and SCE. In addition, all macroalgae extracts did not affect cell morphology in HUVEC cells in tested concentrations.

### Macroalgae ethanol extracts UV absorption analyses

In addition to macroalgae ethanol extracts anti-tumoral effects, in this study, we intended to investigate the cytoprotective activity of macroalgae ethanol extracts against UV radiation. The extracts were dissolved in DMSO, and the extract solution was diluted in water to a concentration of 20 µg/ml. A wavelength from 280 to 380 nm is UV and UV absorption of the macroalgae ethanol extracts was measured (Fig. 4). ASE and DMSO 0.5% for solvent control resulted in absorbance peak close to the baseline. Whereas AM, SPE, and SCE showed considerable capability in UV absorption in the UV-B spectrum region (280–315 nm).

### Cytoprotective activity analyses of macroalgae ethanol extracts against UV-B radiation

The HeLa cells were cultured in DMEM with and without 20 µg/ml of macroalgae ethanol extracts for 24 hours after 3 minutes of UV-B radiation. Figure 5 shows double staining of 24 hours treated HeLa cells with Hoechst 33342/PI. HeLa cells treated

with UV-B radiation resulted in severe morphological changes such as elongated and thin shaped. Furthermore, AME, SPE, and SCE demonstrated the potential cytoprotective effect in cellular DNA against UV-B radiation. This was shown by the significant lower percentage of dead cells (PI-stained cells) incubated with AME, SPE, and SCE compared with cells applied with ASE and control + UV cells (Fig. 6).

### DISCUSSION

Seaweed has reportedly to contain various compounds with various biological activities such as sulfated polysaccharides, polyphenols, and phlorotannins (Alekseyenko *et al.*, 2007; Pavia and Brock 2000; Pavia *et al.*, 1997). In recent years, many researchers have worked to study potential biological activities of seaweeds as antiviral, antitumor, and anti-UV agents (Cerella *et al.*, 2010; Groniger *et al.*, 1999; Ponce *et al.*, 2003). Indonesian tropical warm waters are known to be suitable for macroalgae growth. However, most macroalgae species are largely unexplored for its biological potentials. In this study, we evaluated the biological potentials of non-cultivated macroalgae found in most coastal areas of Indonesia such as ASE, AME, SPE, and SCE crude ethanol extracts.

Chromatographic profiles of macroalgae ethanol extracts shown the existence of various bioactive compounds (Fig. 1). Bioactive compound palmitic acid (C16:O) being the compound present in all macroalgae ethanol extracts. According to the literature, palmitic acid is predominant in macroalgae or seaweeds (Gressler *et al.*, 2010). Alkaloids, flavonoids, terpenoids, polysaccharides, saponins, and others have been documented as natural bioactive products with potent pharmaceutical activities (Avato *et al.*, 2017; Joshi *et al.*, 2017). Our results revealed that different macroalgae species ethanol extracts exhibit different phytochemical profiles. This possibly affects the different biological activities of macroalgae extracts. Further evaluation of the extract solvent is needed to obtain the best pharmaceutical activity of macroalgae species. Pure drugs produced from plants

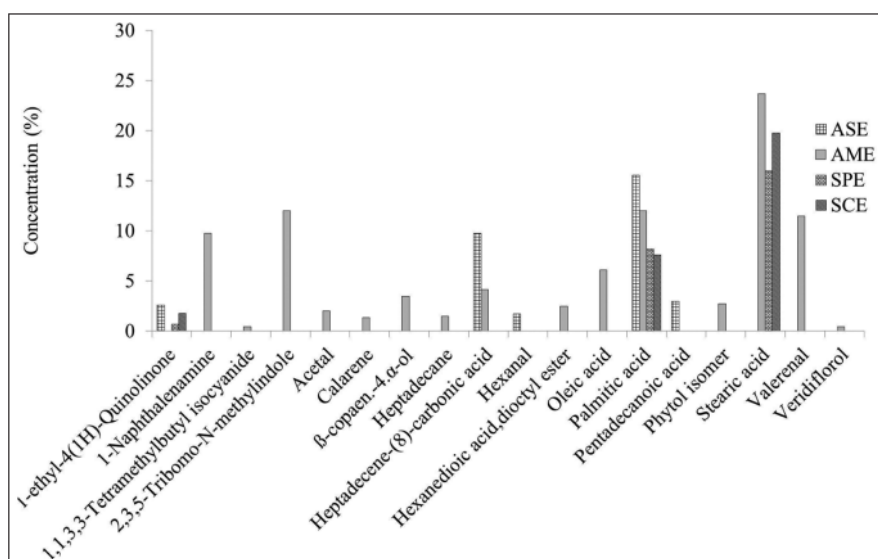


Figure 1. Chemical constituents of macroalgae crude ethanol extracts analyzed with GC-MS spectrometry.

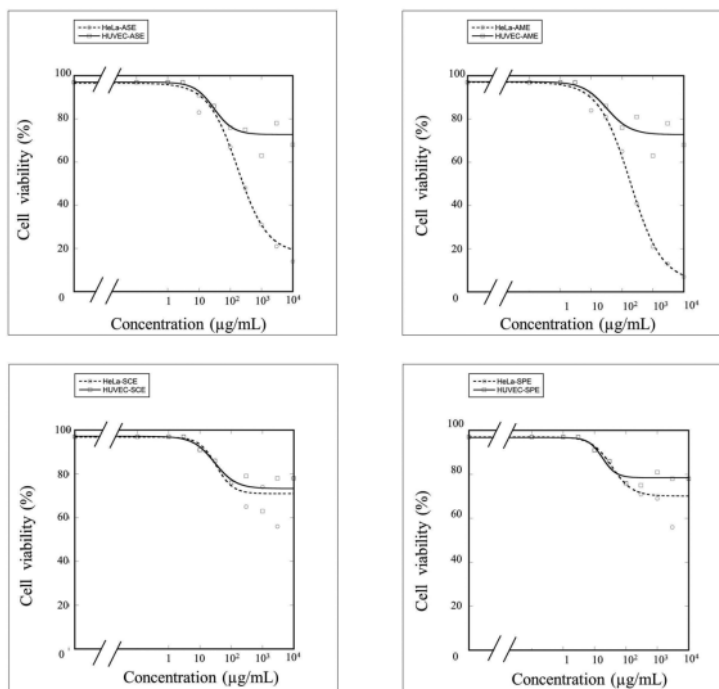


Figure 2. Cytotoxic assay of macroalgae crude ethanol extracts in HeLa and HUVEC cells analysed with MTT assay in 72h treatment.

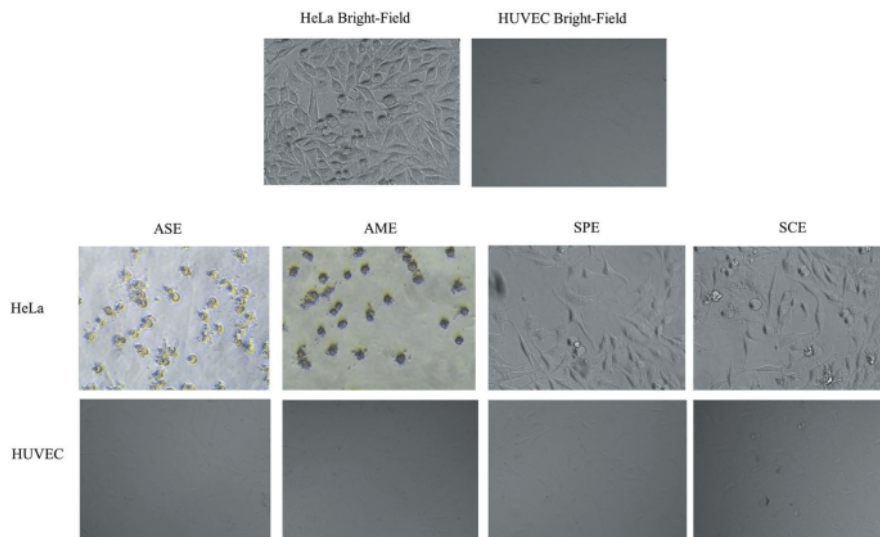


Figure 3. Morphological observation of HeLa and HUVEC cells treated with macroalgae crude ethanol extracts (200 µg/mL) for 72h.

rarely have the same degree of activity as the unrefined extract (Wagner and Ulrich-Merzenich, 2009). This phenomenon is attributed to the absence of interacting substances present in the extract. Hence, early screening of potential biological activities of crude extracts is needed to confirm further investigations toward purification of potential bioactive compounds.

The cytotoxic effects of macroalgae ethanol extracts were determined with MTT assay. Only ASE and AME were seen to exhibit cytotoxic activities in our tested macroalgae samples. The alcoholic extract of *A. spicifera* exhibits tumoricidal activity on Ehrlich's ascites carcinoma cells developed in mice at a dose of 20 mg/kg comparable to the standard drug, 5-fluorouracil



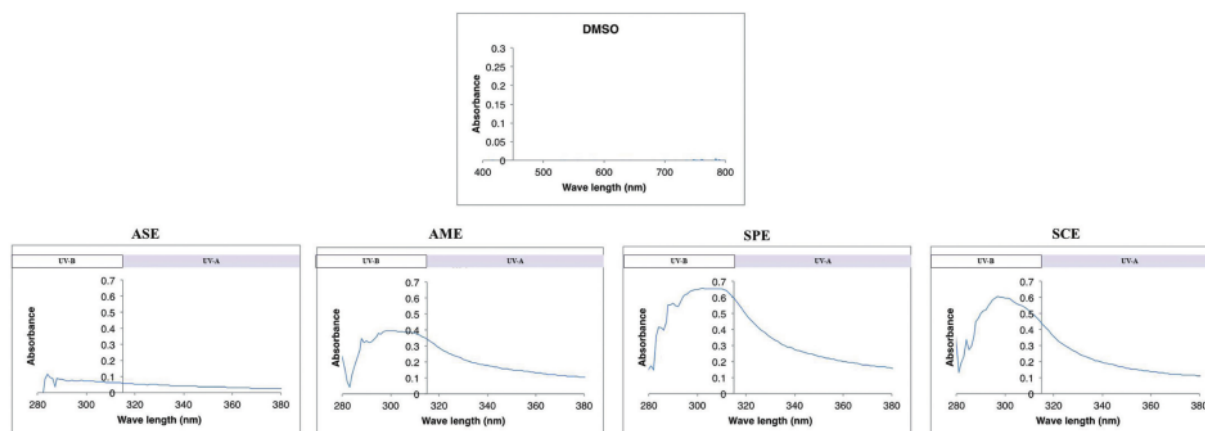


Figure 4. UV-VIS analyses of macroalgae ethanol extracts for determination of UV-absorbing capability.

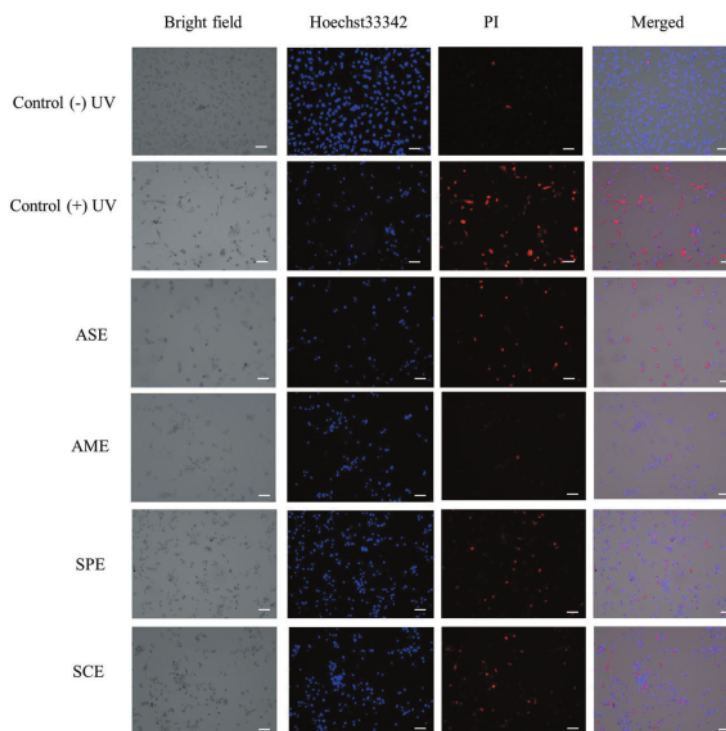
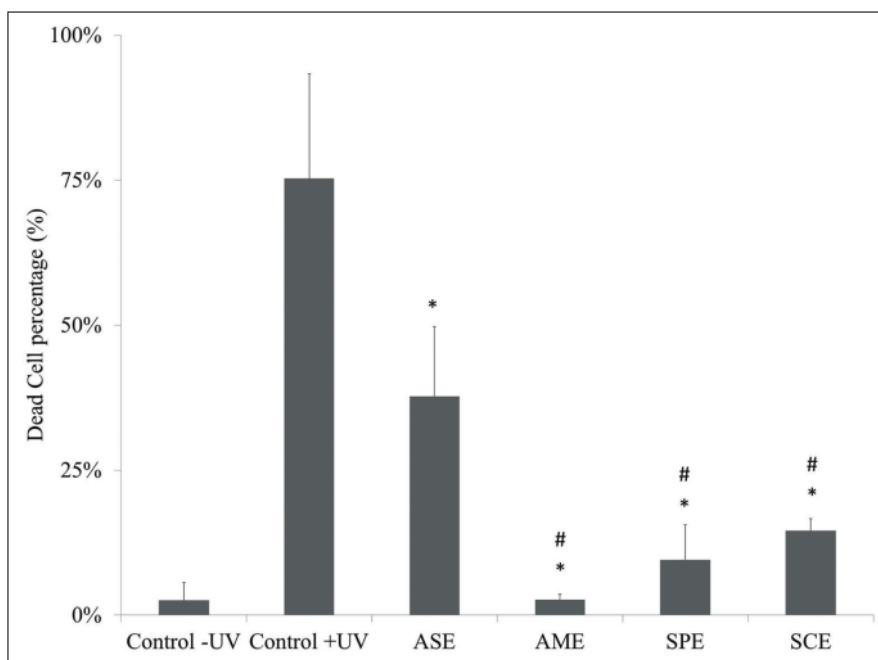


Figure 5. Fluorescence imaging of HeLa cells incubated with macroalgae ethanol extracts (20µg/mL) followed by UV-B radiation for 3 mins. Blue cells indicate live/dead cells stained with Hoechst33342. Red cells indicate dead cells stained with Propidium Iodide (PI). Scale = 100µm.

(Vasanthi *et al.*, 2004). However, this is the first report describing the cytotoxic activity of *A. muscoides*. We assumed that *Sargassum* species would also demonstrate cytotoxic activities in HeLa cells, due to its fucoidan content (Atashrazm *et al.*, 2015). However, SPE and SCE cytotoxic effects were not observable in HeLa and HUVEC cells. This result correlates with literature which reports that crude methanol extract of *Sargassum filipendula* also presented no antiproliferative activity

under any of the tested concentrations in HeLa cells for 72 hours (Gomes *et al.*, 2015). Hence, further investigation of the optimal extraction solvent for *Sargassum* species would be necessary for the determination of its potential pharmaceutical activities. In addition, all macroalgae extracts cytotoxic activity could not be determined in normal cell line HUVEC cells. However, further molecular analysis needs to be conducted for more established confirmation of this result.



**Figure 6.** Dead cell percentage of HeLa cells incubated with macroalgae ethanol extracts (20 $\mu$ g/mL) followed by UV-B radiation for 3 mins. \* indicates  $P < 0.05$  significantly different compared to control +UV; # indicates  $P < 0.05$  significantly different compared to ASE.

Our spectrophotometry results show that ethanol extract of AME, SPE, and SCE shown UV absorption from 280 to 320 nm, which is the specific spectrum range of UV-B (Fig. 4). Only macroalgae ASE resulted in a lower absorbance peak in UV-B spectrum range. Addition to this research, we applied macroalgae ethanol extracts for the investigation of cytoprotective activity against UVB radiation. Previous reports have shown a widespread group of UV-absorbing compounds in algae such as mycosporine-like amino acids. Scytonemins are frequently found in cyanobacteria and sporopollenin in some green algae. Polyphenolics such as phlorotannin are considered as UV inducible screening compounds in some macroalgae, especially red macroalgae such as *Acanthophora* (Pavia and Brock 2000; Pavia *et al.*, 1997). A study by Lee *et al.* (2012) also reported that red algae *Gloiopeltis furcata* has the highest peaks between 280 and 360 nm. However, other species evaluated did not show any UV absorption peaks. This suggests macroalgae species have diverse potentials in absorbing UV spectrum which would be interesting to explore in more advanced research.

HeLa cells exposed with UV-B radiation were seen to experience altered morphology and an increase of dead cells (Fig. 5). UV-B treated cells would also result in a flattened and shrinkage morphological features (Qin *et al.*, 2018). Significant differences were seen in dead cell percentage after UV-B irradiation treatment between HeLa cells incubated with AME, SPE, and SCE compared with control cells and ASE-treated cells. Brown macroalgae *Sargassum* species has well been reported for its potential to inhibit UV-B radiation damage (Kim *et al.*, 2012; Piao *et al.*, 2014). Hence, further exploration of *Sargassum* species

as a potential source of cytoprotective agents against UV radiation would be reasonable.

## CONCLUSION

Our current findings show that the macroalgae crude ethanol extract exhibits diverse phytochemical profiles which affect its unique biological activity. ASE and AME demonstrated moderate selective cytotoxicity. However, cytotoxicity and antiproliferative activities of SPE and SCE were not observable in this study. SPE and SCE shown more significant cytoprotective activity compared with ASE and AME. Interestingly, AME demonstrated both antiproliferative and cytotoxic activity which implies its broad range of possible pharmaceutical applications. Further exploration of non-cultivated/wild Indonesian macroalgae would be interesting for the discovery of potential natural compounds.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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