ANTIOXIDANT POTENTIAL AND CANCER-SPECIFIC CYTOTOXIC EFFECT OF SELECTED MARINE MICROALGAL EXTRACTS

By

FERDOUS UMME TAMANNA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

February 2023

DEDICATION

To

My Parents
Mohammad Abdul Mabud
Mahinur Nesa

My Husband
Dr. Md Shaharul Islam

My Daughter
Alyana Umaiza

My Sister
Tasnia Ferdous

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman : Associate Professor Zetty Norhana Balia Yusof, PhD
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Microalgae derived metabolites have shown potential biological activities, especially antioxidant and cytotoxicity. Marine microalgae are often considered as a mother lode of antioxidant and antitumor compounds due to their inhabitants in the harsh marine environment. Despite having valuable and novel metabolites, the marine microalgae species are still not thoroughly investigated for their pharmaceutical and nutraceutical importance. Since cancer treatment with synthetic drugs shows adverse effects, it is urgent to search for alternative therapy from this promising marine source. Therefore, this study was focused to investigate the crude extracts of six marine microalgae species, Chlorella sp., Tetraselmis sp., Nannochloropsis sp., Isochrysis sp., Chaetoceros sp., and Thalassiosira sp., isolated from Malaysian coastal region in terms of their antioxidant activity and cytotoxicity against human breast cancer cells, MCF-7. These six marine microalgae are considered safe for human and animal usage as well as frequently used as fish feed and dietary supplements. Moreover, microalgae need shorter time, less nutrient and no arable land to grow. These microalgal species were collected and identified based on morphological and molecular characteristics. A total of forty-eight crude extracts from six marine microalgae species were prepared using eight different polarity solvents. From the antioxidant assays, methanol and ethyl acetate extract of Tetraselmis sp. exhibited significantly higher ($p<0.05$) antioxidant activities, revealed through DPPH (54.41 ± 1.18 mg Trolox Equivalent Antioxidant Capacity or TEAC/g extract) and ABTS (41.57±0.83 mg TEAC/g extract) radical scavenging activities, respectively than the rest. Ethyl acetate extract of Tetraselmis sp. also showed high ferric reducing power (113.46±4.83 mg TEAC/g extract). On the other hand, ethanol extract of Isochrysis sp. reduced the viability of human breast cancer, MCF-7 cells to 7.24 ± 0.47% after 72 hours of incubation, at a concentration of 100 µg/ml. The IC50 (half maximal inhibitory concentration) value was 13.37 ± 0.59 µg/ml after 24 hours in MCF-7 cells and >100 µg/ml in non-cancerous human lung fibroblast cells, MRC-5. Ethanol extract of Isochrysis sp. was further investigated for apoptosis induction in MCF-7 cells. With the increasing concentration of the extract, a reduction in MCF-7 cell population was observed. The Annexin V-FITC and propidium iodide staining analysis confirmed that the mode of cell death is mainly apoptosis. Cell cycle analysis revealed the accumulation of cells in the sub-G_0 phase which suggests induction of apoptosis and G_2/M cycle arrest. RT-qPCR analysis revealed an up-regulation of the proapoptotic *Bax* gene and tumor suppressor *p53* gene. Metabolite profiling by Liquid Chromatography/Mass Spectrometry showed the presence of possible metabolites from fatty acid, sphingolipid, carotenoid, and phenolic classes. In conclusion, marine microalgae from indigenous sources have shown antioxidant and cancer-selective cytotoxicity. The data suggest that crude ethanolic extract from marine *Isochrysis* sp. has induced apoptosis and cell cycle arrest in human breast cancer cells, MCF-7, while methanol and ethyl acetate extracts from marine *Tetraselmis* sp. have good radical scavenging and ferric reduction capability. Therefore, indigenous marine *Isochrysis* sp. and *Tetraselmis* sp. may have potential therapeutic value for treating human breast cancer and nutraceutical use, respectively, which needs further investigation along with extensive *in vivo* study.

Keywords: Antioxidant, Apoptosis, Cytotoxicity, Microalgae, MCF-7

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

POTENSI ANTIOKSIDAN DAN KESAN CYTOTOXIC KHUSUS KANSER DARI EKSTRAK MIKROAGAL LAUT TERPILIH

Oleh

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Metabolit terhasil mikroalga telah menunjukkan aktiviti biologi yang berpotensi, terutamanya antioksidan dan sitotoksisiti. Mikroalga marin sering dianggap sebagai induk sebatian antioksidan dan antitumor kerana mendiami persekitaran marin yang keras. Walaupun mempunyai metabolit yang berharga dan baru, spesies mikroalga marin masih belum disiasat secara menyeluruh untuk kepentingan farmaseutikal dan nutraseutikalnya. Oleh kerana rawatan kanser dengan ubat sintetik menunjukkan kesan buruk, adalah mendesak untuk mencari terapi alternatif daripada sumber marin yang menjanjikan ini. Oleh itu, kajian ini difokuskan untuk menyiasat ekstrak mentah enam spesies mikroalga marin, Chlorella sp., Tetraselmis sp., Nannochloropsis sp., Isochrysis sp., Chaetoceros sp., dan Thalassiosira sp., yang diasingkan daripada kawasan pantai Malaysia dari segi aktiviti antioksidan dan sitotoksisiti mereka terhadap sel kanser payudara manusia, MCF-7. Enam mikroalga marin ini dianggap selamat untuk kegunaan manusia dan haiwan serta kerap digunakan sebagai makanan ikan dan makanan tambahan. Selain itu, mikroalga memerlukan masa yang lebih singkat, kurang nutrien dan tiada tanah yang boleh ditanam untuk tumbuh. Spesies mikroalga dikumpul dan dikenal pasti berdasarkan ciri-ciri morfologi dan molekul. Sebanyak empat puluh lapan ekstrak mentah daripada enam spesies mikroalga marin telah disediakan menggunakan lapan pelarut dengan kekutuban yang berbeza. Ekstrak-ekstrak mentah ini didedahkan kepada ujian antioksidan dan ujian kesitotoksikan kepekatan tunggal. Daripada ujian antioksidan, ektrak metanol dan ekstrak etil asetat Tetraselmis sp. menunjukkan aktiviti antioksidan yang jauh lebih tinggi ($p<0.05$), yang didedahkan melalui aktiviti penghapusan radikal DPPH (54.41 ± 1.18 mg TEAC/g) dan ABTS (41.57±0.83 mg ekstrak TEAC/g) daripada yang lain. Ekstrak etil asetat Tetraselmis sp. juga menunjukkan kuasa penurunan ferik yang tinggi (113.46±4.83 mg TEAC/g ekstrak) yang didedahkan melalui ujian FRAP. Ujian MTT kepekatan tunggal mendedahkan bahawa ekstrak etanol Isochrysis sp. mengurangkan kebolehhidupan kanser payudara manusia, sel

MCF-7 kepada 7.24 ± 0.47% selepas 72 jam pengeraman, pada kepekatan 100 µg/ml. Nilai IC50 (separuh kepekatan perencatan maksimum) ialah 13.37 ± 0.59 µg/ml selepas 24 jam dalam sel MCF-7 dan >100 µg/ml dalam sel bukan kanser fibroblas paru-paru manusia, MRC-5. Ekstrak etanol Isochrysis sp. telah dikaji lebih lanjut untuk induksi apoptosis dalam sel MCF-7. Pemerhatian morfologi di bawah mikroskop cahaya mendedahkan pengecutan sel, pembundaran, pemeluwapan kandungan selular, dan pembleban membran dalam sel MCF-7 yang dirawat berbanding dengan sel yang tidak dirawat. Dengan peningkatan kepekatan ekstrak, pengurangan populasi sel juga diperhatikan. Analisis pewarnaan Annexin V-FITC dan PI mengesahkan bahawa mod kematian sel yang utama adalah apoptosis. Analisis kitaran sel mendedahkan pengumpulan sel dalam fasa sub-G0 yang mencadangkan induksi apoptosis dan henti kitaran G2/M. Analisis RT-qPCR mendedahkan peningkatan gen Bax proapoptotik dan gen p53 penindas tumor. Pemprofilan metabolit oleh LC/MS menunjukkan kemungkinan kehadiran metabolit daripada asid lemak, sfingolipid, karotenoid, dan kelas fenolik. Kesimpulannya, mikroalga laut dari sumber asli telah menunjukkan antioksidan dan sitotoksisitas selektif barah. Data menunjukkan bahawa ekstrak etanol kasar dari Isochrysis sp laut. telah menyebabkan apoptosis dan penangkapan kitaran sel pada sel barah payudara manusia, MCF-7, sementara ekstrak metanol dan etil asetat dari Tetraselmis sp laut. mempunyai keupayaan penyingkiran radikal dan pengurangan ferrik yang baik. Oleh itu, Isochrysis sp. laut asli dan Tetraselmis sp. mungkin mempunyai nilai terapi yang berpotensi untuk merawat barah payudara manusia dan penggunaan nutraceutical, yang memerlukan penyelidikan lebih lanjut bersama.

Kata kunci Antioksidan, Apoptosis, Sitotoksisiti, Mikroalga, MCF-7

ACKNOWLEDGEMENTS

In the name of Allah, the Most Gracious and the Most Merciful

All praise to Allah SWT and peace be upon our prophet Muhammad (SAW). Praise Allah for granting me the strength and blessing to pursue and successfully complete this study.

I would like to express my sincere gratitude and appreciation to my supervisor Assoc. Prof. Dr. Zetty Norhana Balia Yusof for her continuous support throughout the study with her guidance, patience, motivation and immense knowledge. I would like to thank my co-supervisors, Prof. Dr. Khozirah Shaari and Dr. Saila Ismail for their insightful comments, suggestions, and unwavering support. My sincerest appreciation to my co-supervisor Dr. Armania Nurdin for her regular guidance, technical support, encouragement, hand-on training and intelligent counseling.

My heartfelt thanks go to all the staff of the Institute of Bioscience, all the research officers of AquaHealth lab, especially Muhammad Farhan Nazarudin and Dr Farah, and also to all the staff of the Faculty of Biotechnology and Biomolecular Science for their support and kindness. I wish to extend my appreciation to my all colleagues and friends who had supported me technically and morally, especially Aisamuddin Ardi Zainal Abidin, Reem A. Dawood, Nor Izzati Husna Noor Hisham, Nur Farhah Nabihan Ismail, Nur Asna Faiqah Johari, Nur Aininie Yusoh, Gan Yian Chee, Tan Hui Teng, Yam Sim Khaw, Nur Amirah Izyan Noor Mazli, Muhammad Raznisyafiq Razak, Chin Yong Kit, Yan Shan, Munirah Adibah, Leen, Ashikin Afzan and all friends from the virology lab, Biotech2.

I would like to acknowledge and thank the Islamic Development Bank (IsDB) for the financial support to carry out my PhD smoothly.

I would like to express my sincerest gratitude to my parents, my father-in-law and my younger sister for their prayers, love and emotional support. I am truly indebted to my husband, Dr. Md. Shaharul Islam for his untiring support, continuous encouragement and understanding. This accomplishment would not have been possible without his support and sacrifice.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by Members of the Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

ABTS	2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid
Abs	Absorbance
ANOVA	Analysis of variance
ATCC	American type culture collection
Bax	BCL2 Associated X protein
BLAST	Basic Local Alignment Tool
CAT	Catalase
CO_2	Carbon dioxide
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
EDTA	Ethylene diamine tetra-acetic acid
FBS	Fetal bovine serum
F-C	Folin-Ciocalteu
FC	Flow cytometry
FITC	Fluorescein isothiocyanate
FRAP	Ferric reducing antioxidant power
g	Gram
GAE	Gallic acid equivalents
GPx	Glutathione peroxidase
HCl	Hydrochloric acid
I-AQUAS	International Institute of Aquaculture and Aquatic Science
kg	Kilogram
LC-MS	Liquid chromatography-mass spectrometry

mg	Milligram
ml	Milliliter
mM	Milimolar
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
nm	Nanometer
OD	Optical density
MCF-7	Michigan Cancer Foundation-7
MRC-5	Medical Research Council cell strain 5
p	Significance difference
p53	Tumor protein
PCR	Polymerase chain reaction
PI	*Propidium iodide*
PMS	Premenstrual syndrome
PS	Phosphatidylserine
QE	Quercetin equivalents
r	Pearson correlation coefficient
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute Medium
SDS	Sodium dodecyl sulfate
SEM	Standard error mean
SOD	Superoxide dismutase
SPSS	Statistical package for the social sciences
TAP	Tris-acetate-phosphate
TEAC	Trolox equivalents antioxidant capacity
TFC	Total Flavonoid Content
TPC	Total Phenolic Content

T_r	Retention time
UV	Ultraviolet
v/v	Volume per volume
w/v	Weight per volume
w/w	Weight per weight
µg	Microgram
µl	Microliter
µM	Micromolar

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Marine organisms reside in a salty aqueous environment that covers 71% of the earth's surface and accounts for 90% of the earth's biosphere (Wang et al., 2020). This is a gigantic reservoir for diversified marine species, with approximately 2500,000 species so far (Khalifa et al., 2019). The marine environment is defined as a harsh and unfavorable domain where scarcity of light, nutrients, high pH, pressure, and continuous encountering of predators make the marine flora tackle this situation with adaptive and symbiotic mechanisms. Their survival strategy, which includes defense against predators, finding a mate, or beating competitors, helps them to produce a broad range of secondary metabolites (Wang et al., 2020). These secondary metabolites from marine organisms are now exploited to design life-saving drugs and drug leads.

An array of natural products, that have pharmaceutical importance, are being offered by marine organisms which can be exploited to treat human diseases, especially cancer. The marine environment represents huge biodiversity with 36 phyla, and it is anticipated that huge taxonomic diversity is related to the broad chemical diversity of these natural products. These diversified marine natural products are assumed to have high bioactivity, especially cytotoxicity, and could be a potential source of anticancer drug candidates. But these colossal reservoirs of natural products are still largely unexplored. Only 18% of marine natural products are discovered so far compared to terrestrial products (Ruiz-Torres et al., 2017). Different medicinal plants, like garlic, ginger, turmeric, black cohosh, burdock, sumac, sundew, and citrus-based plants, showed anticancer activities against breast cancer cell lines, MCF-7, MDA-MB-231 and T47B (Shrihastini et al., 2021). Metabolites isolated from marine invertebrates and seaweed showed cytotoxicity against MCF-7 and MDA-MB-231 cell lines (Veríssimo et al., 2021). Currently, a total of 12 marine-derived cancer drugs, are available on the market but only two of them are for breast cancer treatment and another 23 compounds from the marine organisms are in different phases of cancer clinical trials (https://www.marinepharmacology.org/, accessed on 27 September 2022). Most of these drugs, such as Cytarabine, Vidarabine, Eribulin Mesylate, are extracted from marine invertebrates. A major challenge is associated with cultivating these invertebrates for a sustainable supply of the drug leads. Moreover, some of the marine-derived drugs were suspended from clinical trials or withdrawn from the market due to toxicity (Saeed et al., 2021). Therefore, a search for a safe, sustainable, and less toxic source of marine-derived anticancer agents is warranted.

Marine microalgae are accounted for a major portion of oceanic biomass. Microalgae, both eukaryotic and cyanobacteria, comprise more than 30,000 species and contribute up to 40% of global productivity (Sithranga Boopathy &

Kathiresan, 2010). They contain a wide range of phytochemicals like carotenoids, phenolics, flavonoids, fatty acids, alkaloids, polysaccharides, and vitamins. These phytochemicals make them attractive sources of bioactive compounds that are frequently used in the pharmaceutical, cosmetic, aquaculture, and energy-related industry (Sansone & Brunet, 2019; Abd El-Hack et al., 2019). Microalgae are known to produce different anticancer compounds like, polyunsaturated aldehydes, fucoxanthin, violaxanthin, stigmasterol, eicosapentaenoic Acid (EPA), nonyl 8-acetoxy-6-methyloctanoate, monogalactosyl glycerols and polysaccharides (Martínez Andrade et al., 2018).

Microalgae can withstand all environmental extremities, from cold to hydrothermal vents. On a lab-scale or industrial scale, they can be grown all year-round irrespective of any seasonal variation, which also excludes the need for long-term storage and helps to avoid valuable phytochemical degradation. They can be grown with a limited nutritional supply and the advantageous point is that microalgae can be grown in wastewater as a nutrient source, which in turn, reduces carbon footprint and water usage (Gong & Bassi, 2016). Not only that, microalgae can be grown in large photo bioreactors without competing with arable land and disturbing the human food chain (Rajkumar et al., 2014). Moreover, microalgae can grow faster than terrestrial plants. Their fast replicability, easy cultivation, ecological sustainability and wide adaption capability make them an alternative for the production of high-value products. They are important in terms of drug discovery due to their metabolic plasticity. They can produce pharmaceutically important phytochemicals, especially anticancer compounds (Martínez Andrade et al., 2018). Due to the presence of antioxidants, microalgal biomass is used popularly as dietary supplements and also as food additives (Sansone & Brunet, 2019). Hamidi et al., (2020) mentioned that marine microalgae may produce more carotenoids and EPA than marine bacteria.

Prokaryotic microalgae, cyanobacteria, has long been explored for its antitumor activity against different cancer cells. Compounds like Hantupeptin A, Malyngamide, Pitipeptolides from cyanobacteria, *Lyngbya* sp. showed anticancer activity against breast cancer cells, MDA-MB-231 and MCF-7. Ankaraholide A from *Geitlerinema* sp., coibamide A from *Leptolyngbya* sp. exhibited anticancer activity against MDA-MB-231 cells. One of the most studied cyanobacterila species *Symploca* sp. VP642 produce peptide called dolastatins which has shown anticancer effect on MCF-7 cells (Qamar et al., 2021). Some of the cyanobacterial phytochemicals are now in the clinical trial, as a conjugate with other drugs. Cyanobacterial species, *Symploca* sp. and *Caldora penicillata* have successfully ended up with a few drugs, mainly anti-cancer (Zuo & Kwok, 2021). But a significant challenge exists in cultivating the pure culture of these microalgae since they are in a symbiotic relationship with invertebrate host. Moreover, some of the drugs from *C. penicillata,* which were in clinical trials, have been discontinued due to toxicity (Saeed et al., 2021). Therefore, edible, less toxic and cultivable microalgal species should be prioritized for a sustainable and safe source of pharmaceutically important compounds.

Eukaryotic microalgae have been known for their low toxicity. For instance, *Chlorella* sp. is considered as generally recognized as safe (GRAS) which is approved by the U.S. Food and Drug Administration (FDA). No toxin is found from the microalgae species like, *Isochrysis* sp., *Nannochloropsis* sp., *Tetraselmis* sp., and *Thalassiosira* sp. and these microalgae including *Chaetoceros* sp. are now frequently used in aquaculture industries as fish feed (Lucakova et al., 2022). Moreover, green eukaryotic microalgae, *Chlorella* sp., *Nannochloropsis* sp., *Tetraselmis* sp. are now used as commercial food supplement, while brown microalgae *Isochrysis* sp. is used as food additive (Yasir et al., 2022). These eukaryotic microalgae are considered prolific sources of various bioactive compounds like carotenoids, polyphenols, sulfated polysaccharides, fatty acids, minerals, and peptides but extensive bio-prospection from eukaryotic marine microalgae is warranted. Therefore, all these six microalgae from marine sources need thorough investigation for their bioactive properties (Lauritano et al., 2016; Ferdous & Yusof, 2021c).

1.2 Problem Statement

Cancer is one of the leading causes of mortality worldwide. Breast cancer is the most common cancer type in the world and also in Malaysia**.** This is the second most common cause of cancer-related death in Malaysia (Sung et al., 2021; WHO, 2021). Though early diagnosis can reduce the mortality rate, severe side effects from the treatment and multidrug resistance make this disease a major health complication and engender the need for searching for novel anti-cancer biomolecules from natural sources, as more than 60% of clinically useful anticancer drugs were developed thus (Li et al., 2017; Cragg et al., 2009).

Marine eukaryotic microalgae are an excellent source of valuable bioactive compounds which may have antioxidant and anticancer properties (Martínez Andrade et al., 2018). Indigenous eukaryotic marine microalgae species, *Isochrysis galbana* and *Chaetoceros calcitrans,* isolated from Malaysian coastal areas have shown good fatty acids profile (Natrah et al., 2007; Bustamam et al., 2021; Azizan et al., 2020). Total phenolic content and high antioxidant activities were reported for indigenous marine *Tetraselmis tetrathele*, *Nannochloropsis* sp. and *Chaetoceros calcitrans* (Farahin et al., 2016; Foo et al., 2015; Goh et al., 2010). Phang et al., (2015) reported that the Port Dickson region in Malaysia showed the presence of diversified marine microalgal species which may be attributed to the suitable salinity (32-34 ppt) and pH range (6.88-7.49) and solar irradiance of this region. Hossain et al., (2020) also highlighted the suitability of Malaysian weather and location for microalgal growth in terms of nutrient availability, solar irradiance, salinity and temperature. However, these microalgae remain unexplored vastly in terms of their bioactivities. Therefore, this study aims to investigate the antioxidant and cytotoxic activities of the crude extracts from marine indigenous eukaryotic microalgae, *Chlorella* sp., *Tetraselmis* sp., *Isochrysis* sp., *Nannochloropsis* sp., *Chaetoceros* sp.*,* and *Thalassiosira* sp. and to demonstrate their cell killing mechanism in human breast cancer cell line, MCF-7.

1.3 Hypothesis

a. Marine microalgal extracts from different solvents with different polarities show antioxidant activity, especially radical scavenging activity and ferric reduction capability. There is a correlation between antioxidant activity and total phenolic or flavonoid content of the microalgal extracts.

b. Microalgal extracts are cytotoxic to MCF-7 cancer cell line but show less toxicity towards non-cancerous MRC-5 cell line. The most potential cytotoxic extract induces apoptosis while upregulating apoptosis related genes, *Bax* and *p53* and arrests cell cycle in MCF-7 cells.

c. Microalgal extract contains several phytochemicals like, fatty acids, carotenoids, lipoids, and polyphenols which are attributed to their antioxidant and cytotoxic properties.

1.4 Objectives

1.4.1 Main objective

To study the antioxidant activity of the extracts from six indigenous marine microalgae (*Chlorella* sp., *Tetraselmis* sp., *Isochrysis* sp., *Nannochloropsis* sp., *Chaetoceros* sp., and *Thalassiosira* sp.) and their cytotoxic activity on human breast cancer cell line, MCF-7.

1.4.2 Specific Objectives

1. To identify the morphological and molecular characteristics of six marine microalgae including *Chlorella* sp., *Isochrysis* sp., *Nannochloropsis* sp., *Tetraselmis* sp., *Chaetoceros* sp. and *Thalassiosira* sp.
2. To compare the antioxidant activity, total phenolic and flavonoid contents of different solvent extracts of the marine microalgae.
3. To evaluate the cytotoxic effects, the mechanism of cell death, cell cycle analysis, the expression level of apoptosis-related genes, *Bax* and *p53*, of the selected microalgal extract on human breast cancer cell line (MCF-7)
4. To identify the potential compounds responsible for the cytotoxic activity of the selected microalgae extract using liquid chromatography-mass spectrometry

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