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Marine Algae Extract Effects on Cell Proliferation in a Malignant Melanoma Cell Line and an Immortalized Fibroblast Cell Line

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Abstract

Microalgae are currently used as an important source of valuable natural biologically active molecules in cancer research. The effect of the fractions of Gracilaria salicornia, Padina boergesenii, and Polycladia myrica was evaluated on human melanoma. Cell proliferation and viability were assessed in human malignant melanoma cell lines (A375) and immortalized human foreskin fibroblast (Hu02-KP) through applying ELISA and MTT assays. Seaweed samples were collected from the Persian Gulf (55' 57˚E and 26' 56˚N) at the intertidal zone of Qeshm island coast, Iran. The samples were extracted with EtOH from fresh algae and separated on a chromatography column. A total of 14 fractions were extracted, G. salicornia (G1, G2, G3), P. myrica (F1, F2, F3, F4), and P. boergoseni (P1, P2, P3, P4). 22 components were detected in the fractions by GC-MS. The survival of all fractions (after completely removing EtOH from fractions) was assayed on A375 and Hu02-KP cell lines. The survival of melanoma cell A375 was determined 41-58% in the fraction of G3, G. salicornia, although no significant toxicity was observed on fibroblast Hu02-KP. Furthermore, the fraction P3 of P. boergesenii had more than 85% mortality in melanoma cell line A375 and no significant toxicity was observed on fibroblast Hu02-KP. Finally, 1, 2-benzenedicarboxylic acid, diisooctyl ester and hexadecanoic acid, methyl ester was respectively detected as the most abundant components in P. boergoseni and G. salicornia. In conclusion, Algae have the potential to extract complex substances that may be beneficial in healthcare; however, additional research is needed to confirm the efficacy and safety of algae-derived compounds for cancer treatment.

Keywords: Algae, Anticancer, Melanoma cell, Foreskin fibroblast, Phthalic acid.

Introduction

The diversity of chemicals produced by marine organisms has stimulated exploration of their potential as sources of useful chemicals for a variety of purposes (Ramezanpour et al., 2021). Here we report the effects of extracts of three Persian Gulf Seaweeds,

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Gracilaria salicornia (C. Agardh) E. Y. Dawson, Padina boergesenii Allender & Kraft, and Polycladia myrica (S.G. Gmelin) Draisma, Ballesteros, F. Rousseau & T. Thibaut on proliferation of malignant and non-malignant human cell lines.

Research into the effects of natural compounds on skin cancer treatment has increasingly highlighted the potential of algae extracts. Rich in bioactive compounds such as polyphenols, carotenoids, and vitamins, algae possess antioxidant, anti-inflammatory, and anti-cancer properties. The characteristics of algae extracts position them as a promising field of research for both the prevention and treatment of cancer. (Kim et al., 2018; Xin et al., 2023).

Various studies suggest that algae extracts may promote apoptosis in cancerous cells, inhibit tumor growth (Begum and Hemalatha, 2020), and protect healthy skin cells from ultraviolet (UV) radiation damage. With the rising rates of skin cancer globally, exploring marine-derived solutions like algae extracts could lead to innovative therapeutic approaches and enhance our understanding of skin cancer biology (Álvarez-Gómez et al., 2019).

The antioxidant properties of marine algae help reduce skin damage and may inhibit cancer progression (Teas and Irhimeh, 2017). Algal extracts have been identified as potential sources of chemopreventive agents against skin cancer, with specific extracts demonstrating preventive effects and mechanisms of action (Maher et al 2016).

Algae could be effective against melanoma due to their high antioxidant content, which neutralizes free radicals involved in cancer development. Several studies indicate that extracts from specific algae can inhibit the proliferation of melanoma cells. For example, phycocyanin from blue-green algae (spirulina) and other bioactive molecules have shown cytotoxic effects against melanoma cell lines. Some algae extracts promote programmed cell death (apoptosis) in melanoma cells. This process is crucial in cancer treatment, as encouraging cancer cells to undergo apoptosis can reduce tumor growth. Research suggests that specific compounds from algae can activate pathways that trigger apoptosis in melanoma cells (Begum and Hemalatha, 2020). Inflammation is a known factor in cancer progression, including melanoma. Algal extracts often exhibit anti-inflammatory properties, potentially reducing the processes that contribute to melanoma development (Simpi et al., 2013). Certain algae contain UV-absorbing compounds that may protect the skin from UV radiation, a significant risk factor for melanoma. These compounds may help prevent the onset of melanoma by providing a barrier against UV damage (Vega et al., 2020). Some studies suggest that algae can enhance immune responses through the modulation of cytokines (Álvarez-Gómez et al., 2019) and immune cells, allowing the immune system to recognize and eliminate melanoma cells more effectively (Teas and Irhimeh, 2017). Algae extracts may be formulated into topical treatments aimed at preventing or treating melanoma, providing a natural approach to skin cancer therapy (Wani et al., 2023). Incorporating algal compounds into traditional melanoma treatments could enhance efficacy and reduce side effects, although

further clinical trials are needed to evaluate their effectiveness fully.

Overall, research on algae and melanoma is still developing, but early findings indicate that algae extracts have promising anticancer properties. Their antioxidant, anti-inflammatory, and apoptosis-inducing abilities, along with potential photoprotection, make them an exciting avenue for further investigation in melanoma treatment and prevention.

Material and methods

Extractions have done by methanol as solvent. Because is good to extract a wide range of compounds from non-polar to water soluble.

Sampling

G. salicornia, *P. boergesenii*, and *P. myrica* (formerly *Cystoseira myrica*) were gathered from the intertidal zone of Qeshm Island (26°56˚'N, 55°57˚'E) in the Persian Gulf, Iran. Immediately after collection, they were washed with seawater to remove epiphytes, rinsed with cold water, and transferred to an ice box to the laboratory. There were frozen in liquid nitrogen, freeze-dried, and stored in labeled plastic tubes at −19°C until extraction in the laboratory. *G. salicornia* and *P. boergesenii* were identified and recorded in NCBI GenBank KJ801830.1. *P. myrica* was determined by Michael Wynne.

Extract preparation

For each sample, 10 g of algal tissue wet weight (ww) was extracted four times with 100 mL of methanol using a Soxhlet extractor. Then, the extract was filtered through a 0.2 μm Whatman GF/C filter. Finally, All Extractions have been lyophilized in order to remove organic solvents. Powder obtained and followed by weighing and storing at −19°C for further use.

2.3. Isolation of Major compounds of extracts by column chromatography

The residue of powder extract obtained of *G. salicornia, P. boergesenii* and *P. myrica* was separately mixed with a pinch of silica gel and then subjected to different silica gel 60 (0.063-0.200 mm) column chromatography and eluted in sequence with 20 mL of each composition of hexane: chloroform (6:12), hexane: chloroform: acetone (4:6:12) and finally more polar compounds were separated with hexane: methanol (4:12). Finally for *G. salicornia*, three major fractions (G1-G3), for *P. boergesenii* four fractions (P1-P4) and also for *P. myrica* four fraction were obtained (F1-F4). Again, each extraction (fraction) has been lyophilized in order to remove organic solvents.

Chemical composition determination through applying gas chromatography–mass spectrometry (GC-MS)

An Agilent 5975c mass selective detector was used in the present study. Additionally, an ion source temperature of 300°C and electron energy of 70 eV were used to acquire an electron ionization mass spectrum. The gas chromatograph was equipped with a HP-5MS capillary column and helium carrier gas at the rate of 3 mL min^{-1}. In ethanol extract analysis, the oven temperature program was initially set at 50°C and maintained for 2 min, followed by a steady climb to 120°C for 10 min and an increase to 270°C for 5 min. GC-MS analysis was performed in triplicate.

NMR

The ^{1}H NMR spectra were obtained on a Bruker Avance 500 spectrometer. $CDCl_3$ was used as solvent.

Effect of the extract components on the cell proliferation of human malignant melanoma cell line (A375) and immortalized human foreskin fibroblast cells (Hu02-KP)

Melanoma cell line (A375) and human foreskin fibroblast cells (Hu02-KP) were cultured in complete medium containing 10% FBS. The cells were seeded in a 96-well plate (5×10^3 cells per well), cultured, and incubated at 37 **°C overnight.**

Following the incubation, various concentrations of the algae extracts were introduced to the A375 and Hu02-KP cells. The cells were stored under identical conditions for 24 and 48 hours. Subsequently, MTT solution (at a final concentration 5 mg. mL^{-1}) was added to each well, and the plate was incubated at 37˚C. The controls group included 100 **µL** of the medium and 10 **µL** of MTT color, which were set for negative control and other wells containing total medium and 2% of DMSO substance were set as positive control of the test. Well absorption, including samples, negative control, and positive control, was read by a spectrophotometer at 570 nm. All test is repeated 3 times.

Results

The bioactive methanol extracts of *G. salicornia*, *P. boergesenii*, and *P. myrica* were fractionated by polar compounds elution. A total of 22 bioactive compounds were obtained from the peaks of fractions by GC-MS analysis (Table 1). Based on the results, the cell toxicity of the fractions of *G. salicornia* (G1, G2, and G3) exhibited a minimum cell survival of 19% at 15 mg mL^{-1} concentration on fibroblasts after 24 h, as well as a maximum at 1 mg.mL^{-1} concentration. However, the cell survival of G1 and G2 fractions showed no significant difference in fibroblasts and melanoma cell lines. Further, G3 showed no significant difference on melanoma and fibroblast cells except at concentrations of 0.5-2.5 mg mL^{-1}, it was not observed to be the same as in fibroblast cells with significant mortality, but in melanoma cells the survival was 41-58% (Figure 1).

Four distinct fractions, labeled P1, P2, P3, and P4, were isolated from *P. boergesenii*, each exhibiting a different color, as illustrated in Figure 2.

Significant difference was observed in the impact of fractions P1, P2, P3, and P4 at the sameconcentrations on melanoma cells A375 and Hu-02 fibroblasts. Significant results were obtained for the effect of fraction P3 after 24 and 48 h so that the 2.5 mg. mL^{-1} concentration of P3 led to the highest inhibition of A375 melanoma cells (>85%) and Hu-02 fibroblast cells (88%). In contrast, fraction P2 demonstrated an average inhibition of approximately 55% for A375 melanoma cells and around 88% for Hu-02 fibroblasts. Ultimately, the impacts associated with the various fractions of *P. myrica* (F1, F2, F3, and F4) did not show any significant differences in their effects on melanoma cells and fibroblasts
(Figure 3).

^{1}H NMR *spectra analysis*

The ^{1}H NMR spectrum was recorded for the two fractions isolated from the chromatog-

Table 1. GC-Mass analysis of major fractions of methanol extract of *Polycladia myrica*, *Gracilaria salicornia* and *Padina boergesenii* separated by column chromatography

Compound	*P. boergesenii*				*G. salicornia*			*P. myrica*			
	P1	P2	P3	P4	G1	G2	G3	F1	F2	F3	F4
Cyclopentasiloxane, decamethyl-											3.73
Dianhydromannitol							3.05				
1-(3,6,6-Trimethyl-1,6,7,7a-tetrahydrocyclopenta[c]pyran-1-yl)ethanone						2.77					
1,4-Benzenedicarboxylic acid, dimethyl ester			1.95	0.96				3.53	7.88	4.97	
Hexadecane											2.44
Cyclododecene, 1-methyl-							2.37				
Methyl tetradecanoate		2.60			4.25	5.01	7.41	4.59	6.34	7.70	3.01
Tridecanoic acid, 12-methyl-, methyl ester			1.25								
Octadecane											2.65
Bicyclo[3.1.1]heptane, 2,6,6-trimethyl-, [1R-(1.alpha.,2.beta.,5.alpha.)]- (PINANE)						7.67	5.47				
2-Pentadecanone, 6,10,14-trimethyl-					4.89		5.02	5.72	5.27	4.10	3.03
1,2-Benzenedicarboxylic acid, butyl octyl ester								1.89			
9-Hexadecenoic acid, methyl ester							3.36				

Cyclohexadecane					2.54			1.89			
Hexadecanoic acid, methyl ester	64.31	25.43	10.07	3.33	28.79	35.30	39.23	33.22	53.62	62.62	27.61
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester			0.98								3.35
Ethylhexylmethylphthalate (1,2-Benzenedicarboxylic acid, butyl methyl ester)			1.16	2.10				1.87			
9-Octadecenoic acid, methyl ester	12.08	2.38	1.43			6.43	4.36				
9,12-Octadecadienoic acid, methyl ester		2.63			2.57	2.17	2.80	2.32	3.85	4.99	
Octadecanoic acid, methyl ester	9.08	2.88	2.35	1.08	3.29	2.96		3.45	9.87	5.22	3.75
1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester						2.05	2.88	14.06			13.20
1,2-Benzenedicarboxylic acid, diisooctyl ester		64.07	78.77	92.53	8.78						

raphy column, which had better anticancer activity. Based on the ^{1}H NMR spectrum of the fraction separated from *G. salicornia* in deuterated chloroform, no signal was detected in the 6-9 ppm range assigned to aromatic protons (Figure 4). All peaks appeared at the chemical shift of 0.84-5.1 ppm, which are attributed to aliphatic protons. Additionally, three peaks were observed respectively at 5.11 (broad), 4.85, and 4.18-4.60 ppm (broad) with the peak area of 2, 1, and around 3, which may be related to the protons on the carbon unsaturated bond and/or those adjacent to the electron-withdrawing group. The other peaks emerged at the chemical shift of 2.28 (peak area: 0.2), 2.00 (2, triplet), 1.74-1.84 (1.5, two broad merged ones), 1.53 (0.4), 1.23 (2.8, sharp and tall), and 0.86 (0.6, triplet).

Further, the ^{1}H NMR spectrum of the fraction from *P. boergesenii* (Figure 5) was measured in deuterated chloroform, which ex-

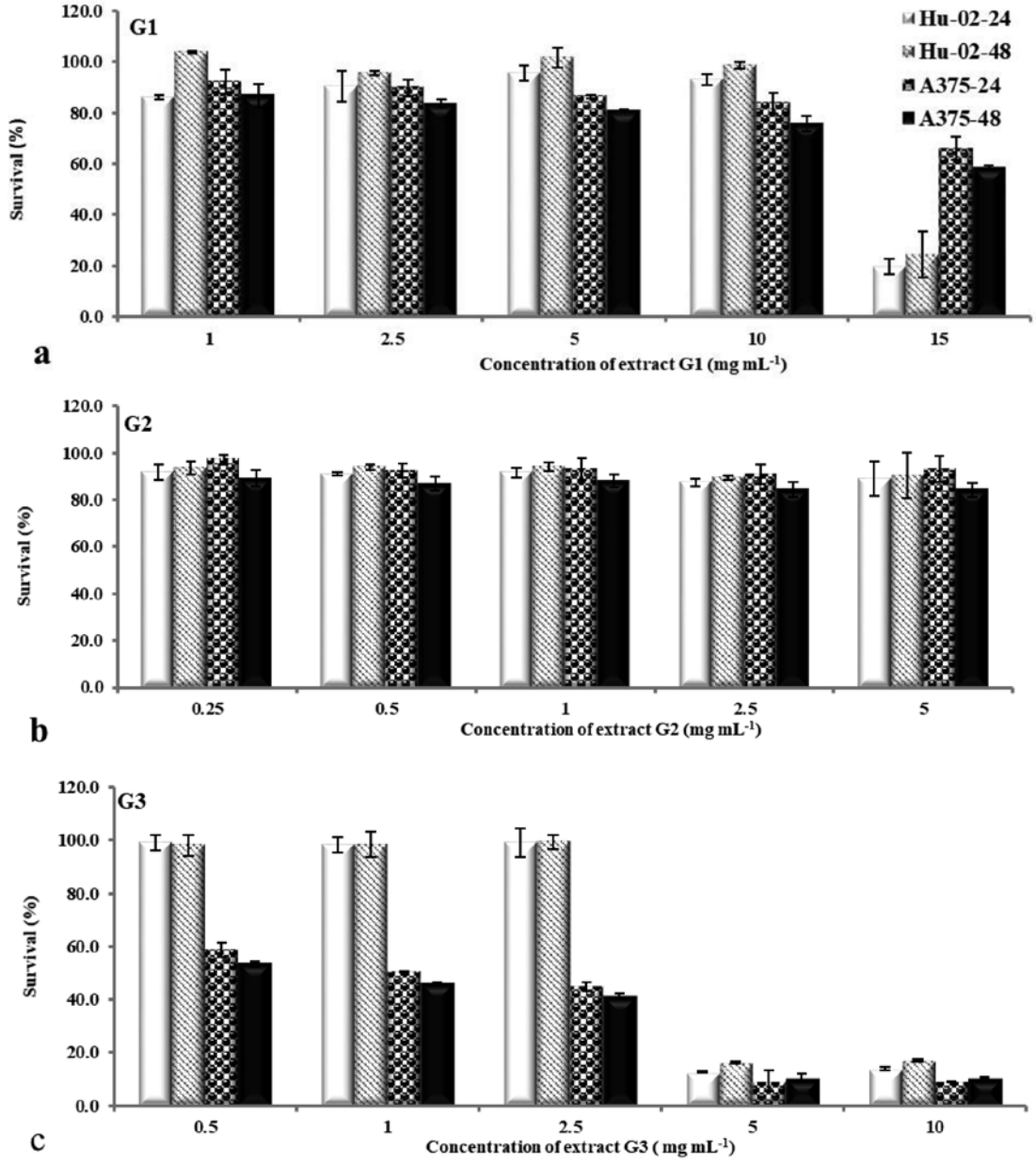

Fig. 1. Survival percentage (Mean ± standard deviation, n=3) of melanoma cells (A375) and healthy skin cells (Hu-02) after 24 and 48 hours of exposure to the material isolated from the chromatographic column from the material extracted from the alga *Gracilaria salicornia* a.G1, b.G2 and c.G3

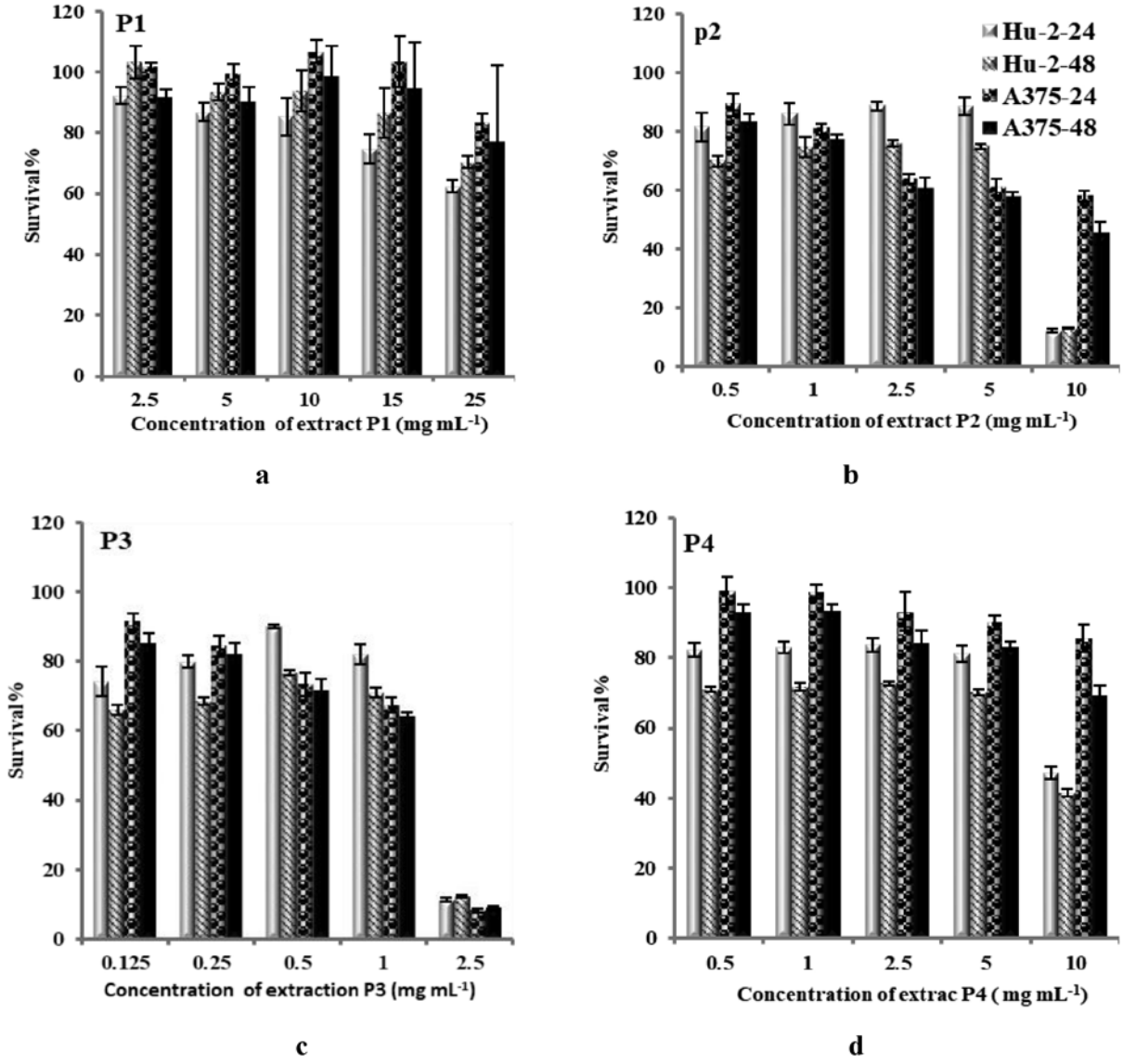

Fig. 2. Survival percentage (Mean ± standard deviation, n=3) of melanoma cells (A375) and healthy skin cells (Hu-02) after 24 and 48 hours of exposure to the material isolated from the chromatographic column from the material extracted from the alga *Padina boergesenii* *a.* P1, b. P2, c. P3 and d. P4

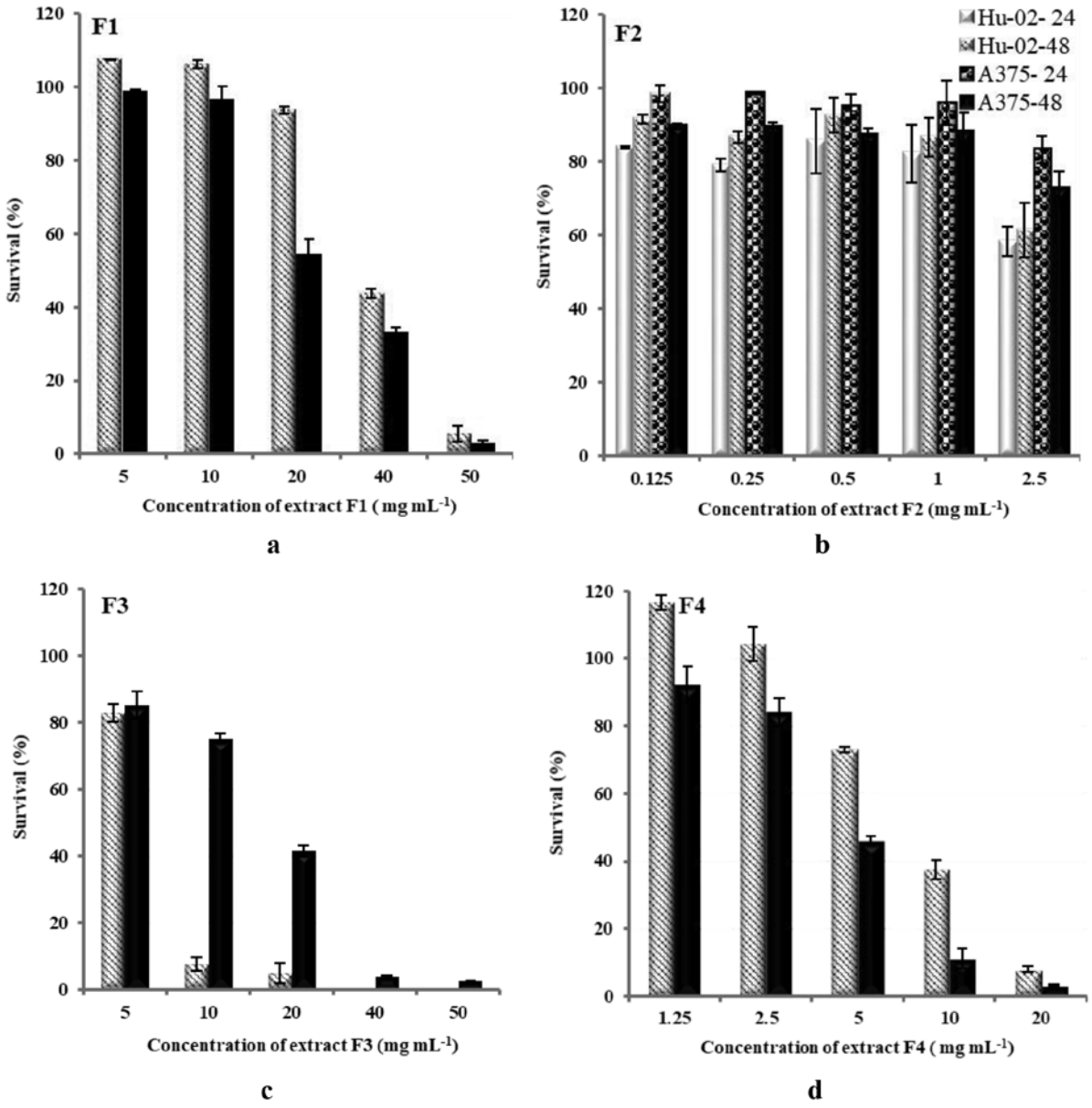

Fig. 3. Survival percentage (Mean ± standard deviation, n=3) of melanoma cells (A375) and healthy skin cells (Hu-02) after 24 and 48 hours of exposure to the material isolated from the chromatographic column from the material extracted from the alga *Polycladia myrica* a. F1, b. F2, c.F3, and F4

hibited no signal corresponding to aromatic protons (6-9 ppm). Furthermore, two broad peaks appeared at 5.13 and 3.99 with the peak area of 13 and 7, respectively. Finally, a sharp and a triplet peak were detected at 1.24 (3) and 0.86 (1), respectively.

Discussion

Many chemicals extracted from marine organisms have different mechanisms of antitumor and cell growth effects (Lichota and Gwozdzinski, 2018). In the present study, methanol was used to maximize the potential for extracting organic components from each sample.

Cancer starts when cells begin to grow out of control. Melanoma is one of the most problematic cancers that starts in certain skin cells (melanocytes) and can develop anywhere on the skin.

Ning and Andl (2013) reported the significant roles of microRNAs in the pathogenesis of some skin cancers, such as squamous cell carcinoma (SCC) and melanoma.

In melanoma, the over expression of *miR-182* promotes survival, migration, and metastasis, repressed by the tumor suppressor FOXO3 and microphthalmia-associated transcription Factor-M, while its expression increases with the development from primary to metastatic melanoma (Segura et al., 2009).

The most active anticancer compounds include the psammaplin isolated from marine microalgae, cyanobacteria, and heterotrophic bacteria (Lichota and Gwozdzinski, 2018). In addition, the alkaloids from marine algae produce anticancer compounds

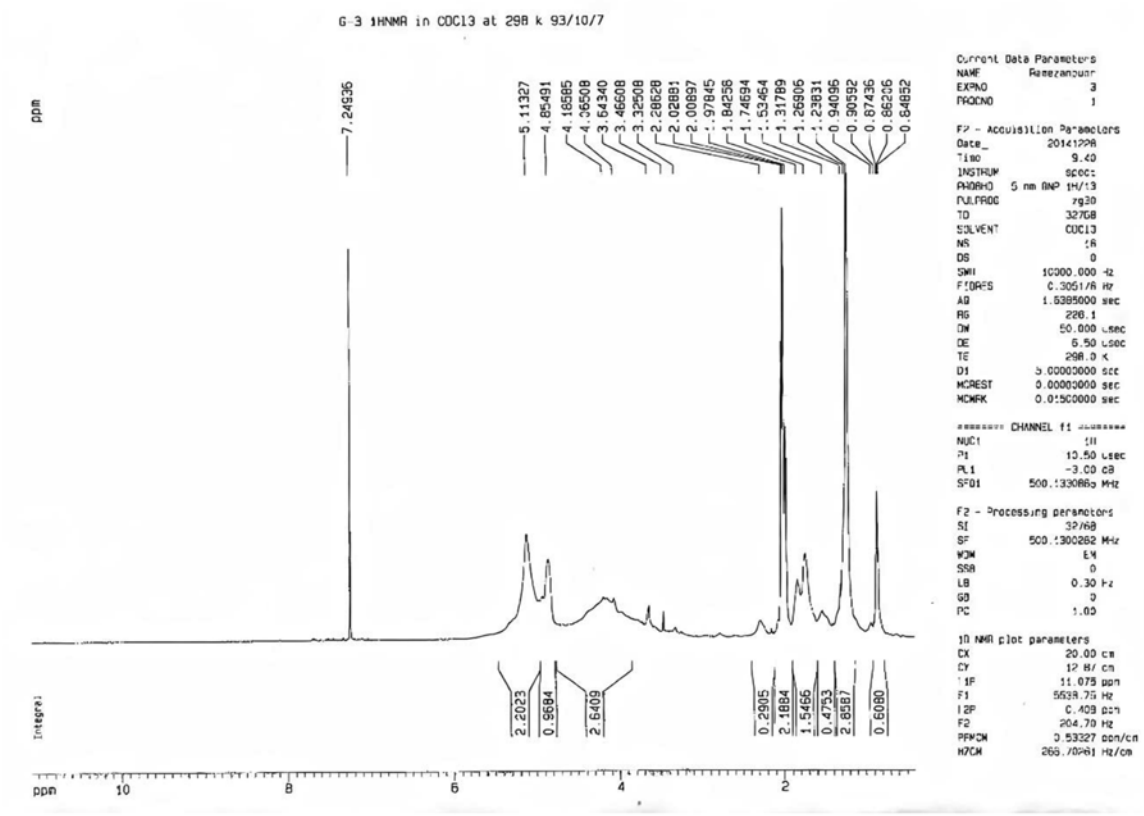

Fig. 4. H-NMR spectrum of the third fraction (G3) of the methanol extract in *Gracilaria salicornia*

(Güven et al., 2010; Tohme et al., 2011). Polyphenols and polysaccharides are extracted from marine flora (Boopathy and Kathiresan, 2010). Further, bryostatins, halichondrins, spongistatin, discodermolide, hemiasterlins, and salinosporamides derived from the marine organism metabolites exhibit cytostatic activity. Some researchers outlined the antiproliferative activity of the 3-Epi-29-hydroxystelliferin E derivative of stelliferin against melanoma cells (MALME-3M) (Meragelman et al., 2001). This compound is an isomalabaricane-type triterpenoid, which is extracted from the sponge *Jaspis stellifera* (McCabe et al., 1982). According to Bergé et al., (2002), the sulfolipid classes (SLs) in the total lipids of *Porphyridium cruentum* (S.F.Gray) Nägeli show inhibitory effects on malignant melanoma (M4 Beu) cancer cells. The sulfolipids in algae were considered to be high in palmitic acid (C16:0) in *Galaxaura cylindrica* (J. Ellis & Solander) J.V. Lamouroux and *Taonia atomaria* (Woodward) J. Agardh. Furthermore, sulfoquinovosyl-di-acylglycerol and sulfoquinovosylacylglycerol (SQAG) have been recognized as the main sulfolipids in algae (El Baz et al., 2013).

The results of our GC-MS analysis demonstrated several important sources of anticancer agents. The compounds were effective in vitro due to their anti-proliferative activities against melanoma and fibroblast cell lines. In addition, 1,4-benzenedicarboxylic acid,1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, diisooctyl ester, ethylhexyl methyl phthalate (1,2-benzenedicarboxylic acid, butyl methyl ester), and butyl octyl ester were found in the fractions from *P. boergeseni* and *P. myrica*. The

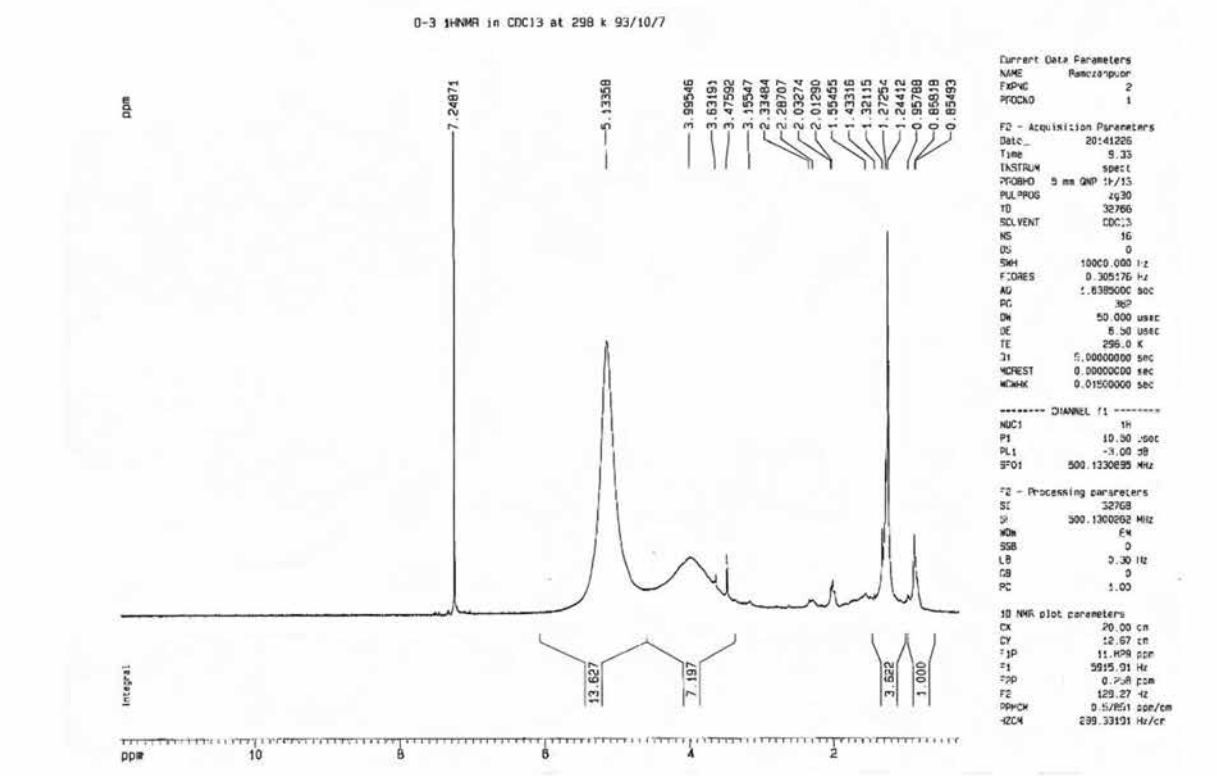

Fig. 5. H-NMR spectrum of the third fraction (P3) of the methanol extract of *Padina boergesenii*

compounds have been reported in many medicinal plants (Save *et al*., 2015; Gnana Priyanka Beulah *et al*., 2018) and in red algae such as *Jania rubens* (L.) Lamouroux, *Corallina mediterranea* J.E. Areschoug and *Pterocladia capillacea* (S.G. Gmelin) Bornet (El-Din, & El-Ahwany, 2016). The presence of 1,2-benzenedicarboxylic acid and diisooctyl ester has been identified in Allium autumnale, which is linked to two human breast cancer cell lines, MDA-MB-231 and MCF-7. (Isbilen et al., 2018). Furthermore, 1,2-benzenedicarboxylic acid showed effectiveness on human prostate, breast, and colon cancers with strong immunomodulatory B-cell stimulation (Save et al., 2015).

Wang and Tao (2009) suggested the antitumor activities of 1, 4-benzenedicarboxylic acid, dimethyl ester, as the volatile component of Stigmatella WXNXJ-B, on mouse melanoma cell lines. According to Kannabiran *et al*. (2014), 1 2-benzenedicarboxylic acid, mono 2-ethylhexyl ester from marine *Streptomyces* sp. VITSJK8 exhibits above 80% the cytotoxic activity on the growth of mouse embryonic fibroblast cancer cell lines and normal human keratinocytes.

The human melanoma cell lines are more resistant to the toxic effect of fatty acids. Cytotoxicity is observed in SK-Mel 23 cells after treatment with arachidonic, linoleic (LA), palmitic, and palmitoleic acids (Andrade et al., 2005). Palmitic acid or hexadecanoic acid is the most common saturated fatty acid in the fractions of *G. salicornia* and *P. myrica*, and the second most common compound in the fractions of *P. boergesenii*.

The identified fractions also included octadecanoic acid methyl ester, 9, 12-octadecadienoic acid methyl ester, and 9-octadecenoic acid methyl ester. Altuner et al. (2018) emphasized the antimicrobial bioactivity of 9,12-octadecadienoic acid. Additionally, 9,12-octadecadienoic acid plays an inhibitory role in the metabolites of cancer metastasis (Horrobin and Ziboh, 1997; Maggiora et al., 2004). Researchers proposed different anticancer activities for 9,12-octadecadienoic acid. At low concentration, it stimulates cell proliferation in the human breast cancer and lung cancer cell lines in vitro, as well as promoting colon and prostate tumorigenesis, and tumor growth in animal models (Xu and Qian, 2014). Horrobin and Ziboh (1997) reported the endogenous conversion of 9, 12-octadecadienoic acid into various downstream ω-6 PUFAs. Thus, the effects of 9, 12-octadecadienoic acid on cancer growth can be related to a combination of the effects of its downstream products.

Lu et al. (2010) showed that the relative resistance of colorectal cancer cell lines to the cytotoxic action of 9, 12-octadecadienoic acid is related to its concentration and a reduction in caspase-3 activation, which induces cancer cell apoptosis. Kachhap et al. (2000) observed a synergistic effect of linoleic acid and endogenous estrogen in a diet rich in ω-6-polyunsaturated fatty acid, which may modulate BRCA1 gene expression, thereby promoting breast cancer.

9-Octadecenoic acid or oleic acid has the potential for antibacterial and antifungal activities (McGraw et al., 2002). Regarding the present study, it was the second most abundant component of *P. boergesenii* (P1) and *G. salicornia* (G2 and G3) although no significant effect was obtained for the frac-

tions P1 of *P. boergesenii* and G3 of *G. salicornia* on melanoma cell lines.

Based on the ^{1}H NMR spectra of the third fraction (P3 and G3) in the methanol extract of *P. boergesenii* and *G. salicornia*, all protons appeared at high field and low chemical shifts, which can be attributed to aliphatic protons rather than aromatic ones. Finally, the compounds detected in the two fractions possessed aliphatic protons and were devoid of any aromatic substitution.

The present research has shown that additional and continued exploration of the diverse chemicals produced by the metabolism of marine algae may continue to result in discovery and identification of new resources of potential benefit to human health and welfare.

Conclusions

Some methanol extracted fractions of *Gracilaria salicornia*, *Padina boergesenii*, and *Polycladia myrica* inhibited proliferation and viability of human malignant melanoma cell lines (A375) and human foreskin fibroblast (Hu02-KP). Fractions G3, *G. salicornia,* and P3 of *P. boergesenii* showed mortality in the melanoma cell line A375, but no significant toxicity was observed in fibroblast Hu02-KP cells. The most abundant components detected in the effective methanol extracts were 1, 2-benzenedicarboxylic acid, diisooctyl ester, and hexadecanoic acid, methyl ester, which were respectively detected as the most abundant components in effective fractions of *P. boergesenii* and *G. salicornia* on A375 cell lines.

Studies have highlighted their antioxidant effects, which contribute to anticancer activities, positioning them as a promising avenue for nutraceutical and pharmaceutical exploration in the fight against cancer. It is important to emphasize that although the research shows potential, additional studies and clinical trials are required to confirm the efficacy and safety of compounds derived from algae in the treatment of cancer.

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