

# Screening for Anti-Cancer Compounds in Marine Organisms in Oman

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## الكشف عن المكونات البيولوجية التي تحتوي عليها الكائنات البحرية والتي تتسم بأنشطة مضادة للسرطان في عمان

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**ABSTRACT: Objectives:** Marine organisms are a rich source of bioactive molecules with potential applications in medicine, biotechnology and industry; however, few bioactive compounds have been isolated from organisms inhabiting the Arabian Gulf and the Gulf of Oman. This study aimed to isolate and screen the anti-cancer activity of compounds and extracts from 40 natural products of marine organisms collected from the Gulf of Oman. **Methods:** This study was carried out between January 2012 and December 2014 at the Sultan Qaboos University, Muscat, Oman. Fungi, bacteria, sponges, algae, soft corals, tunicates, bryozoa, mangrove tree samples and sea cucumbers were collected from seawater at Marina Bandar Al-Rowdha and Bandar Al-Khayran in Oman. Bacteria and fungi were isolated using a marine broth and organisms were extracted with methanol and ethyl acetate. Compounds were identified from spectroscopic data. The anti-cancer activity of the compounds and extracts was tested in a Michigan Cancer Foundation (MCF)-7 cell line breast adenocarcinoma model. **Results:** Eight pure compounds and 32 extracts were investigated. Of these, 22.5% showed strong or medium anti-cancer activity, with malformin A, kuanoniamine D, hymenialdisine and gallic acid showing the greatest activity, as well as the soft coral *Sarcophyton* sp. extract. Treatment of MCF-7 cells at different concentrations of *Sarcophyton* sp. extracts indicated the induction of concentration-dependent cell death. Ultrastructural analysis highlighted the presence of nuclear fragmentation, membrane protrusion, blebbing and chromatic segregation at the nuclear membrane, which are typical characteristics of cell death by *apoptosis* induction. **Conclusion:** Some Omani marine organisms showed high anti-cancer potential. The efficacy, specificity and molecular mechanisms of anti-cancer compounds from Omani marine organisms on various cancer models should be investigated in future *in vitro* and *in vivo* studies.

**Keywords:** Anticancer Agents; Cancer Screening; Breast Cancer; Marine Organisms; Biological Products; Apoptosis; Oman.

**المخلص:** أهداف: تعتبر الكائنات البحرية مصدر غني بالمكونات الحيوية والجزيئات النشطة التي قد تكون لها تطبيقات في الطب والتكنولوجيا الحيوية والصناعة. وقد تم استخراج عدد قليل فقط من المركبات والمكونات الحيوية النشطة. من كائنات بحرية تعيش في منطقة الخليج العربي وبحر عمان. يهدف هذا البحث إلى عزل واستخلاص مركبات طبيعية والتحرري عن النشاط المضاد للسرطان فيها في 40 من المنتجات الطبيعية التي تم جمعها من بحر عمان منهجية: أجريت هذه الدراسة بين يناير 2012 و ديسمبر 2014 في جامعة السلطان قابوس في مسقط/سلطنة عمان. تم جمع الفطريات والبكتيريا والإسفننج والمرجان البحري الناعم والخيار البحري من منطقة مارينا بندر الروضة ومنطقة بند الخيران بسلطنة عمان. عملية عزل البكتيريا والفطريات تمت باستخدام مرق البحر. أما المكونات الحيوية فقد تم استخلاصها بالميثانول والإيثيل أسيتيت وتم تحديدها على أساس البيانات التي تم الحصول عليها بالتحاليل المطيافية. تمت تجربة الأنشطة المضادة للسرطان المتواجدة في الكائنات البحرية على خلايا سرطانية منشقة من الثدي والمعروفة بالنموذج MCF-7. نتائج: عدد 8 مركبات نقية و 32 مستخلصات من الكائنات البحرية قد تم دراستها. أظهرت 22.5% من جميع العينات التي تم فحصها نتائج إيجابية مضادة للسرطان. التجربة على خلايا MCF-7 بكميات مختلفة من مستخلصات كائنات الساركوفايتون *Sarcophyton* تشير إلى أن موت الخلايا السرطانية خاضع إلى الكمية المستعملة من المواد الخاضعة للتجربة. يشير الفحص الدقيق للخلايا الخاضعة للتجربة إلى وجود تجزئة في نواة الخلية، مع بروز على الغشاء وتكوين فقاعات إلى جانب انزعاج الكروماتين عند الغشاء النووي والتي تعتبر من السمات المميزة في حالة موت الخلية المبرمج. خاتمة: تحتوي بعض الكائنات البحرية العمانية على مواد مضادة للسرطان عالية الفعالية. الدراسات المستقبلية ينبغي أن تسلط الضوء على فعالية هذه المواد، وخصوصياتها، والإطلاع على آليات التحكم الجزيئية للمواد مضادة للسرطان من الكائنات البحرية العمانية وذلك باستخدام نماذج سرطانية مختلفة في تجارب معملية وعلى فئران التجارب. كلمات مفتاحية: مواد مكافحة للسرطان؛ فحص السرطان؛ سرطان الثدي؛ الكائنات البحرية؛ المنتجات البيولوجية؛ الموت الخلوي؛ عمان.

### ADVANCES IN KNOWLEDGE

- This is the first study from Oman showing the anti-cancer potential of Omani marine organisms. Very few studies of this kind have been conducted in the Gulf Cooperative Council region.
- The greatest activity against the breast adenocarcinoma model was observed with the malformin A, kuanoniamine D, hymenialdisine and gallic acid compounds as well as the soft coral *Sarcophyton* sp. extract.

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- Ultrastructural analysis and staining of the Michigan Cancer Foundation-7 cell line indicated the role of the apoptotic pathway in triggering cell death.

#### APPLICATION TO PATIENT CARE

- The results of this study indicate possibilities for the development of new treatments for breast adenocarcinomas and other cancers.

THE MARINE ECOSYSTEM COVERS TWO-thirds of the Earth's surface and has diverse environmental conditions, facilitating the specialisation and diversity of marine organisms; as such, these organisms are a rich source of as-yet-untapped bioactive molecules.<sup>1-3</sup> Soft-body sessile marine organisms—such as algae, sponges, soft corals and tunicates—are important sources of bioactive compounds.<sup>4-6</sup> This is due to the fact that sessile organisms often accumulate toxic and repellent compounds in their body, not only to compensate for their lack of mechanical defences and protective structures, but also to protect themselves from predators, pathogens and the accumulation of unwanted material on their surfaces.<sup>7</sup> Few secondary metabolites have yet been isolated from marine organisms and transformed into pharmaceuticals, but it is expected that novel drugs will be isolated from marine organisms in the future.<sup>4,8-11</sup>

Cancer remains one of the major causes of mortality worldwide; unsurprisingly, many research groups are currently focusing on finding novel anti-cancer drugs to enhance chemotherapy treatment and increase survival rates.<sup>12</sup> A significant number of anti-cancer compounds have been isolated from marine organisms but only a few have been approved for treatment, for example the chemotherapy drugs cytosine arabinoside (arabinoside cytosine isolated from the sponge *Cryptotethya crypta*) and eribulin (halichondrin B isolated from the sponge *Halichondria okadaei*) and the anti-tumour drug trabectedin (ecteinascidin isolated from the tunicate *Ecteinascidia turbinata*).<sup>12-14</sup> Bryostatin-1 is a macrolide compound produced by endosymbiotic bacteria of the bryozoan *Bugula neritina* which induces apoptosis at nanomolar concentrations in cancer cells and is enhanced by protein kinase C overexpression; it is currently in phase II clinical trials.<sup>13</sup> Another product, didemnin B, was isolated from the tunicate *Trididemnum solidum* and revealed high activity against myelomas and breast, ovarian, cervical and lung cancers; unfortunately, it was excluded from any further consideration as an anti-cancer agent after it was found to be highly toxic.<sup>7,13</sup>

Data are limited regarding natural products from marine organisms and their application as traditional medications in the Arabian Gulf area, particularly Oman. While the activity of pure anti-cancer com-

pounds isolated from marine organisms has been reported previously, it is possible that new anti-cancer compounds can be isolated from Omani organisms. Several novel natural products have been isolated from *Spatoglossum variabile* and *Dictyota dichotoma* algae gathered from the coast of the Arabian Sea in Karachi, Pakistan, but their pharmaceutical activity has not yet been investigated.<sup>15,16</sup> An antifungal phenolic compound with aromatic unsaturation was produced from the bacterium *Pseudomonas aeruginosa* CMG1055, also isolated from the Arabian Sea coast of Pakistan.<sup>17</sup> *Gelliodes* spp. and *Spheciospongia* spp.1 and spp.2 sponges from the Persian Gulf coast in Bushehr, Iran, were identified as the most active against a panel of bacterial pathogens such as *Bacillus subtilis*, *Staphylococcus aureus*, *P. aeruginosa* and *Escherichia coli*; unfortunately, no bioactive compounds were identified.<sup>18</sup> In a previous study in Oman, researchers screened the anti-microbial, antidiatom and antilarval properties of *Holothuria atra* and *H. edulis* sea cucumbers collected from the Bandar Al-Khayran region; their findings suggested the presence of cytotoxic compounds.<sup>19</sup> To the best of the authors' knowledge, there is no information in the literature about anti-cancer compounds derived from marine organisms in Oman. Therefore, the aim of this study was to screen the anti-cancer activity of natural products and extracts of marine organisms collected from the Gulf of Oman.

## Methods

This study was carried out between January 2012 and December 2014 at the Sultan Qaboos University, Muscat, Oman. A total of 40 natural products were obtained from different species of fungi, bacteria, marine sponges, algae, soft corals, tunicates, bryozoa, mangrove tree samples and sea cucumbers collected from seawater at Marina Bandar Al-Rowdha (23° 34.55' North, 58° 36.27' East) and Bandar Al-Khayran (23° 75' North, 58° 75' East) in Oman.<sup>20</sup>

Bacteria and fungi were isolated from the seawater using a marine broth (Oxoid Ltd., Basingstoke, UK) according to previously described methods.<sup>21</sup> All macroorganisms were freeze-dried and extracted with methanol and ethyl acetate solvents (Sigma-Aldrich Corp., St. Louis, Missouri, USA). For microbes,

cultures were centrifuged at 5,000 g and the bacterial cell pellets and fungi *mycelium* were extracted using the methanol and ethyl acetate solvents. All extracts were filtered using filtration paper (Whatman® grade 1 filtration paper, Sigma-Aldrich Corp.) and the solvents were removed by evaporation under reduced pressure using a rotary evaporator (Büchi Labortechnik AG, Flawil, Switzerland). The extracts were separated and purified using open-air silica for non-polar extracts or C18 columns for polar extracts. High-performance liquid chromatography was performed using a Shimadzu system (Shimadzu Corp., Kyoto, Japan) in order to further purify the fractions. Finally, the structure of pure secondary metabolites was elucidated on the basis of spectroscopic data, including infrared and ultraviolet radiation, high-resolution mass spectrometry and nuclear magnetic resonance spectroscopy. The novelty of the isolated compounds was assessed using the Royal Society of Chemistry MarinLit® database of marine natural products.<sup>22</sup> The dry extracts and pure compounds were then re-dissolved either in dimethyl sulfoxide (DMSO; Sigma-Aldrich Corp.) or methanol.

A breast adenocarcinoma cell line, Michigan Cancer Foundation (MCF)-7 (ATCC® HTB-22™, American Type Culture Collection, Manassas, Virginia, USA), and a control line of human fibroblasts were cultured in Dulbecco's Modified Eagle medium (DMEM; Gibco®, Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA). This was supplemented with 10% fetal bovine serum (FBS) and a 1% antibiotic antimycotic cocktail (Gibco®, Thermo Fisher Scientific Inc.) containing 10,000 units/mL of penicillin, 10,000 µg/mL of streptomycin and 25 µg/mL of amphotericin B. The cells were maintained in a humidified incubator at 37 °C with a 5% carbon dioxide atmosphere. Extracts or solutions of pure compounds (1 µL) were applied to each well of a 96-well plate (Nunc™ MicroWell™ plate, Thermo Fisher Scientific Inc.). The MCF-7 cells or human fibroblasts were then seeded in the 96-well plate at a density of 1,500 cells per well in 100 µL of DMEM supplemented with 10% FBS before being incubated for 24 hours. At the end of the experiment, the cells were observed with an inverted microscope and the status of the cells was determined. The experiment was repeated three times.

Due to its activity and availability, the crude extract of *Sarcophyton* sp. was selected for further analysis to determine the mode of its anti-cancer action. The MCF-7 cells were treated for 24 hours with different concentrations (12.5, 25.0, 50.0, 100.0, 150.0, 200.0, 300.0, 350.0 and 400.0 µg/mL) of the crude extract prepared in DMEM, without phenol red solution or

FBS. Cells treated with DMSO were included as negative controls for each concentration. Cells were seeded in a six-well plate and treated with the determined inhibitory concentration 50% (IC<sub>50</sub>) of *Sarcophyton* sp. extract on attainment of 70–80% confluence. The cells were subsequently stained with Hoechst dye in order to identify the mode of cell death induced by the bioactive extracts of *Sarcophyton* sp. in the MCF-7 breast cancer model. Treated cells were harvested, suspended in 40 µL of Hoechst-formalin solution (ratio: 1:50) and incubated overnight in the dark at 4 °C. Hoechst-stained cells were then mounted on a glass slide and examined under the microscope using the 4',6'-diamidino-2-phenylindole filter (excitation: 350 nm; emission: 461 nm). Cells treated with DMSO were included as a negative control. Following the cell viability assay, electronic microscopy analysis of the treated cells was used to elucidate the mechanism by which the extracts destroyed the cells. The MCF-7 cell lines were visualised using a transmission electron microscope (TEM; JEOL, Peabody, Massachusetts, USA).<sup>23</sup> Briefly, the cell samples were fixed, dehydrated using an alcohol series and embedded in epoxy resin. Ultra-thin sections were obtained using an ultramicrotome and stained with uranyl acetate and Reynolds' lead citrate.

## Results

A total of eight pure compounds and 32 extracts of marine organisms in Oman were investigated, with 22.5% showing strong or medium anti-cancer activity against the MCF-7 cells, including 62.5% of the compounds and 12.5% of the extracts [Table 1]. The greatest anti-cancer activity was observed for malformin A, kuanoniamine D, hymenialdisine and gallic acid compounds, as well as the soft coral *Sarcophyton* sp. extract. Medium activity was observed for the aptamin compound and the bryozoan *Schizoporella unicornis*, gorgonian coral *Acanthogorgia* sp. and sponge *Mycale* sp. extracts. No quantifiable activity on the control human fibroblast cells was detected.

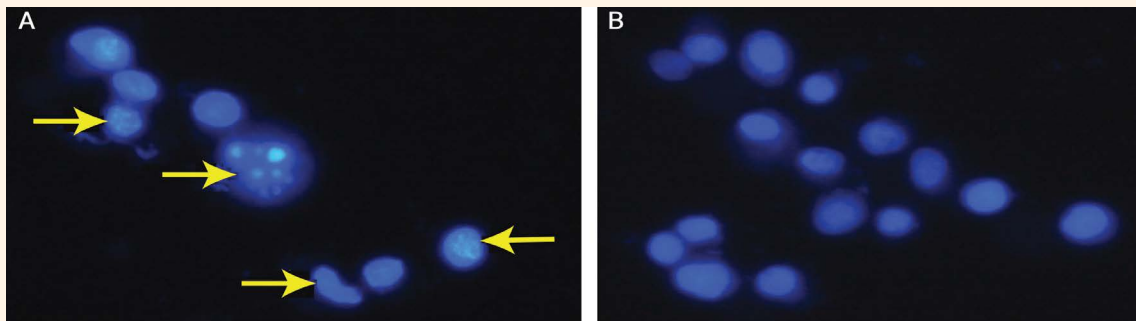
Treatment of MCF-7 cells with different concentrations of *Sarcophyton* sp. extract indicated a gradual increase in anti-cancer bioactivity as observed from escalating levels of cell death with increasing treatment concentration. The IC<sub>50</sub> was 97 µg/mL; concentrations of cell death induction were most potent at doubled IC<sub>50</sub>. The presence of fragmented nuclei was observed in treated cells in comparison to the negative control cells [Figure 1]. This highlighted the role of the apoptotic pathway in triggering cell death. Furthermore, the TEM ultrastructural analy-

**Table 1:** Pure compounds\* and extracts isolated from Omani marine organisms and their activity against the breast cancer Michigan Cancer Foundation-7 cell line

	Isolate	Organism	Species	Phylum	Solvent	ACA <sup>†</sup>
Compound	Aptamin	Sponge	<i>Hemiasterella</i> sp.	Porifera	DMSO	Medium
	Hymenidin	Sponge	<i>Halichondria</i> sp.	Porifera	DMSO	Weak
	2-Bromoaldisine	Sponge	<i>Thethya</i> sp.	Porifera	DMSO	None
	Hymenialdisine	Sponge	<i>Hemiasterella</i> sp.	Porifera	DMSO	Strong
	Malformin A	Fungus	<i>Aspergillus niger</i>	Ascomycota	DMSO	Strong
	Kojic acid	Fungus	<i>Aspergillus</i> sp.	Ascomycota	MeOH	None
	Kuanoniamine D	Tunicate	<i>Didemnum</i> sp.	Chordata	DMSO	Strong
	Gallic acid	Mangrove tree	<i>Avicennia marina</i>	Tracheophyta	MeOH	Strong
Extract	Methanol	Soft coral	<i>Sarcophyton</i> sp.	Cnidaria	DMSO	None
	Ethyl acetate	Soft coral	<i>Sarcophyton</i> sp.	Cnidaria	DMSO	Strong
	Methanol	Soft coral	<i>Sinularia</i> sp.	Cnidaria	DMSO	None
	Ethyl acetate	Soft coral	<i>Sinularia</i> sp.	Cnidaria	DMSO	None
	Methanol	Soft coral	<i>Cladiella</i> sp.	Cnidaria	DMSO	Weak
	Ethyl acetate	Soft coral	<i>Cladiella</i> sp.	Cnidaria	DMSO	Weak
	Methanol	Soft coral	<i>Scleronephthya</i> sp.	Cnidaria	DMSO	None
	Ethyl acetate	Soft coral	<i>Scleronephthya</i> sp.	Cnidaria	DMSO	Weak
	Methanol	Soft coral	<i>Dendronephthya</i> sp.	Cnidaria	DMSO	None
	Ethyl acetate	Soft coral	<i>Dendronephthya</i> sp.	Cnidaria	DMSO	None
	Methanol	Tunicate	<i>Phallusia nigra</i>	Chordata	DMSO	None
	Ethyl acetate	Tunicate	<i>Phallusia nigra</i>	Chordata	DMSO	None
	Methanol	Sponge	<i>Chondrosia</i> sp.	Porifera	DMSO	None
	Ethyl acetate	Sponge	<i>Chondrosia</i> sp.	Porifera	DMSO	None
	Ethyl acetate	Fungus	<i>Penicillium</i> sp.	Ascomycota	DMSO	None
	Methanol	Fungus	<i>Penicillium</i> sp.	Ascomycota	DMSO	None
	Methanol	Sea cucumber	<i>Holothuria edulis</i>	Echinodermata	DMSO	Weak
	Ethyl acetate	Sea cucumber	<i>Holothuria atra</i>	Echinodermata	DMSO	Weak
	Methanol	Gorgonian coral	<i>Acanthogorgia</i> sp.	Cnidaria	DMSO	Weak
	Ethyl acetate	Gorgonian coral	<i>Acanthogorgia</i> sp.	Cnidaria	DMSO	Medium
	Methanol	Bryozoan	<i>Schizoporella unicornis</i>	Bryozoa	DMSO	None
	Ethyl acetate	Bryozoan	<i>Schizoporella unicornis</i>	Bryozoa	DMSO	Medium
	Methanol	Sponge	<i>Mycale</i> sp.	Porifera	DMSO	Medium
	Ethyl acetate	Sponge	<i>Mycale</i> sp.	Porifera	DMSO	None
	Methanol	Bacterium	<i>Halomonas</i> sp.	Proteobacteria	DMSO	None
	Ethyl acetate	Bacterium	<i>Halomonas</i> sp.	Proteobacteria	DMSO	None
	Methanol	Bacterium	<i>Marinobacter</i> sp.	Proteobacteria	DMSO	None
	Ethyl acetate	Bacterium	<i>Marinobacter</i> sp.	Proteobacteria	DMSO	None
	Methanol	Green alga	<i>Ulva</i> sp.	Chlorophyta	MeOH	None
	Ethyl acetate	Green alga	<i>Ulva</i> sp.	Chlorophyta	MeOH	None
	Ethyl acetate	Bryozoan	<i>Bugula</i> sp.	Bryozoa	MeOH	None
	Methanol	Bryozoan	<i>Bugula</i> sp.	Bryozoa	MeOH	Weak
Control	-	-	-	DMSO and MeOH	None	

ACA = anti-cancer activity; DMSO = dimethyl sulfoxide; MeOH = methanol. \*All compounds were dissolved either in MeOH or DMSO prior to the experiments and MeOH solutions were also evaporated beforehand. Correspondent MeOH and DMSO controls were included. <sup>†</sup>Anti-cancer activity was classified as either none (no activity), weak (<1,000 µg/mL), medium (100–1,000 µg/mL) or strong (>100 µg/mL).





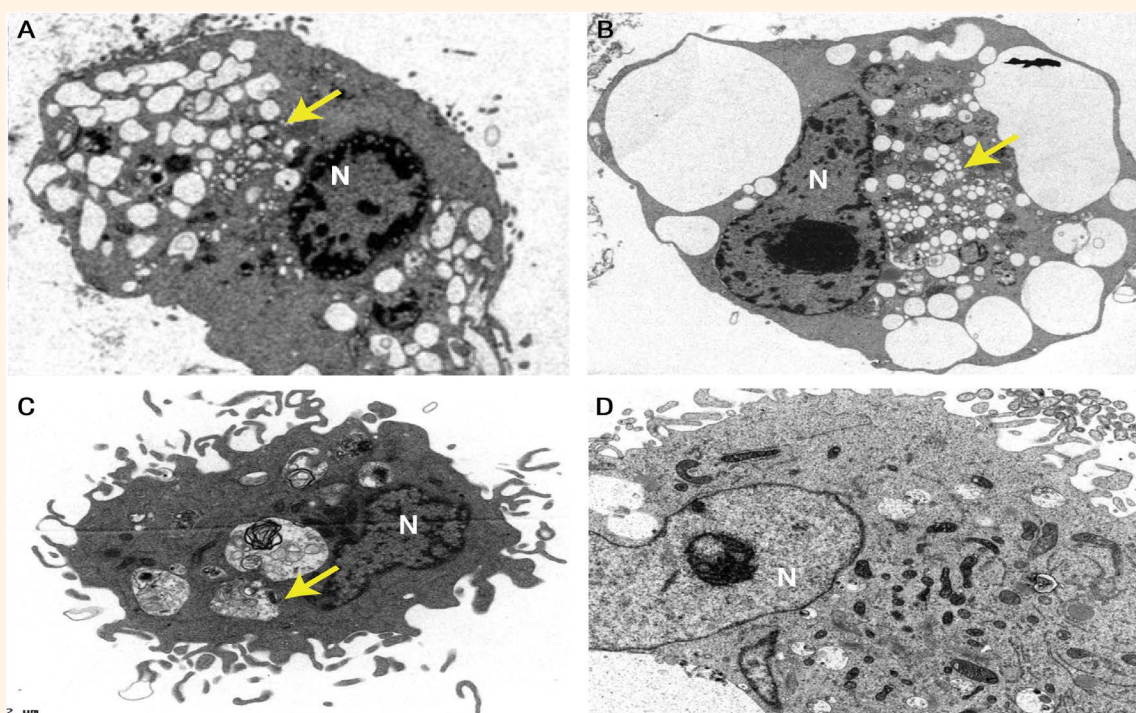
**Figure 1A & B:** Hoechst stains at x40 magnification of Michigan Cancer Foundation-7 breast cancer cells treated with (A) 97 µg/mL of *Sarcophyton* sp. extract for 24 hours and (B) dimethyl sulfoxide as a negative control. Note the presence of nuclear fragmentation in the cells treated with the *Sarcophyton* sp. extract (arrows).

sis of the *Sarcophyton* sp.-treated cells indicated the presence of cell membrane blebbing, intense vacuolisation and chromatic segregation at the periphery of the nucleus [Figure 2]. These changes confirmed the activation of *apoptosis* in the treated MCF-7 cells.

## Discussion

Numerous studies have indicated the benefits of marine flora and fauna extracts in various fields, including improvement in the prognosis of several diseases such as cancer.<sup>24–26</sup> The complexity, poor prognosis and patient-, type- and stage-specificity of

cancer requires the investigation and identification of novel compounds with effective clinical utility. In this study, the aim was to investigate the anti-cancer activity of extracts and compounds isolated from marine organisms in Oman. Almost a quarter of the investigated extracts and compounds showed medium or strong anti-cancer activity. The strongest activity against the MCF-7 breast adenocarcinoma model was observed for the malformin A, kuanoniamine D, hymenialdisine and gallic acid compounds and the soft coral *Sarcophyton* sp. extract. Hagimori *et al.* observed that malformin can disrupt the cell cycle at the G2 checkpoint in cancer cells.<sup>27</sup> Similarly, kuanoniamine



**Figure 2A–D:** Transmission electron microscopy ultrastructural analysis at x40 magnification of (A–C) Michigan Cancer Foundation (MCF)-7 breast cancer cells treated with 97 µg/mL of *Sarcophyton* sp. extract for 24 hours and (D) control cells treated with solvents. Intensive blebbing, vacuolisation and chromatic segregation (arrows) due to *apoptosis* were observed in the MCF-7 cells.

*N* = nucleus.

A and C isolated from sponges has been found to inhibit the growth of tumour and non-tumour cell lines, as well as an oestrogen-dependent breast cancer cell line.<sup>28</sup> Smith *et al.* revealed that hymenialdisine has anti-cancer properties against human colorectal carcinomas.<sup>29</sup> Furthermore, gallic acid has been shown as a potent compound with antimicrobial, anti-oxidant, quorum-sensing inhibitory and anti-cancer properties.<sup>30–32</sup>

In the current study, the tested compounds had no measurable effects on human fibroblast cells. This may suggest that these compounds are non-toxic, although alternatively this could indicate that fibroblasts are very resistant compared to the MCF-7 breast cancer cell line. This observation is in agreement with earlier findings regarding the resistance of fibroblasts to several toxic compounds.<sup>32</sup> Moreover, MCF-10A cells are not considered a good control model since they have a transformed phenotype and are abnormal epithelial cells.<sup>33</sup> New epithelial non-transformed cells are commercially available; however, they are difficult to handle and propagate.<sup>33</sup> As such, there is a need for future *in vivo* studies to be carried out in order to assess the toxicity of marine natural products using immunosuppressed mice.

Analysis of the anti-cancer activity of *Sarcophyton* sp. extracts in the present study indicated the potency of this extract in inducing cell death in the MCF-7 breast cancer model at the IC<sub>50</sub> of 97 µg/mL. Moreover, TEM microscopic analysis and Hoechst staining indicated the presence of fragmented nuclei within the treated cells. Typical characteristics of cell death induction by *apoptosis* were noted, such as nuclear fragmentation, membrane blebbing and increased vacuolisation. The anti-cancer activity of soft coral extracts has been previously reported.<sup>34,35</sup> For example, diterpenes from the soft coral *Xenia elongata* were found to induce *apoptosis* in a genetically engineered mouse cell line which was D3-deficient in the *BAK1* and *BAX* genes.<sup>35</sup> The preliminary results of the current study therefore indicate the potential benefit of *Sarcophyton* sp. extracts in cancer treatment. An in-depth analysis of the molecular effects, specificity and efficacy of the extract for breast, ovarian, colon and prostate cancers is required through further *in vitro* and *in vivo* studies; this may potentially lead to the development of new treatments for breast adenocarcinomas and other cancers.

## Conclusion

The results of this study highlight the anti-cancer potential of various marine organisms in Oman. The active anti-cancer compound extracted from

*Sarcophyton* sp. is of particular interest and should be isolated in future experiments. The compound should be tested on *in vitro* models of various cancers to determine the specificity of its anti-cancer activity. Finally, the molecular mechanism and pathways activated in response to treatment with this compound should be investigated. Such an investigation will provide possibilities for the development of new cancer treatments.

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## CONFLICT OF INTEREST

The authors report no conflicts of interest.

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