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HR-LCMS assisted phytochemical screening and an assessment of anticancer activity of Sargassum Squarrossum and Dictyota Dichotoma using in vitro and molecular docking approaches

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Highlights

- Use of novel technologies like HR-LCMS, NMR for isolation and characterization of bioactive compounds from marine algae.
- Isolation and characterization of bioactive compounds from Sargassum squarrossum and Dictyota dichotoma for the first time.
- Evaluation of the in vitro anticancer activity against MCF7 and A549 cell line.
- Compounds were docked against AXL and VEGFR an important enzyme in the cancer drug targets.
- Bioactive compounds show good binding affinity with AXL and VEGFR.

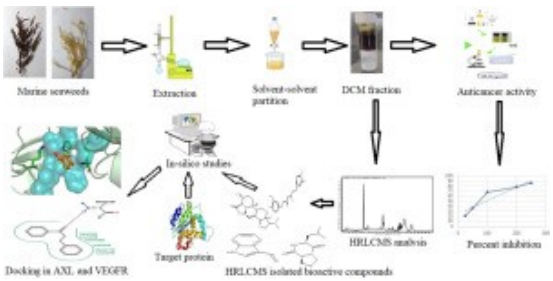
Abstract

The research in the area of marine bioactives have substantially improved in the last few decades. The identified marine algae namely Sargassum squarrossum and Dictyota dichotoma were subjected to phytochemical profiling using the most sophisticated High-resolution-LCMS, ^{1}H NMR and revealed the presence of many bioactive compounds.

In vitro MTT tests on lung and breast cancer cells revealed that the DCM fractions of Sargassum squarrossum and Dictyota dichotoma have anticancer characteristics, and they also demonstrated significant dose-dependant cytotoxicity on tumour cell lines. In MCF7 cells, the IC50 values for Sargassum squarrossum and Dictyota dichotoma were 139.51µg/ml and 241.89µg/ml whereas in A549 the cell line, the IC 50 values for the DCM fractions of Sargassum squarrossum and Dictyota dichotoma were 95.37µg/ml and 92.09µg/ml, respectively. Sargassum squarrossum shows potent anticancer activity in MCF7 and A549 whereas Dictyota dichotoma has potent anticancer activity in A549 and moderate activity in MCF7 cell lines.

The most prevalent enzymes VEGFR-2 and AXL tyrosine kinase, contribute to the development of cancer. A computational method was used to confirm the anticancer effects of the newly identified compounds targeting the above enzymes. According to the molecular docking studies, most of the detected compounds from marine algae were selectively interacting with AXL and VEGFR receptors with good binding affinity scores. The current work demonstrated the phytochemical assessment of marine algae and showed the ability of marine natural products to provide unique metabolites with significant biological activity.

Graphical Abstract



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Introduction

Cancer is a class of disorders characterized by the uncontrolled proliferation of cells that can lead to death. Despite the availability of numerous curative treatments for cancer, survival and cure rates are relatively low [1]. In economically developing countries, lifestyle changes such as smoking, poor diet, lack of physical activity, and low birth rates, are likely to exacerbate the future burden of

cancer [2]. Cancer is a dreaded disease that is one of the world's leading health problems and requires a proactive approach to treatment [3]. The drugs now available to treat cancer are not only expensive but also perilous, damaging both cancer and healthy cells. Finding new, efficient, and safe molecules from natural sources is more essential than ever [4].

Natural products are increasingly being used as medicines to treat human ailments due to their potential biological activity and lack of adverse effects as compared to synthetic compounds [5]. Marine organisms make up around a quarter of all species on the planet. Many compounds found in water possess unique biological activity as well as chemical properties that were considered key treatments for a wide range of ailments [6].

Over 80% of the world's biodiversity is found in marine ecosystems, and most such animals had created specialized modifications that allow them to survive in a variety of hard settings. The world's ocean biodiversity represents a nearly unexplored potential for identifying and providing innovative drugs, treatments, and remedies to human illness [7].

Chemical structural diversity and various biological activities have been used to characterise marine natural products [8].Seaweed refers to a broad variety of organisms with various therapeutic properties that are separated into two categories: microalgae and macroalgae (seaweed) [9].

Macroalgae are categorized into three taxonomic groups depending upon the colour of their pigments: Rhodophyceae (red algae), Phaeophyceae (brown algae) and Chlorophyceae (green algae) [10].

Sargassum (F. Sargassaceae), of the order Fucales, subclass Cyclosporeae, and class Phaeophyceae, is a genus of brown algae, commonly known as gulfweed or sea holly, and is considered one of the most complex Phaeophyceae genera. Sargassum was discovered by Agardh in 1820 and is reported to contain 537 species names in the algae database, of which 358 species have been accepted taxonomically. It comprises many different species that are distributed worldwide, although primarily found in tropical and subtropical marine waters, and also generally growing on rocky reefs [8].

According to the literature survey, *Sargassum* species are promising sources of several classes of secondary metabolites such as steroids, glycerides, chromanols, chromenes and plastoquinones that possess antibacterial, antifungal, antioxidant, anticancer, anti-herpes, hepatoprotective, antiallergic, antihistamine, anticholinergic anti-inflammatory activities [10].

The genus Dictyota is represented by more than 40 species, thus being the richest genus of the family Dictyotaceae. It is also one of the most abundant seaweeds in tropical marine habitats such as the Atlantic and Indian Oceans, where plenty of Dictyota species are found. Biological studies have shown a significant number of Dictyota secondary metabolites to possess cytotoxic, anti-bacterial, ichthyotoxic and antifeedant activities [11].

Novel bio-actives found in marine seaweeds are widely utilised in food, medical, cosmetic and pharmaceutical industries [12]. Seaweed, which is amongst the largest plentiful yet possibly endless sources in the ocean, has drawn increased interest from experts as a vital aspect of the marine environment. More than 1000 unique bioactive metabolites have been discovered in marine creatures, including a variety of physiologically active compounds [13].

Terpenoids, sulphated polysaccharides, pigments, polyphenolics, flavonoids, PUFAs (polyunsaturated fatty acids), MUFAs (monounsaturated fatty acids) and HUFAs (highly unsaturated fatty acids), vitamins (A, C, D, E, K and B1, B2, B9, B12), essential amino acids and essential minerals are all found in seaweeds (iron, magnesium, calcium, phosphorus, iodine, zinc, manganese, potassium, fluoride, copper and selenium) [14].

Algae contain phycocolloids like carrageenan, agar and alginate, which have been extensively employed in pharmaceutical and food industries as gelling agents and emulsifiers [15].

Seaweed extract has biological action as a result of the phytoconstituents composition of active substances like antiproliferative, antioxidants, antimicrobial, anti-cancer agents and treatment of ailments such as thyroid, hyperlipidaemia, cardiovascular diseases, atherosclerosis and with the addition of nutritionally important components [16].

Several anticancer chemicals have been discovered in marine species in recent decades, but only a handful of chemotherapeutic medications have received FDA approval for clinical use, such as eribulin (halichondrin B extracted from the sponge Halichondria okadai), trabectedin (ecteinascidin 743 obtained from the tunicate Ecteinascidia turbinata) and the macrolides lactones bryostatins, for example, are anticancer drugs (isolated from the brown bryozoan Bugula neritina). Trabectedin is being used to treat soft tissue sarcomas and ovarian cancer and eribulin to treat late-stage breast cancer [17].

Many proangiogenic pathways control cancer angiogenic activity, including vascular endothelial growth factor receptor 2 (VEGFR2) and Axl receptor tyrosine kinase (Axl) [18].

Angiogenesis is a crucial phase in the growth, survival, and spread of cancer. Angiogenesis is mediated by a variety of pro-and anti-angiogenic agents, as well as signalling pathways that aid cancer growth and metastasis. Activation of vascular endothelial growth factor receptor 2 (VEGFR2) is a fundamental driver of angiogenesis [19].

The VEGF pathway is an attractive anti-angiogenic treatment target for a variety of reasons, including endothelial cells involved in blood vessel development that binds to the VEGF pathway. it is produced by a huge number of primary tumours being grown; the VEGF pathway promotes the creation of new blood vessels; endothelial cells are likewise genetically stable, with spontaneous mutations being uncommon as compared to mutations caused by stress [20].

In many human malignancies, the AXL receptor tyrosine kinase and its primary ligand, GAS6, are

overexpressed and active (like in pancreatic, breast and lung cancer) [21].

As a result, targeting the AXL and VEGF/VEGFR signalling pathways has been thought to be a highly promising target in reducing tumour proliferation and angiogenesis.

For the first time, an attempt was made to investigate various bioactive compounds from these marine algae using state-of-the-art HR-LCMS and ^{1}H NMR tools. Anticancer activity was evaluated in a wet laboratory assay using two cancer cell lines, MCF7 and A549. Plausible targets of VEGFR2 and AXL kinase receptors were confirmed using docking experiments.

Section snippets

Collection of seaweeds

During low tide, the two algae samples were collected around the Mandapam, Rameshwaram coasts south-east coast of India. After being collected to eliminate epiphytes, calcareous particles and sand, and other waste materials, the seaweed was extensively thoroughly rinsed with seawater, freshwater, and distilled water. The seaweed was dried in the shade, cut into small pieces, and pulverised in a mixer grinder after being blotted to remove excess water [22].…

Authentication of the seaweed species

Seaweeds were taken to the laboratory,…

HR-LCMS analysis of DCM fraction of Sargassum squarrossum and Dictyota dichotoma

The presence of 100 compounds was identified by HR-LCMS analysis of the DCM fraction of Sargassum squarrossum and Dictyota dichotoma. HR-LCMS chromatogram of the dichloromethane fraction of Sargassum squarrossum and Dictyota dichotoma were depicted in Figs. 3 and 4, respectively. Three major compounds were identified based on their retention period, mass and chemical formula from Sargassum squarrossum and seven major compounds from Dictyota dichotoma were confirmed. These active compounds are…

Interactions of the metabolites from *Sargassum squarrossum* and *Dictyota dichotoma* with AXL kinase

Tables7 and 9 show the results of the research for interaction with AXL kinase. Compounds from Sargassum squarrossum, such as 16-hydroxyhexadecanoic acid and 18-hydroxy-9Z-octadecenoic

acid, are in polar interaction with Asp690's side chain. Similarly, Asp690 was discovered to interact with 5-Methoxy-7-(4-hydroxyphenyl)−1-phenyl-3-heptanone from Sargassum squarrossum also Icaceine from Dictyota dichotoma. Asp690 is the first DFG loop residue in Axl Kinase Crystallographic studies [33] provided …

Conclusion

The phytochemical analysis was conducted to investigate various bioactive compounds from marine algae Sargassum squarrossum and Dictyota dichotoma using sophisticated HR-LCMS and ^{1}H NMR spectroscopic methods. These results suggest that metabolites from seaweeds may be exploited to create novel anticancer drugs with unique modes of action.

Bioactive compounds from seaweeds show promising cytotoxic properties, hence, they can be used as new chemotherapeutic agents or as inspiration for the…

CRediT authorship contribution statement

Mohini Salunke: Conceptualization, Methodology, Investigation, Software. **Balaji Wakure:** Writing – original draft. **Pravin Wakte:** Supervision, Writing – review & editing.…

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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