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Oral cancer: Advances in diagnosis and treatment of oral cancer using biomarkers and marine algal drugs

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Abstract
Oral cancer, or oral squamous cell carcinoma (OSCC), is the sixth most common cancer in the world. For screening and diagnosis of this dreaded malignancy, sensitive and specific biomarkers for oral cancer probably sound the most useful strategy. Biomarkers are specifically used for early cancer detection, particularly for cancers of the mouth. For early diagnosis and evaluation of prospective therapeutic targets for oral cancer a thorough exploration is required regarding the various cellular metabolites that are specifically expressed only in the cancer cell. This review also aims to work with the therapeutic potential of oral cancer through the use of natural compounds. There has been ample investigation for the use of natural products for the discovery of anticancer compounds besides other diseases. Numerous metabolites have been found in marine biomasses and these compounds have demonstrated a variety of pharmacological effects, particularly antioxidant and antitumor activity. As nutritional products, marine algal drugs perform a variety of biological functions in the marine flora and it has been reported that possible effects of the phytochemicals on carcinogenesis include activating macrophages causing apoptosis.
This review summarizes current findings on marine algal based drugs or chemicals and their potential medicinal uses in the field of oral cancer with additional investigations on the role of the various biomarkers in detection.

Keywords: Apoptosis, biomarkers, marine algal drugs, oral cancer, phytochemicals

Introduction
Oral cancer is a significant public health concern, accounting for a substantial portion of malignancies worldwide. The two main risk factors for oral cancer are excessive alcohol use and tobacco use in any form. These elements together account for more than 90% of oral malignancies, along with dietary deficits. According to studies, metabolites like valine and lactic acid can signal the development of oral cancer. Lysine, proline, citrulline, and ornithine have also been linked to early-stage oral cavity squamous cell carcinoma, according to research. For screening, diagnosis, and follow-up for this dreaded malignancy, sensitive and specific biomarkers for oral cancer are probably most useful (Shah *et al*. 2011) [1]. The purpose of biomarkers are aiding in characterizing tumour changes. They can also be used to track the progression of a disease or assess how well a treatment is working. It is useful to know a patient's oral cancer risk in order to determine whether risk reduction measures or screening have been successful. These tactics are far more effective when used with high-risk populations than when extended broadly to the entire community (Yoon *et al*. 2007) [2]. DNA, RNA, protein, or metabolomic profiles particular to the tumour which serve as biomarkers. As a result, a large number of possible biomarkers have been proposed, but their clinical application is hampered by widely dissented results (Sinevici *et al*. 2016) [3]. Blood, serum, plasma, body secretions (Sputum, saliva), or excretions (Stool, urine) can all be used to create biomarkers, either alone or in combination. There are non-invasive, minimally invasive, and invasive methods for collecting body fluid samples for biomarker research (Henry *et al*. 2012) [4]. As a crucial predictor for OSCC recurrences, the angiogenetic marker cluster of differentiation factor 34 (CD34) plays a key role (Kademani *et al* 2009) [5].

The prognosis of malignancies and distant metastases have been positively associated with genomic indicators such as integrin α3 and integrin β4 (Nagata *et al*. 2013) [6]. Saliva can be collected easily and non-invasively, making it a promising tool for illness diagnosis and health monitoring (Cheng *et al*. 2014) [7]. Using salivary biomarkers specifically for early cancer detection has garnered a lot of research interest over the past 20 years, particularly for cancers of the mouth and oropharynx, for which the five-year survival rate (62%) is still one of the lowest among all significant human cancers. Human salivary proteins have a huge potential for medical uses (Sivadasan *et al*. 2015) [8]. Proteases are responsible in breakdown of protein. The proliferation, apoptosis, and spread of cancer cells are just a few examples of how proteases play a key role in many physiological and pathological processes that occur within the human body (Feng *et al*. 2019) [9]. In order to aid in early diagnosis, malignant potential prediction, and evaluation of prospective therapeutic targets for oral cancer, we need to explore the role of programmed cell death and the genes related with it in the development of oral cancer. Understanding the fundamental molecular processes driving the development of oral tumours is crucial to the development of preventive and treatment strategies (Ali *et al*. 2017) [10]. Studies over several years have shown that oral cancer has significantly higher levels of the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway. It has also been revealed that oral cancer-related risks such alcohol, cigarettes, and human PV can start the Akt/mTOR pathway (Roy *et al*. 2019) [11].

In recent years, the use of phytochemical factors to prevent or treat cancer has received increasing attention. Normal activity, such as an increase in the production of growth factors (transforming growth factor [TGF]), TGF and others can be deregulated by gene changes. The RAS gene is one of many of these cellular oncogenes that are homologous to retroviral oncogenes; other oncogenes are brand-new. The survival rates of conventional therapies including surgery, radiation, and chemotherapy have increased, but they frequently have serious adverse effects. The investigation and use of nature, particularly for the discovery of antibacterial, antidiabetic, and anticancer compounds, have increased in the search for new and better medications (Khan *et al*. 2018) [12]. More than half of the commonly used anti-cancer medications available today come from natural source (Song *et al*. 2014) [13]. Numerous metabolites have so far been found in marine biomasses. The compounds found in marine flora have demonstrated a variety of pharmacological effects, particularly antioxidant, immuno-stimulatory, and antitumor activity. As nutritional products, cyanobacteria (Blue-green algae) perform a variety of biological functions as well as benefits to human health (Bajpai *et al*. 2018) [14]. The marine environment is a special resource with a wide range of biological species that, if properly studied, might produce ground-breaking treatments. The use of phytochemical components to cure or prevent cancer has drawn more and more interest in recent years. These phytochemicals are excellent chemo-preventive agents since they have low to no harm to healthy tissues. In particular, polyphenols and sulphated polysaccharides are the most abundant medicinally active compounds in the marine flora (Natarajan 2022) [15]. Possible effects of the phytochemicals on carcinogenesis include activating macrophages, causing apoptosis, and preventing DNA oxidative damage (Sithranga Boopathy *et al*. 2010) [16]. However, there hasn't been much focus on the development of novel, risk-free anticancer compounds in the marine environment. The cause is a result of numerous shortcomings in this region (Bhatnagar *et al*. 2010) [17]. In fact, it has been shown that the marine environment is an important source of chemicals with peculiar and distinctive chemical properties that can be employed to develop novel treatments with greater potency and specificity.

Oceans cover around 70% of the earth's surface and are home to a diverse range of animals (Barzkar 2019) [18]. These organisms produce a variety of metabolic products. Particularly in lower species, a large number of secondary metabolites are produced that act as "defense and attack" signalling molecules. These compounds, which belong to many chemical classes, could be applied as medical treatments (Parate *et al*. 2021) [19]. Among other marine species, bacteria, fungus, corals, micro- and macro algae, gorgonians, sponges, nudibranchs, bryozoans, sea cucumbers, tunicates, and sea hares have produced several potential treatments in recent years (Kumar *et al*. 2021) [20]. More than 10,000 natural products (NPs) with potential biotechnological interest have been found as a result of efforts to isolate these compounds. One of the most significant resources in the ocean is algae, both economically and ecologically (Sultana *et al*. 2014) [23]. Only a very small number of trials have been published for oral cancer, despite the 20 marine-based chemicals having potential anticancer effects in other forms of cancer. Thus, in the current investigation, we concisely tried to highlight the different marine drugs involved in curing oral cancer by identifying prospective oral cancer inhibitors by examining the possible role of the 20 compounds against the molecules implicated in the advancement of oral cancer based on the data from the literature.

Phyto-chemicals from marine algal drugs

Due to their positive impacts on human health, phytochemicals are of great interest and have a strong antioxidant potential. *In vitro* antioxidants and *in vivo* antioxidants are the two subcategories of natural antioxidants. Many marine anticancer chemicals have recently been isolated, described, and identified, and they are currently undergoing human usage studies.

Several bioactive compounds have been isolated from a number of marine organisms which are rich in polyphenols, xanthophyll, carotenoids which are been recognized for their potent application in cancer therapy. When treated with extracts of *Enteromorpha compressa*, a green alga against oral cancer cell lines like Cal 33 and FaDu the proliferation of the cells were halted due to autophagy and apoptosis (Pradhan *et al*. 2020) [21]. *Fucus vesiculosus* a brown algae are rich in fucoidan extracts that have shown significant anti-cancer effect against Ca 99 and CAL 27 cell lines via elevated levels of reactive oxygen species and reduced cellular glutathione (Shiau *et al*. 2022) [22]. A number of carotenoids are been isolated from large number of marine algae that has been recognized to target cancer cells but their specific action on oral cancer are yet to be investigated.

Clinical applications and considerations of oral cancer biomarkers

Biomarkers can be generically categorized as either metabolomic, proteomic, or genomic (Santosh *et al* 2016).

In a variety of clinical contexts, biomarkers can be utilized to examine patients. They can be utilized for a variety of purposes, including assessing prognosis, screening for occult primary tumours, separating benign from malignant findings, and identifying one form of malignancy from another. Biomarkers can be used to track the course of a condition or assess how well it is responding to treatment. If risk-reduction measures or screening have been successful, knowing a patient's oral cancer risk is important. When these tactics are used with high-risk groups, they are significantly more effective than when they are administered broadly to the entire community. L-phenylalanine, for example, is a screening biomarker that aids in the early detection and monitoring of oral squamous cell carcinoma (OSCC). To distinguish between squamous cell carcinoma and adenocarcinoma, a proteomic biomarker called the cloning of an acidic laccase gene 2 is utilized (Shinmura *et al*. 2014) [25]. In order to predict recurring OSCC instances, the angiogenetic marker cluster of differentiation factor 34 (CD34) is a crucial tool (Kademani *et al*. 2009) [5]. Positive correlations have been found between distant metastases and tumour prognosis and genomic indicators such as integrin α3 and integrin β4. Initially discovered in OSCC, aberrant expression of miR-375, miR-200a, and miR-200c-144 methylation was proposed as a potential clinical use for OSCC diagnosis (Majem *et al*. 2015) [27].

Salivary biomarkers are much acclaimed for their potential to diagnose oral cancers. Salivary cytokine levels are found to be excellent biomarkers as their levels gets unregulated during oral cancer. There are elevated levels of IL-8 and IL-10 as observed in patients with oral cancers (Chiamulera *et al*. 2021) [28]. A number of metabolites may lead to the sensing of the oral cancer as high levels of betaine, choline were seen in saliva samples of the cancer patients with low L-carnitine (Wang *et al*. 2014) [29].

Conclusion

Oral carcinogenesis is a multi-step, complex process that is characterized by genetic changes, abnormal expression, and erratic cellular proliferation.

In this review the benevolence of a few marine algae derived bioactive compounds are been investigated that can be valuable anti-proliferative compounds against oral cancer. Besides the aim of the review was to search for a number of biomarkers that are non-invasive and could be harnessed for the diagnosis of vast array of oral cancer.

Conflict of Interest

The authors have no potential conflict of interest.

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