

Review

Microalgae-derived bioactive compounds - A natural ally in cancer immunotherapy

Divya Mittal^{1*}, Rahul Thakur^{2*}, Sukhpal Singh³, Aman Chauhan⁴ & Rooma Devi⁴

Abstract

Microalgae, a diverse group of photosynthetic microorganisms, have emerged as a promising source of bioactive compounds with significant therapeutic potential. While extensively studied for their applications in nutrition, biofuels, and cosmetics, their role in immunomodulation, particularly in cancer therapy, remains underexplored. This review delves into the intricate relationship between the immune system and cancer, emphasizing the dual role of immune surveillance and immune escape in tumor progression. We highlight the unique potential of microalgae-derived metabolites such as phycocyanin from *Spirulina platensis*, sulfated polysaccharides from *Porphyridium cruentum*, fucoxanthin from *Phaeodactylum tricornutum*, and eicosapentaenoic acid (EPA) from *Nannochloropsis* spp. in enhancing anti-tumor immunity, modulating the tumor microenvironment, and overcoming immune suppression. These compounds have demonstrated preclinical efficacy in activating macrophages, promoting dendritic cell maturation, stimulating cytotoxic T lymphocytes, and enhancing natural killer (NK) cell activity. Unlike conventional immunotherapies, which often induce adverse effects and resistance, these compounds offer a dual action potential as they exhibit direct antitumor and immune activation properties. In addition to this, algal compounds are natural, potentially less toxic alternatives with multi-targeted immunomodulatory effects. This review stands apart from existing literature by comprehensively integrating insights into cancer immune-editing with the emerging role of microalgae in immune-based therapies. We suggest microalgae as a novel and sustainable approach for upcoming cancer immunotherapy research and chemical application by bridging the gap between marine biotechnology and oncology.

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¹ Department of Industrial Biotechnology, COBT, CCSHAU, Hisar, Haryana, India

² Department of Bio-sciences and Technology and Central Research Cell, MMEC, Maharishi Markandeshwar University, Mullana, Ambala, Haryana, India

³ Adesh Medical College and Hospital, Shahabad (M), Kurukshetra, Haryana, India

⁴ Department of Biochemistry, MMIMSR, Maharishi Markandeshwar University, Mullana, Ambala, Haryana, India

*Correspondence:

divyamittal@gmail.comrahul.unahp@gmail.com

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Introduction

Marine microalgae, which include red, blue-green (e.g., *Nostoc*), green, and some brown species like *Phaeodactylum tricornutum*. They are some of the earliest photosynthetic organisms. They are mostly unicellular and, depending on the environment, can develop in a photoautotrophic, heterotrophic, or mixotrophic manner (Barsanti *et al.*, 2008; Barsanti & Gualtieri, 2019). Strong antioxidant systems and the production of bioactive substances such as carotenoids, phycobiliproteins, and chlorophylls with immunomodulatory and anticancer properties have resulted from their response to oxidative stress caused by phototrophic metabolism (Eze *et al.*, 2023). Marine microalgae can create a variety of metabolites with pharmaceutical uses because of their vast range of growth rates, nutrient requirements, and light utilization. These bioactive substances are utilized in a variety of industries such as food, cosmetics, nutraceuticals, and biofuels (Dolganyuk *et al.*, 2020). Marine microalgae are abundant in protein, lipids, vitamins,

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carbs, minerals, and species like *Nostoc* were historically eaten during famines due to their nutritional significance (Galasso *et al.*, 2019). Although *Chlorella* and *Spirulina* are well recognized for their nutritional value, research on marine microalgae does not focus on them because of their freshwater origin (Spolaore *et al.*, 2006). Furthermore, because of their lipid content and antioxidant qualities, marine microalgae support cosmetic products and renewable energy (Wang *et al.*, 2015). Immunomodulation, the ability to regulate immune responses, is critical in managing infectious diseases, autoimmune conditions, neurological disorders, and cancer (Manoutcharian *et al.*, 2017; Ferrari *et al.*, 2019). The innate immune system provides a first line of defense via macrophages, NK cells, and neutrophils, while the adaptive system utilizes antigen-specific responses through T and B lymphocytes. Both are regulated by signaling molecules like cytokines and chemokines (Zhao *et al.*, 2021; Khaligh & Asoodeh, 2022).

Given the adverse effects of conventional cancer treatments, marine microalgae have emerged as promising natural sources of immunotherapy. Compounds such as sulfated polysaccharides from *Porphyridium cruentum* enhance dendritic cell function and antigen presentation. Omega-3 fatty acids like EPA from *Nannochloropsis* spp. exert anti-inflammatory and tumor-suppressive effects. Fucoxanthin from *P. tricornutum* causes cancer cells to undergo apoptosis, whereas phycocyanin from *Nostoc* spp. stimulates NK cells. Carotenoids and fatty acids with anticancer properties are produced by other species such as *Tisochrysis lutea* and *Isochrysis galbana* (Lai, 2015). Additionally promising are therapeutic peptides derived from marine microalgae. These consist of tumor-targeting peptides, antimicrobial peptides implicated in innate immunity, and cell-permeable for drug administration (Boohaker *et al.*, 2012; Marqus *et al.*, 2017). Peptides provide benefits such as increased tissue penetration, less toxicity, and superior selectivity when compared to bigger proteins or antibodies (Craik *et al.*, 2013). Marine microalgae are a powerful and sustainable source of anticancer and immunomodulatory substances. Their metabolites improve immunological monitoring and the effectiveness of current immunotherapies by interacting with important immune pathways. Through the combination of marine biotechnology, immunology, and oncology, this review highlights their potential as innovation agents in the treatment of cancer.

Cancer and the Role of the Immune System

Cancer is a major health issue worldwide, accounting for around 10 million deaths in 2020 (Sung *et al.*, 2021). It results from aberrant cells that elude regulatory systems, proliferating out of control. Early diagnosis and effective treatment are crucial for improving outcomes. Hanahan and Weinberg (2000) outlined six hallmarks of cancer that define tumor behavior: sustained proliferative signaling, resistance to growth suppressors, evasion of apoptosis, replicative immortality, angiogenesis induction, and metastasis. Subsequent studies have added metabolic reprogramming and immune evasion, reflecting the evolving understanding of tumor biology.

Immune Surveillance and Cancer Progression

The immune system plays a dual role in cancer, acting both as a barrier to and facilitator of tumor progression (Figure 1). Tumors evade immune detection by

disrupting immune surveillance, which is responsible for identifying and eliminating abnormal cells (De *et al.*, 2006; Narendra *et al.*, 2013). Given the limitations of traditional treatments, marine microalgae-derived immunomodulators represent a promising therapeutic strategy. Compounds such as polysaccharides, carotenoids, and peptides from marine microalgae have shown potential in enhancing immune functions by stimulating cytokines, T lymphocytes, and natural killer (NK) cells (Wu *et al.*, 2025). Sulfated polysaccharides from *Porphyridium cruentum* activate antigen-presenting cells, while omega-3 fatty acids like eicosapentaenoic acid (EPA) from *Nannochloropsis* spp. modulate inflammation to support anti-cancer immunity (Tsvetanova & Yankov, 2022). Immunoediting, a key concept in tumor-immune interaction, consists of three phases: elimination, equilibrium, and escape (Zamarron & Chen, 2011). In the elimination phase, innate and adaptive immune cells, including NK cells, macrophages, cytotoxic T lymphocytes (CTLs), and dendritic cells, coordinate to destroy tumor cells. Marine microalgae-derived phycocyanin from *Synechococcus elongatus* enhances NK cell-mediated cytotoxicity (Chang & Beatty, 2020).

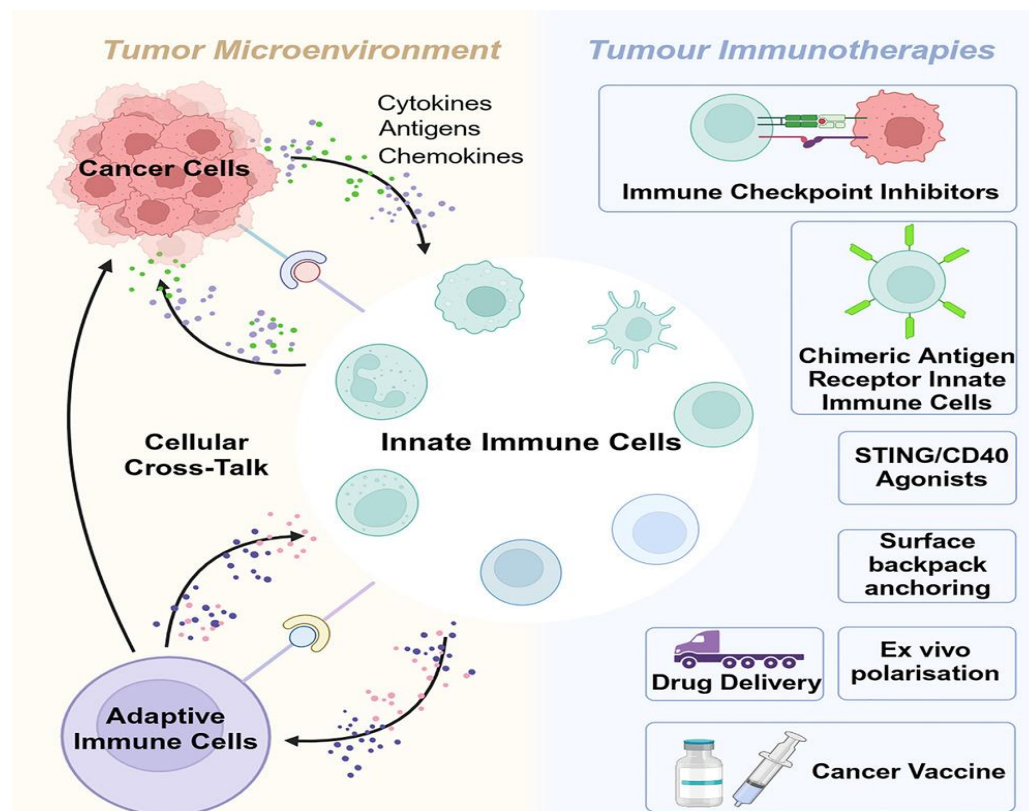


Figure 1. Interactions between tumor microenvironment, immune cells, and tumor immunotherapies. Cancer cells interact with innate and adaptive immune cells within the tumor microenvironment by secretion of cytokines, antigens, and chemokines, resulting in complex cellular cross-talk. Various tumor immunotherapy strategies aim to harness or modify innate immune cells, including immune checkpoint inhibitors, chimeric antigen receptor (CAR) innate immune cells, STING/CD40 agonists, surface backpack anchoring, ex vivo polarization, targeted drug delivery, and cancer vaccines.

During the equilibrium phase, residual tumor cells may enter a dormant state under immune pressure. Astaxanthin from *Haematococcus pluvialis* has been demonstrated to alter T cell activity, perhaps maintaining tumour dormancy (Li *et al.*, 2024). During the escape phase, tumors create defenses against immune response

by recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), downregulating MHC molecules, and secreting immunosuppressive cytokines (e.g., TGF- β , IL-10) (Yu & Fu, [2006](#)). Through cytokines regulation, fucoxanthin from *Phaeodactylum tricornutum* can lessen tumor-induced immune suppression (Spada & Mukherjee, [2024](#)). *Tetraselmis suecica* bioactive peptides enhance tumor antigen presentation by activating dendritic cells. Tumor stromal endothelial and immune cells make up the tumor microenvironment (TME), which significantly impacts cancer development. Depending on local signaling, TME immune cells may promote or prevent tumor progression (Riccio & Lauritano, [2019](#); Lei *et al.*, [2020](#)). Compounds found in marine microalgae can reprogram the TME to favor anti-tumor responses. EPA and DHA from *Isochrysis galbana* reduced the invasion of immunosuppressive cells such as Tregs and MDSCs, improving the effectiveness of immunotherapy (Costa *et al.*, [2021](#)). Furthermore, some polysaccharides found in marine microalgae increase macrophage activity and cytokine production, which contributes to proinflammatory TME.

Immunotherapy in Cancer

Even though they are fundamental, traditional cancer treatments like chemotherapy, radiation, and surgery frequently have low specificity, systemic toxicity, and limited long-term efficacy (Tannock, [1998](#)). These limitations have catalyzed the emergence of cancer immunotherapy, which harnesses the immune system to selectively target tumor cells and has significantly transformed oncologic care. By infusing foreign immune components or by stimulating the host immune system, immunotherapy improves anti-tumor immunity. Active and passive methods are the two general categories into which it falls. The immune system is stimulated by active immunotherapies to produce a long-lasting reaction to tumor antigens. These include non-specific tactics like cytokines (IL-2 and INF- α) and immune checkpoint inhibitors, as well as specialized tactics such as vaccines based on peptides or dendritic cells (Kumar *et al.*, [2021](#)). Conversely, immune effectors that directly target cancer cells, such as monoclonal antibodies, CAR-T cells, or immune-modulating drugs, are administered as part of passive immunotherapies (Nagasawa *et al.*, [2012](#)). Checkpoint blockade therapies targeting PD-1/Pd-L1 and CTLA-4 have achieved clinical success in several malignancies, ushered in by the work of James P. Allison and Tasuku Honjo, who were awarded the Nobel Prize in 2018 (Ballas *et al.*, [2018](#)). The immunotherapies landscape is growing thanks to innovation like CAR-T treatment and combination regimens with customized vaccines and nanoparticles (Garg *et al.*, [2024](#)). Nevertheless, problems still exist, such as immune-related side effects, immune evasion by the tumor, and limited effectiveness in solid tumors because of a suppressive tumor microenvironment and low T cell infiltration (Melero *et al.*, [2014](#); Hegde & Chen, [2020](#)).

Marine microalgae have become a prospective source of new immunomodulatory drugs to overcome these constraints. Numerous bioactive metabolites, including phycobiliproteins, polysaccharides, carotenoids, and omega-3 fatty acids, are produced by this unicellular, photosynthetic organism. These metabolites have been shown to have anticancer and immunoregulatory effects (Capa-Roble *et al.*, [2021](#); Liaqat *et al.*, [2023](#)). Rapid biomass output environment-friendly farming and may be included in decreased reliance on overfished marine macro sources are some benefits of marine microalgae. Notably, it has been demonstrated that sulfated polysaccharides derived from *Porphyridium cruentum* increase the activity of T cells

and Natural killer cells (NK), which may increase the efficacy of checkpoint blockade treatment (Talero *et al.*, 2015). The marine carotenoid fucoxanthin, which is present in *Odontella aurita* and *Phaeodactylum tricornutum*, has strong anti-inflammatory and antioxidant qualities that may lessen immune toxicity and resistance mechanisms (Méresse *et al.*, 2020). Furthermore, microalgae glycolipids and omega-3 fatty acids can stimulate dendritic cell maturation, improve T cell infiltration in tumors, and alter immunosuppressive cytokine networks. Compounds obtained from marine microalgae may be included in immunotherapeutic approaches to enhance anti-tumor response, modify the tumor microenvironment, and enhance clinical results.

Interactions Between Immune Cells and Tumor Cells

Immune cells such as cytotoxic T lymphocytes (CD8+), Helper T cells (CD4+), dendritic cells (DC), NK cells, and M1 macrophages play a crucial role in tumor surveillance and eradication (Gonzalez *et al.*, 2018). CD8⁺ T cells induce tumor apoptosis via perforin and granzyme release, while CD4⁺ Th1 cells amplify these responses by producing pro-inflammatory cytokines (Takeuchi & Akira, 2010; Palucka & Banchereau, 2012). NK cells target tumor cells with reduced MHC I expression (Vivier *et al.*, 2011), and M1 macrophages secrete TNF- α and IL-12 to support anti-tumor immunity (Biswas & Mantovani, 2010). However, tumor cells can reprogram immune components within the TME to adopt immunosuppressive phenotypes, facilitating immune evasion (Tie *et al.*, 2022). Marine microalgae-derived bio-actives can counteract this. Fucoxanthin from *Phaeodactylum tricornutum* enhances NK cell function by upregulating activation receptors like NKG2D (Akao *et al.*, 2009). EPA from *Nannochloropsis* spp. promotes M1 macrophage polarization and reduces the activity of tumor-associated macrophages. *Tetraselmis suecica* polysaccharides promote dendritic cell maturation and antigen presentation, whereas *Isochrysis galbana* boosts CD8⁺ T-cell responses. Marine microalgae-derived chemical shows promise for improving anti-tumor immunity and overcoming immune evasion mechanisms, underlining their potential in cancer immunotherapy.

Tumor-Induced Immunosuppression and the Potential of Marine Microalgae-Derived Compounds

Despite extensive immune surveillance, tumors frequently generate an immunosuppressive microenvironment that allows them to survive and grow. While cytotoxic T lymphocytes (CTLs), M1 macrophages, and NK cells work to kill cancer cells, tumors counteract these defenses by recruiting immunosuppressive cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages (Liu *et al.*, 2024). These cells work together to suppress anti-tumor immunity and allow immune evasion. Tregs limit CTL activity by secreting inhibitory cytokines such as IL-10 and TGF- β , fostering immunological tolerance in the tumor microenvironment (Sakaguchi *et al.*, 2008). MDSCs inhibit T-cell activity through arginase-1, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), whereas M2 macrophages secrete anti-inflammatory cytokines and pro-angiogenic factors that promote tumor growth and metastasis (Biswas & Mantovani, 2010; Gabrilovich *et al.*, 2012). Marine microalgae-derived compounds show great promise in combating tumor-induced immunosuppression by targeting specific immune pathways (Table 1). Fucoxanthin, a carotenoid isolated from

Phaeodactylum tricornutum, modulates the NF- κ B and MAPK pathways, leading to decreased production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. It also inhibits M2 macrophage polarization by reducing IL-10 and TGF- β expression, thereby promoting an anti-tumor immune response. Omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from *Nannochloropsis* and *Schizochytrium* species, exert their effects via the GPR120 and PPAR- γ signaling pathways, resulting in downregulation of COX-2 and TNF- α , suppression of arginase-1, and reduced ROS generation, thereby mitigating MDSC-mediated immunosuppression (Ávila-Román *et al.*, [2021](#)). Sulfated exopolysaccharides from *Porphyridium cruentum* engage the TLR4 pathway, enhancing the secretion of IFN- γ and IL-12, promoting macrophage activation, and stimulating innate immunity through the complement system, which increases opsonization and pathogen clearance. These polysaccharides also limit Treg expansion, restoring the balance between regulatory and effector T cells (Ju *et al.*, [2023](#)).

Table 1. Anticancerous extracts/components from microalgae and their mode of action.

Microalgae	Compounds/ Extracts	Target Cell/ Mechanism	Reference
<i>Haematococcus pluvialis</i>	Astaxanthin	Colon, oral fibrosarcoma, breast, prostate cancer cells	Yuan <i>et al.</i> , 2011
<i>Dunaliella tertiolecta</i>	Violaxanthin	MCF-7 (breast cancer) and LNCaP (prostate cancer) cell lines	Pasquet <i>et al.</i> , 2011
<i>Phaeodactylum tricornutum</i>	Fucoxanthin	Human gastric adenocarcinoma cell line	Kim <i>et al.</i> , 2011
<i>Arthrospira platensis</i>	Extracellular polysaccharide	Colon cancer cell lines "Caco-2" and kidney cell lines "Vero" from green monkey kidney	Challouf <i>et al.</i> , 2011
<i>Spirulina platensis</i>	Phycobiliproteins	TNF- α	Romay <i>et al.</i> , 2003
<i>Chlorella pyrenoidosa</i>	Peptides	Human liver cancer HepG2 cells	Wang & Zhang, 2013
<i>Lyngbya majuscula</i>	Amides	HT29 colon cancer cells	Kwan <i>et al.</i> , 2010
<i>Spirulina platensis</i> , <i>Mastigocladus laminosus</i> , <i>Agmenellum quadruplicatum</i>	C-phycocyanin (C-PC)	Caspases-dependent apoptosis	Li <i>et al.</i> , 2006
<i>Jaspis johnstoni</i>	Jasplamide	Caspase-3 activation, decreasing Bcl-2 protein expression	Cioca <i>et al.</i> , 2002
<i>Skeletonema marinoi</i> , <i>Alexandrium minutum</i> , <i>Alexandrium andersoni</i>	Extract	Human melanoma A2058 cells	Lauritano <i>et al.</i> , 2016
<i>Phaeodactylum tricornutum</i>	Sulfated polysaccharides	HepG2 cells	Yang <i>et al.</i> , 2019
<i>Chlorella sorokiniana</i>	Extracts	Human lung adenocarcinoma cell lines A549 and CL1-5 xenograft	Lin <i>et al.</i> , 2017

Moreover, glycolipids from marine microalgae interact with the CD1d/iNKT cell pathway, promoting the release of both IL-4 and IFN- γ , which contribute to immune regulation and anti-tumor activity. Finally, bioactive extracts from *Tisochrysis lutea* exhibit anti-inflammatory and immunomodulatory properties, suggesting their

potential to reprogram the tumor microenvironment into a more immunostimulatory and less suppressive state.

Immunotherapies and the Role of Marine Microalgae in Enhancing Anti-Tumor Immunity

Advances in tumor immunology have led to the development of therapies that enhance anti-tumor immunity by reactivating exhausted T cells and disrupting immunosuppressive pathways. Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 have demonstrated success in treating various cancers by restoring T cell activity and enhancing immune responses (Roy *et al.*, 2022; Kong *et al.*, 2024). Recent studies suggest that marine microalgae-derived bioactive compounds could potentiate these effects by modulating T cell responses and overcoming immunosuppressive tumor microenvironments. For instance, although *Haematococcus pluvialis* is a freshwater species, its carotenoid astaxanthin, structurally similar to marine-derived xanthophylls, has been shown to augment CD28-mediated T cell co-stimulation and enhance the efficacy of PD-1 blockade by increasing IFN- γ production and cytotoxic T lymphocyte (CTL) activity in murine melanoma *in vivo* models (Rausch & Hastings, 2017; Eliote *et al.*, 2023). Similarly, polysaccharides from *Porphyridium cruentum* have been reported to reduce PD-1 expression on CD8⁺ tumor-infiltrating lymphocytes by inhibiting NF- κ B signaling and promoting IL-2 secretion, as shown in *in vitro* assays with co-cultured lymphocytes and cancer cells (Nuzzo *et al.*, 2022). Carotenoids and polyunsaturated fatty acids (PUFAs) such as EPA (eicosapentaenoic acid) from *Isochrysis galbana* and *Tisochrysis lutea* have demonstrated immunomodulatory potential. EPA has been shown to downregulate PD-L1 expression on tumor-associated macrophages and dendritic cells through PPAR- γ activation, leading to enhanced T cell infiltration and improved responsiveness to PD-1/PD-L1 checkpoint blockade in murine models of colon cancer (*in vivo*) (Gutting *et al.*, 2021). Moreover, lipidomic profiling reveals that EPA treatment increases the ratio of M1 to M2 macrophages, contributing to a more immunostimulatory tumor milieu. EPA and DHA from marine microalgae also contribute to improved immunotherapy outcomes by decreasing immunosuppressive mediators and enhancing T cell infiltration into tumors (Skjånes *et al.*, 2021). Collectively, these findings suggest that marine microalgae-derived compounds may serve as effective adjuvants to current immunotherapies, enhancing their efficacy and overcoming resistance mechanisms.

Inclusion and Exclusion Criteria of Selected Compounds

To ensure scientific rigor and therapeutic relevance, a systematic literature screening was conducted using databases such as PubMed, Scopus, and ScienceDirect with search terms like “marine microalgae,” “bioactive compounds,” “immunomodulation,” and “cancer.” From an initial pool of 150 articles (2000–2024), 109 studies were shortlisted based on marine microalgal origin and evidence of immunomodulatory effects in cancer-relevant *in vitro* or *in vivo* models. Final selection focused on compounds targeting key immune pathways, including NF- κ B, MAPK, TLR4, PPAR- γ , and the CD1d/iNKT axis, while excluding reviews, opinion papers, and studies lacking mechanistic insights. The included compounds fucoxanthin, sulfated polysaccharides (fucoidans, carrageenans, porphyrans), EPA, and marine glycolipids met strict inclusion criteria regarding purity (≥ 90 –95%), dosage, and immune-specific endpoints such as cytokine modulation, T-cell

differentiation, and NK cell activation. Studies using non-standardized mixtures, sub-therapeutic doses, or lacking immune relevance were excluded. These bioactives were selected for their demonstrated ability to modulate immune responses within the tumor microenvironment, supporting their potential use in cancer immunotherapy. The inclusion and exclusion strategy is visualized in Figure 2.

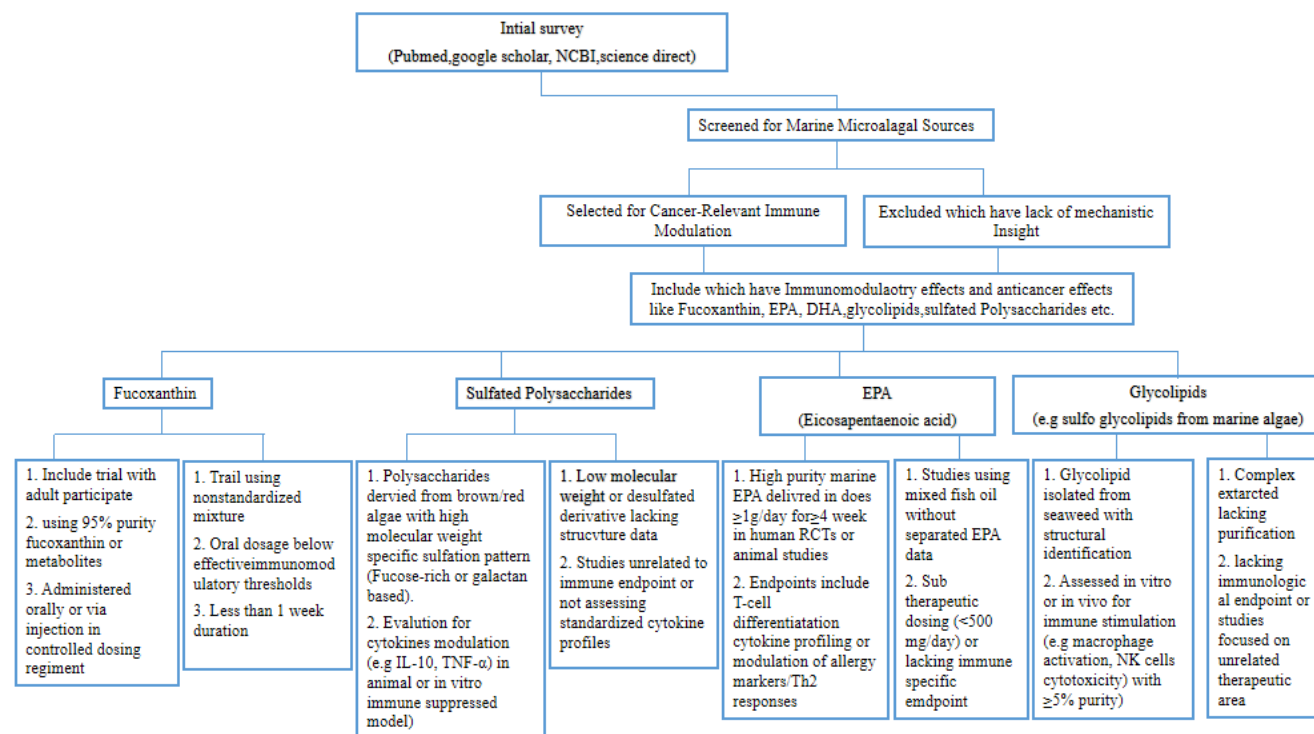


Figure 2. Selection process of marine microalgae-derived compounds based on source, immunomodulatory activity, and mechanistic relevance to cancer immunotherapy.

Microalgae Species with Anticancer Properties

Marine microalgae have emerged as an important source of bioactive secondary metabolites with many therapeutic applications, notably in cancer. Microalgae-derived compounds such as polysaccharides, polyunsaturated fatty acids (PUFAs), peptides, carotenoids, and alkaloids have antioxidant, anti-inflammatory, and anticancer properties. These metabolites have distinct benefits over traditional immunotherapies, such as decreased immune-related side effects and increased effectiveness against solid tumors by modifying the tumor microenvironment (Minhas *et al.*, 2024). Several investigations have highlighted the cytotoxic and antiproliferative properties of marine microalgae extract. For example, Lauritano and Ianora (2016) discovered that *Ostreopsis ovata* is a powerful source of anticancer chemicals against hepatocellular carcinoma (HepG2) cells. Similarly, extracts from *Chlorella ovalis* and *Amphidinium carter* reduced the multiplication of HL-60 Leukaemia cells (Samarakoon *et al.*, 2013). *Nostoc* spp. generate cryptophycin, a microtubule targeting chemical effective against multidrug-resistant tumors (Eggen & Georg, 2002), whereas *Lyngbya majuscula*-derived Apratoxin A promotes apoptosis by inhibiting protein synthesis (Costa *et al.*, 2012).

Marine diatoms such as *Melosira*, *Amphora*, *Phaeodactylum*, and *Nitzschia* show anticancer effects via triggering apoptosis and autophagy in leukaemia models

(Prestegard *et al.*, 2014). *Phaeodactylum tricornutum*, high in fucoxanthin, has anticancer properties via modulating signaling pathways implicated in tumor growth and immune evasion (Méresse *et al.*, 2020). Microalgal polysaccharides, including β -glucans from *Chlorella* spp. and *Spirulina platensis*, stimulate dendritic cells and macrophages, leading to anti-tumor immunity (Capek *et al.*, 2020). Glycolipids and lipopolysaccharides also serve as immunological adjuvants, increasing vaccination effectiveness by stimulating both innate and adaptive immune responses (Plouguerné *et al.*, 2014). *Chloromonas reticulata* extract inhibited colon cancer (HCT116) cells and macrophages by lowering pro-inflammatory mediators such as IL-6, COX-2, iNOS, and TNF- α (Riccio & Lauritano, 2019). Similarly, extracts of *Micractinium* spp. obtained from Antarctic water showed antiproliferative action against colon cancer cells. Other investigations have shown that microalgae metabolites exhibit specific cytotoxicity against aggressive tumors, including melanoma (Bajetta *et al.*, 2002; Lauritano *et al.*, 2016). Marine microalgae have therapeutic promise as new anticancer drugs. Their ability to control immune response, specifically target tumor cells, and lower systemic toxicity makes them potential candidates for overcoming the limits of existing immunotherapy.

Mechanistic Insights into Marine Algae-Derived Cancer Inhibitors

Growing data support the anticancer potential of marine microalgae via several molecular pathways. Compounds generated from microalgae, including peptides, polysaccharides, alkaloids, and carotenoids, have been shown to cause cytotoxicity, induce apoptosis, and modulate important oncogenic pathways. Curacin A, a blue-green algae chemical, disrupts microtubule dynamics and inhibits tubulin polymerization, causing cytotoxicity in kidney, breast, and colon cancer cells (Abd El-Hack *et al.*, 2019). Microtubule disruption, which is required for mitosis and intracellular trafficking, is still a well-validated cancer therapeutic method (Hadfield *et al.*, 2003). Similarly, Somocystinamide A, a depsipeptide derived from *Lyngbya majuscula*, has been demonstrated to be effective against glioblastoma and pancreatic cancer cells by eliciting mitochondrial-mediated apoptosis while blocking angiogenesis. Carotenoids, notably astaxanthin from *Haematococcus pluvialis*, have been demonstrated to prevent chemically induced colon carcinogenesis by downregulating COX-2, MMP-9, MMP-2, ERK-2, and NF- κ B pathways (Prabhu *et al.*, 2009). Similarly via controlling the expression of BCL-2, caspase 3, Bax, and β - β -carotene from *Dunaliella salina* induces death in lung cancer (Ming *et al.*, 2021). By inhibiting VEGF expression and production of vascular tubules polysaccharides like fucoidan from *Cladosiphon novae-caledoniae* have anti-angiogenic properties in HeLa cells (Ye *et al.*, 2005). Brown algae β -glucan, laminarin, activates caspase-8 and releases cytochrome c, which causes stomach and colon cancer cells to undergo apoptosis.

Furthermore, by downregulation of P-glycoprotein, a key efflux transporter linked to multidrug resistance, sulfated polysaccharides from *Porphyridium cruentum* improve the effectiveness of doxorubicin and paclitaxel (Pradhan *et al.*, 2020). By altering ABC transporters, indole alkaloids from *Rhizoclonium hieroglyphicum* also overcome medication resistance in colorectal cancer. Additionally, marine microalgae have potential as immunotherapeutic agents. For example, *Spirulina platensis*'s pigment protein complex C-phycoerythrin (C-PC) causes HeLa cells to undergo apoptosis by upregulating Fas and ICAM-1, activating caspases through the downregulation of Bcl-2 (Jiang *et al.*, 2017). Furthermore, eicosapentaenoic acid

(EPA), which is produced by *Phaeodactylum tricornutum*, improves anti-tumor immune response and regulates inflammatory pathways. *Tetraselmis suecica*, high in polyunsaturated fatty acids, has cytotoxic effects that may be induced by immunological regulation and oxidative stress. Marine microalgae metabolites have anticancer effects through a variety of pathways, including immunological boosting, drug resistance modification, angiogenesis suppression, and apoptosis induction. Marine algae are a promising source of new medicine for integrated cancer treatment because of these characteristics.

Immunomodulation from Marine Microalgae and Mode of Action

Bioactive chemicals produced from marine microalgae have significant immunomodulatory qualities in addition to their anticancer action, making them an attractive option for cancer immunotherapy (Table 2, Figure 3). By controlling inflammatory mediators, cytokine production, and macrophage activity, these substances improve both innate and adaptive immunity (Arango & Descoteaux, 2014). One of the immunomodulatory substances that has been explored the most in sulfated polysaccharides (sPS). *Tribonema* spp. sPS promotes a tumor suppressive immunological milieu by increasing the production of pro-inflammatory cytokines (IL-6, IL-10, and TNF- α in RAW 264.7 macrophages (Bahramzadah *et al.*, 2019). Similarly, without substantially changing TNF- α or IL-6 expression, sPS from *Gonyaulax impudicum* increases nitric oxide generation and macrophage cytotoxicity, further enhancing antitumor immunity. Important thylakoid membrane constituents, sulfolipids, have also shown immunostimulatory potentials. The synthetic sulfolipid β -SQDG18 improves antigen-presenting and tumor-specific lymphocytes in mouse models. Toll-like receptor 4 (TLR4) signaling is activated by glycolipid from species such as *Navicula directa*, which increases the production of proinflammatory cytokines and chemokines that are crucial for tumor immune surveillance (Ho *et al.*, 2023).

Table 2. Immunomodulatory components of microalgae and their mechanism of action.

Microalgae	Compounds / Extracts	Target Cells / Mechanism	Reference
<i>Alexandrium tamarense</i> , <i>Chaetoceros socialis</i> , <i>Dunaliella salina</i> , <i>Skeletonema dohmii</i> , <i>S. marino</i> , <i>S. costatum</i>	Extract	Activation of IL-6/ Human PBMC	Cutignano <i>et al.</i> , 2015
<i>Gyrodinium impudicum</i>	Sulfated exopolysaccharides	Macrophage activation/ Murine	Yim <i>et al.</i> , 2007
<i>Phaeodactylum tricornutum</i> , <i>Chlorella vulgaris</i>	Sulphated extracellular polysaccharide, Sulphated polysaccharide β -(1,3)-glucan	Activate phagocytic	Guzmán <i>et al.</i> , 2003
<i>Gyrodinium impudicum</i>	Sulphated polysaccharide	NF-kappa B and JNK pathway	Bae <i>et al.</i> , 2006
<i>Porphyridium</i> sp.	Sulphated polysaccharide	Skin cells	Matsui <i>et al.</i> , 2003
<i>Tribonema</i> sp.	Sulphated Polysaccharides	Stimulate RAW264.7 macrophage cells	Chen <i>et al.</i> , 2019

Microalgae generate polyunsaturated fatty acids (PUFAs), particularly EPA and DHA, which are essential for immunological regulation. According to Han *et al.* (2017), EPA stimulates macrophages' activity and cytokines release by activating GPR120-mediated MAPK pathways. On the other hand, DHA reduced tumor-promoting microenvironments by inhibiting NF- κ B and downregulating cytokines, which lowers chronic inflammation (Gutiérrez *et al.*, 2020). Astaxanthin, a carotenoid from *Haematococcus pluvialis* and other microalgae, enhances lymphocyte proliferation and cytokine production (IL-2, IFN- γ), bolstering cytotoxic T cell and NK cell activity. By regulating oxidative stress and immunological responses, it also reduces inflammation brought on by *Helicobacter pylori* (Pereira *et al.*, 2021). *Galbana's* fucoxanthin increases macrophages' activity and cytokines production while inducing death in colon cancer cells through mitochondrial pathways (Lourenço-Lopes *et al.*, 2021). Phycobiliprotein such as C-phycocyanin (C-PC) from *Spirulina platensis* activates Fas signaling and caspase-3 to cause death in HeLa and other cancer cells while also boosting T cell activation and antigen-presenting cells (APC) activation (Li *et al.*, 2006; Grover *et al.*, 2021). Through TLR2/4 pathways essential for tumor-specific immune responses, other polysaccharides such as those from *Porphyridium* and *Ulva* species promote dendritic cells maturation, activate macrophages, and improve the generation of nitric oxide and TNF- α (Xia *et al.*, 2021). Marine microalgal chemicals have a variety of immunomodulatory pathways, highlighting their potential as an adjunct in cancer immunotherapy through both direct cytotoxicity and immune boosting effects.

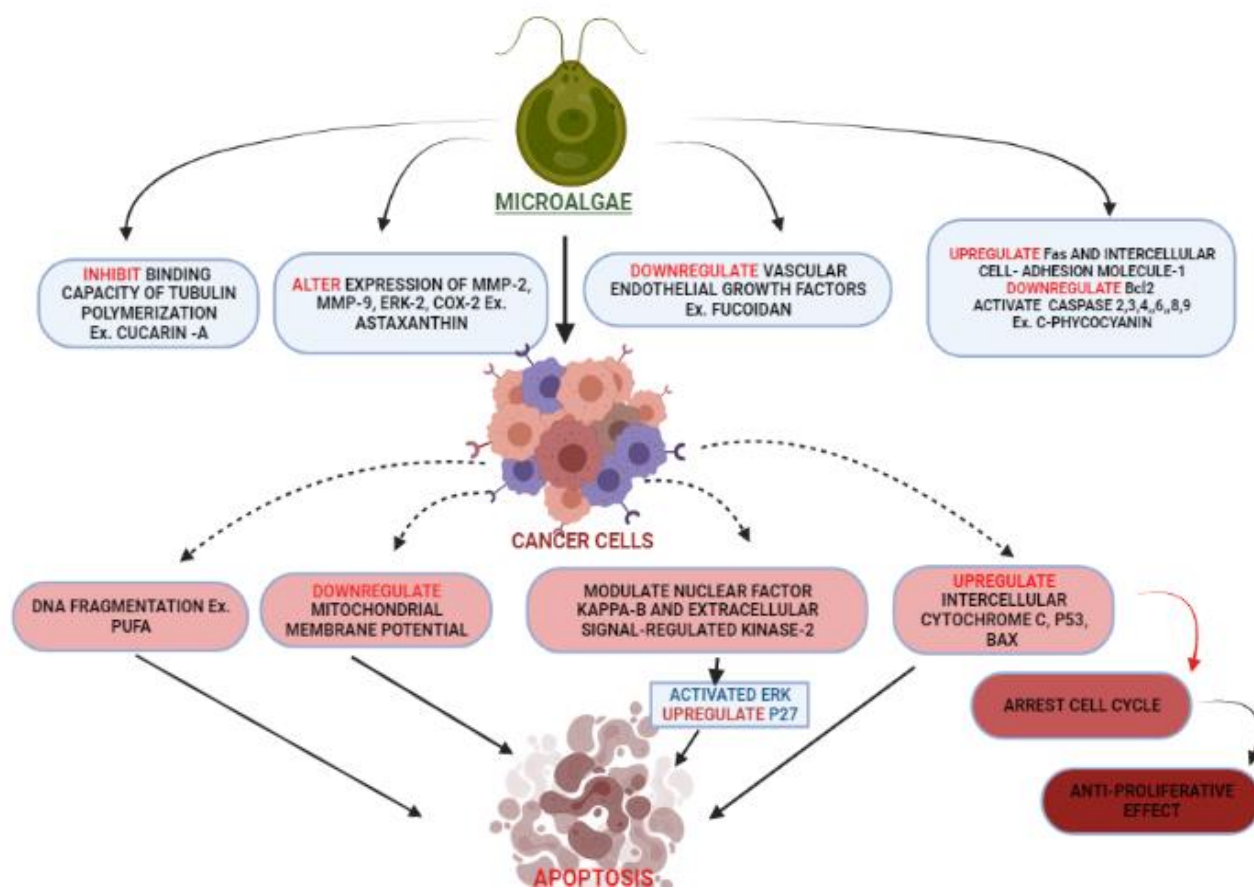


Figure 3. Mechanistic insight for killing cancer cells by microalgae-based bioactive compounds. Modified from (Abd El-hack *et al.*, 2019).

Microalgae as a Promising Approach for Cancer Therapy

Marine microalgae are emerging as a sustainable source of structurally diverse bioactive compounds with significant potential in cancer therapy. These unicellular photosynthetic organisms produce polyunsaturated fatty acids (PUFAs), carotenoids, sulfated polysaccharides, phycobiliproteins, and other metabolites with documented anticancer and immunomodulatory properties. Unlike conventional chemotherapeutic agents that often affect both malignant and healthy cells, microalgal-derived compounds offer more targeted mechanisms with reduced systemic toxicity (Dutta *et al.*, [2025](#)). A key advantage of microalgal compounds lies in their ability to modulate multiple cancer hallmarks, including uncontrolled proliferation, apoptosis resistance, immune evasion, and angiogenesis. PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) inhibit pro-tumorigenic signaling and inflammatory responses (Minhas *et al.*, [2024](#)). Carotenoids like astaxanthin and fucoxanthin induce apoptosis, arrest cell cycle progression, and mitigate oxidative DNA damage. Phycobiliproteins and sulfated polysaccharides enhance immune surveillance by activating macrophages, cytotoxic T lymphocytes, and natural killer (NK) cells. Specific microalgal species, such as *Phaeodactylum tricornutum* and *Gymnodinium impudicum*, produce bioactive metabolites that modulate the tumor microenvironment and enhance antitumor immunity. For instance, *P. tricornutum* synthesizes sulfated polysaccharides that promote macrophage activation (Xia *et al.*, [2021](#)), while *G. impudicum* boosts nitric oxide production and macrophage cytotoxicity (Bae *et al.*, [2006](#)).

Beyond their pharmacological properties, microalgae offer practical advantages over traditional sources. They exhibit rapid growth, minimal land and freshwater demands, and are amenable to year-round cultivation in controlled bioreactor systems (Ahmed *et al.*, [2022](#)). Advances in metabolic engineering and synthetic biology have further enabled the enhancement of specific metabolite yields, thereby optimizing therapeutic efficacy (Razzak *et al.*, [2024](#)). Microalgal bioactives also show promise in overcoming chemoresistance, a major limitation of conventional therapies. Certain compounds inhibit multidrug resistance (MDR) proteins and restore chemosensitivity in resistant cancer cells (Matin *et al.*, [2024](#)). When combined with standard chemotherapy or immunotherapy, these agents may enhance efficacy while minimizing adverse effects. However, challenges remain in the development of microalgae-derived anticancer agents. Issues such as poor solubility, limited bioavailability, and metabolic instability must be addressed to facilitate clinical translation. Nanotechnology-based delivery systems, including lipid nanoparticles and polymeric micelles, are under investigation to improve tumor-targeted delivery and reduce off-target toxicity. Further mechanistic studies and clinical evaluations are essential to validate the safety and therapeutic potential of these novel agents.

Conclusion

Microalgae are a viable and sustainable source of bioactive chemicals that have enormous potential in immunotherapy and cancer treatment. Microalgae produce structurally diverse molecules, which include polyunsaturated fatty acids, phycobiliproteins, sulfated polysaccharides, metal-containing polyketides, sulfolipids, carotenoids, alkaloids, depsipeptides, and sterols that have shown

remarkable immunomodulatory and anticancer properties. These compounds not only cause selective cytotoxicity in cancer cells by inducing apoptosis, inhibiting proliferation, and modulating oxidative stress, but they also improve immune surveillance by activating macrophages, dendritic cells, and lymphocytes while controlling key cytokines and inflammatory pathways. Unlike traditional chemotherapeutics, microalgal-derived compounds provide focused therapeutic advantages with few side effects, making them an appealing option for cancer treatment. This study focuses on the various immunomodulatory features of microalgal bioactive compounds and their potential to reshape cancer immunotherapies. This review makes an important addition by integrating mechanistic insights into how these chemicals impact immune-related cancer processes, notably through pathways such as TLR activation, MAPK signaling, and cytokine modulation.

We also highlight technical breakthroughs such as synthetic biology and metabolic engineering that improve the bioavailability and therapeutic efficacy of micro algal derive drug hence increasing their potential for clinical translation despite these encouraging discoveries significant obstacles remain in optimizing large scale manufacturing, perfecting extraction and purification methods and undertaking comprehensive preclinical and clinical studies to confirm medicinal of action for each compound in specific cancer model improving bioengineering strategies for increased metabolite production, developing targeted delivery systems to maximize clinical efficacy an conducting well designed clinical trials to bridge the gap between laboratory finding and real world application. Furthermore, a better knowledge of the synergistic effects of microalgae bioactive compounds and current immunotherapies might lead to new possibilities for combination treatments. With ongoing advances in biotechnology and pharmacology, microalgae-derived bioactives have the potential to revolutionize cancer treatment by providing a new paradigm in precision oncology and immunotherapy. As research progresses, these natural chemicals may emerge as critical components in next-generation cancer treatment, offering new long-term and highly effective remedies to cancer and immune-related illnesses.

Declarations

Author Contribution: Conceptualization, methodology, formal analysis, and investigation by DM and RT; preparing original draft, review, and editing by DM, RT, SS, AC, RD, & ASS; guidance by DM. All authors have read and agreed to the final version of the manuscript for submission.

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