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Protective effect of microalgae extracts in breast cancer

Mikroalg ekstraktlarının meme kanserinde koruyucu etkisi

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ABSTRACT

Breast cancer is a major global health problem, with an estimated 2.3 million new cases in 2020, making it the most commonly diagnosed cancer in women. Advances in the understanding of genetic and environmental risk factors have contributed to a significant decline in mortality rates over the past three decades and have led to improved diagnosis and treatment strategies. While significant progress has been made in breast cancer awareness and treatment, inequalities in access to care and early diagnosis, particularly in low-resource settings, remain a major challenge. Addressing these gaps is critical to improving outcomes worldwide. Natural treatments for breast cancer are gaining increasing attention as they can complement or enhance conventional treatments while minimizing side effects. Several natural products, including phytochemicals, have shown significant anti-cancer properties through multiple mechanisms, making them promising candidates for the treatment of breast cancer. Microalgae contain several bioactive compounds, including flavonoids and phenolic acids, which have been shown to induce apoptosis and inhibit the proliferation of cancer cells. Microalgae extracts have a significant protective effect against breast cancer through antioxidant activity, apoptosis induction, and immune modulation. Studies show that microalgae such as *Spirulina* and *Haematococcus pluvialis* can inhibit tumor growth and promote cell death in breast cancer models, highlighting their potential as complementary therapies. Although the protective effects of microalgae extracts are promising, to completely comprehend their workings and possible incorporation into traditional cancer treatments, more investigation is required. This review highlights the potential of microalgae and microalgae extracts as a source of anticancer agents based on their efficacy against breast cancer.

Keywords: Microalgae, breast cancer, anticancer, biocompounds, bioactivity

ÖZET

Meme kanseri, 2020 yılında tahmini 2,3 milyon yeni vaka ile kadınlarda en sık teşhis edilen kanser türü haline gelen önemli bir küresel sağlık sorunudur. Genetik ve çevresel risk faktörlerinin anlaşılmasındaki ilerlemeler, son otuz yılda ölüm oranlarında önemli bir düşüşe katkıda bulunmuş ve iyileştirilmiş tanı ve tedavi stratejilerine yol açmıştır. Meme kanseri farkındalığı ve tedavisinde önemli ilerlemeler kaydedilmiş olsa da özellikle düşük kaynaklı ortamlarda bakıma ve erken tanıya erişimdeki eşitsizlikler büyük bir zorluk olmaya devam etmektedir. Bu boşlukları ele almak, dünya çapında sonuçları iyileştirmek için kritik öneme sahiptir. Meme kanseri için doğal tedaviler, yan etkileri en aza indirirken geleneksel tedavileri tamamlayabilmeleri veya geliştirebilmeleri nedeniyle giderek daha fazla ilgi görmektedir. Fitokimyasallar da dahil olmak üzere çeşitli doğal ürünler, birden fazla mekanizma yoluyla önemli kanser karşıtı özellikler göstermiştir ve bu da onları meme kanserinin tedavisi için umut verici adaylar haline getirmektedir. Mikroalgler, apoptozu indüklediği ve kanser hücrelerinin çoğalmasını engellediği gösterilen flavonoidler ve fenolik asitler de dahil olmak üzere çeşitli biyoaktif bileşikler içerir. Mikroalg özleri, antioksidan aktivite, apoptozis indüksiyonu ve bağışıklık modülasyonu yoluyla meme kanserine karşı önemli bir koruyucu etkiye sahiptir. Çalışmalar, *Spirulina* ve *Haematococcus pluvialis* gibi mikroalglerin meme kanseri modellerinde tümör büyümesini engelleyebileceğini ve hücre ölümünü teşvik edebileceğini göstererek, tamamlayıcı terapiler olarak potansiyellerini vurgulamaktadır. Mikroalg özlerinin koruyucu etkileri ümit verici olsa da bunların işleyişini ve geleneksel kanser tedavilerine olası katılımını tam olarak kavramak için daha fazla araştırma gerekmektedir. Bu derleme, meme kanserine karşı etkinliklerine dayanarak, mikroalglerin ve mikroalg özlerinin antikanser ajanları kaynağı olarak potansiyelini vurgulamaktadır.

Anahtar kelimeler: Mikroalgler, meme kanseri, antikanser, biyobileşikler, biyoaktivite

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Introduction

Cancer covers a wide group of diseases related to the uncontrolled proliferation of cells in the body (Farshi, 2024). There are more than 200 different types of cancer, some of which have the potential to spread to other tissues, often causing fatal metastases. According to data from 2022, approximately 20 million new cases and more than 9.7 million cancer-related deaths occurred worldwide (Liao et al., 2024). Numerous studies have shown that cancer progression is due to activation of tumor formation, DNA damage, abnormal DNA repair mechanisms, inactivation of tumor suppressor activity, metastasis, and increased cell survival through angiogenesis (Niranjana et al., 2015; O'Connor, 2015). Although cancer treatments can be successful in some cancer cases, the applicability of these drugs is limited due to their side effects. Generally, drugs used to treat cancer are highly toxic not only to cancer cells but also to normal cells in the body. Chemotherapy and radiotherapy are some of the current standard therapeutic approaches for cancer treatment. However, there are many side effects of chemotherapy with these chemotherapeutic agents, such as hematopoietic toxicity, anorexia and hair loss, which are usually serious side effects. Therefore, the search for new potential therapeutic agents for cancer treatment is remarkable for the scientific world. Particular focus has recently been placed on some marine substances, including lipids, peptides, carotenoids, and carbohydrates, which have anti-cancer, anti-inflammatory, antimicrobial, and antioxidant properties. Microalgae are very important components of the aquatic ecosystem. Known for their rapid growth cycles, microalgae are increasingly used in the production of food and drugs for human/animal consumption due to their ability to survive in a foreign environment. Prior *in vitro* research has demonstrated that a large number of these bioactive microalgal chemicals exhibit potent anti-human cancers, including breast cancer and leukemia. As a consequence, several mechanisms underlying these bioactive chemicals' anticancer activity have been clarified, including their capacity to target molecular, cellular, and subcellular checkpoints linked to the development and spread of cancer. Recent findings have brought to light a number of the processes by which the bioactive substances generated by microalgae work, including as the inhibition of telomerase and protein kinases and the triggering of autophagy and death. In addition to a decrease in tumor volume, further *in vivo* investigations have demonstrated a potent anti-angiogenesis impact on solid tumors.

These bioactive microalgae compounds have also been studied in the context of clinical trials for various types of cancer, making them strong candidates for the development of antitumor drugs.

Breast cancer

Breast cancer is a heterogeneous disease in which genetic and environmental factors play a role. Breast cancer is a global health problem and the most common cancer in women worldwide (Ferlay et al., 2019; Narayan et al., 2020). Many malignant tumors can metastasize, which means the invasion of cancer cells, and this is the most dangerous feature of cancer (McSherry et al., 2007).

Breast cancer begins primarily in breast cells. Malignant tumors, which are clusters of cancer cells, can spread and damage surrounding tissue and also spread throughout the body. Cancer can cause changes in breast cells that prevent them from growing or functioning normally. These alterations may result in benign tumors like intraductal papillomas or non-cancerous breast conditions like atypical hyperplasia and cysts (Sinha, 2018). However, breast cancer can develop due to modifications in the breast cells. It usually begins in the cells of the ducti, the tubes that carry milk from the mammary glands to the nipple, and is called ductal carcinoma (Edward et al., 2021; Obeagu et al., 2023).

Classification of breast cancer

There are various classification methods for breast cancer in the literature. However, the most commonly used method is the method based on the presence or absence of receptors. Breast cancer is categorized into four groups based on the presence or absence of three receptors for estrogen, progesterone and human epidermal growth factor receptor 2 (HER-2) (Hon et al., 2016). Invasive breast cancer is categorized into four main molecular subtypes using an immunohistochemical technique according to the estrogen receptors expression (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Joshi & Press, 2018). The luminal A subtype (ER+ and/or PR+ and HER2-) accounts for approximately 60% of breast cancer cases and is associated with a favorable prognosis (Gao & Swain, 2018). The luminal B subtype (ER+ and/or PR+ and HER2+) accounts for 30% of cases and is associated with a high Ki67 index (>14%), a marker of cell proliferation, and a poor prognosis (Ades et al., 2014). HER2-positive breast cancer (ER-, PR- and HER2+) accounts for 10% of cases and is also associated with a poor prognosis (Loibl & Gianni, 2017). Lastly, 15–20% of cases are triple-negative breast cancer/TNBC (ER-, PR-, and HER2-), which is notorious for its high aggressiveness, propensity to strike young women, and exceptionally poor prognosis (Bergin & Loi, 2019). Triple-negative breast cancer (TNBC) is the type with the worst prognosis. It is

characterized by the complete absence of three receptors, which makes it difficult to treat with hormonal and targeted therapies (Podo et al., 2010). These are aggressive tumors, accounting for approximately 12% to 17% of cases, and are characterized by a high nuclear grade, high mitotic activity and significant metastatic potential to internal organs (Foulkes et al., 2010).

Risk factors for breast cancer

Breast cancer is a disease with high risk factors that can be influenced by many factors, including genetic, environmental, behavioral and major lifestyle elements (Mahdavi et al., 2019; Obeagu EI et al., 2021; Ibekwe et al., 2022). Poor lifestyle choices, environmental and socio-psychological factors are all associated with the onset of the disease. Studies have shown that 5-10% of breast cancer cases are due to genetic mutations and family history, while 20-30% are associated with modifiable factors (Sun et al., 2017). Major risk factors for breast cancer include family history, diet, obesity, mutations such as BRCA1 and BRCA2, genetic predisposition, including smoking and alcohol consumption. Other factors such as exposure to ionizing radiation, menstrual cycles, pregnancy and breastfeeding can also play a role in the development of breast cancer (Mahdavi et al., 2019). Other risk factors for breast cancer include older age, female sex, early menstruation, late menopause, nulliparity, non-breastfeeding, dense breast tissue, hormone replacement therapy and a history of breast radiotherapy (O'Sullivan et al., 2018).

Breast cancer treatment

Most cases of breast cancer are detected by mammography or clinical examination (Ruddy & Ganz, 2019), and there are different strategies for its treatment (Barzaman et al., 2020).

Treatment strategies for breast cancer vary depending on the molecular subtype. In addition to locoregional treatments such as surgery and radiotherapy, there are multidisciplinary approaches that also include systemic treatments. These include endocrine therapy for hormone receptor-positive cancers, chemotherapy, anti-HER2 therapy for HER2-positive cancers, bone-stabilizing agents, poly (ADP-ribose) polymerase inhibitors for patients with BRCA mutations, and, more recently, immunotherapy (Harbeck et al., 2019).

Considering the serious side effects, chemical resistance, high cost, and shortage of cancer drugs, scientists have started to look for natural therapeutics to develop new cancer drugs. Natural medicines have minimal side effects and the potential to act on various signaling pathways related to tumor formation. Considering all these advantages, research on natural products is rapidly increasing to search for new anticancer drugs not only from land plants and microorganisms but also from marine organisms (Sung et al., 2021). Future therapeutic approaches aim to personalize treatment and adjust treatment intensity according to tumor biology and initial response to treatment (Harbeck et al., 2019).

Microalgae

Microalgae are a wide range of prokaryotic and eukaryotic microorganisms that are mostly photoautotrophic and occur singly or in colonies. They play an important role on Earth and form the largest biomass on Earth, responsible for at least 32% of global photosynthesis (Priyadarshani et al., 2011). Moreover, these photosynthetic microorganisms have colonized all marine and terrestrial ecological niches and also represent the largest group of living organisms in terms of biodiversity on Earth (Irigoien et al., 2004). Although they are highly biodiverse, they are an almost untapped resource. There are an estimated 200,000 to 800,000 species in many genera, of which only 50,000 are known (Priyadarshani et al., 2011). Because of their high ecological adaptability and constant exposure to a variety of biotic and abiotic stressors, microalgae are a rich source of interesting and useful components (Pulz & Gross, 2004; Spolaore et al., 2006). As photoautotrophic organisms, they are also an effective source of high value-added biomolecules due to their simple growth requirements and short life cycle (Spolaore et al., 2006; Kim et al., 2014; Plaza et al., 2009). Bioactive compounds of microalgal origin can be sourced directly from primary metabolism, such as proteins, fatty acids, vitamins, and pigments, or can be synthesized from secondary metabolism (de Morais et al., 2015). These substances are used in various fields, including medicine, pharmaceuticals, nutraceuticals, cosmetics, energy, etc. Some extensive studies have confirmed the potential of microalgae as a reliable and environmentally friendly raw material for the production of important valuable resources, paving the way for new advances in biotechnology (Bürck et al., 2024). Microalgae such as *Haematococcus pluvialis*, *Dunaliella salina*, *Blakesleatrispora* sp., *Desmodesmus* sp., *Euglena gracilis*, *Tisochrysis lutea*, *Isochrysis galbana*, *Phaeodactylum tricornutum* and *Cylindrotheca closterium* are among the most studied, as they are capable of producing significant amounts of carotenoids (Razz, 2024; Huang et al., 2024). They are microorganisms that synthesize a variety of rare carotenoids and pave the way for innovative industrial and scientific applications. These carotenoids, such as fucoxanthin, xanthophylls and astaxanthin, are

characterized by their high antioxidant and anti-inflammatory properties and contribute to human health and protection against various chronic diseases (Gong et al., 2024).

Microalgae as a source of biocompounds

Nowadays, many industries from various sectors are investing in natural and biologically produced products with high added value (Mahapatra et al., 2018). Pharmaceuticals, cosmetics, food and pet food, polymers, chemicals, and energy products are just a few of the industries that use these products. The use of microalgae is particularly interesting and important due to their cellular composition, which enables the extraction of high-quality commercial products (Kumar et al., 2021; Premaratne et al., 2021). Microalgae synthesize two categories of metabolites, namely primary metabolites and secondary metabolites. Lipids, proteins, and carbohydrates are examples of primary metabolites that are essential to the survival of some microorganisms, whereas carotenoids, astaxanthin, and polyhydroxyalkanoates are examples of secondary metabolites that are functional substances connected to physiological systems (Japar et al., 2021; Liu et al., 2022). They are microorganisms that represent a potential source of raw materials for various bioproducts, mainly due to the primary and secondary metabolites they contain. Lipids can be converted into high-value polyunsaturated fatty acids such as omega-3, while carbohydrates can be potential sources of biohydrogen. Proteins can likely be converted into biopolymers such as bioplastics, and pigments can reach high concentrations of valuable carotenoids (Calijuri et al., 2022). These microorganisms are rich in bioactive components, mainly lipids (7-65%), proteins (5-74%), carbohydrates (8-69%) and to a lesser extent other metabolites such as pigments and vitamins (1-14%), depending on their cell structure (Becker, 2007; Ejike et al., 2017; del Mondo et al., 2020; Siddiki et al., 2022). Proteins, essential amino acids, carbohydrates like glucose and starch, omega-3 and omega-6 fatty acids, and vitamins B1, B2, B5, B6, B9, A, C, and E are all known to be abundant in microalgae (Yan et al., 2016; Chu, 2012). Microalgae extracts (chemical composition) contain carbohydrates, proteins, lipids, vitamins, micronutrients, macronutrients and phytohormones like gibberellins, ethylene, cytokinins, auxins, abscisic acid and other bioactive compounds such as fucoxanthin and phycobiliproteins (Bello et al., 2021). Microalgae biomass is an excellent raw material for the production of biofuels, biomaterials (peptides, proteins, saccharide polymers) and carbohydrates ($Cn(H_2O)n$) for the animal and human food sector (Maurya et al., 2016; Corre et al., 2017). As microorganisms, algae have a lipid composition that generally varies between 20% and 50%, but, based on the strain and culture conditions, can increase to 80%. (Sun et al., 2018). Among the compounds extracted from microalgae, lipids are the most studied and offer significant potential for expansion and commercialization of the process (Maltsev & Maltseva, 2021). Linoleic acid (C18:2 or omega-6) and linolenic acid (C18:3 or omega-3) are among the most popular polyunsaturated fatty acids, mainly because of their benefits and advantages for human health (Sharma et al., 2020), as they can combat numerous diseases such as coronary heart disease, thrombosis, macular degeneration, dementia, diabetes, allergies, asthma, osteoporosis and some cancers. They are currently being investigated as a potential adjuvant treatment for cardiovascular complications associated with COVID-19 as well as many other diseases (Oliver et al., 2020). In addition, long-chain omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (C20:5 or EPA) and docosahexaenoic acid (C22:6 or DHA), are used to feed aquatic organisms in aquaculture (Fernández et al., 2021).

Microalgae are rich sources of phenolic compounds, which are well known for their strong antioxidant and anticancer properties (Cichoński & Chrzanowski, 2022). These bioactive molecules can modulate various cellular pathways, including oxidative stress reduction, apoptosis induction, and inhibition of cancer cell proliferation. Several studies have highlighted the role of microalgal phenolics in suppressing tumor growth through mechanisms such as cell cycle arrest and modulation of key signaling pathways involved in carcinogenesis (Matulja et al., 2022). Moreover, their ability to enhance the efficacy of conventional chemotherapy while minimizing side effects makes them promising candidates for breast cancer treatment. Further research is needed to explore their bioavailability and molecular interactions to fully unlock their therapeutic potential.

Carotenoids are secondary metabolites produced by microalgae. As natural pigments, they are considered healthier than chemically synthesized pigments and are attracting the attention of various industries such as pharmaceuticals, cosmetics, food, and health (Henríquez et al., 2016). The most well-known carotenoids that come from microalgae in the commercial market are β-carotene, lutein, and astaxanthin (Hu et al., 2018; Rammuni et al., 2019). The increasing interest in these substances is due to the antioxidant, anti-inflammatory, vitamin A precursor and neuroprotective properties of microalgae-derived carotenoids (Cezare-Gomes et al., 2019; D'Alessandro & Antoniosi Filho, 2016; Hu et al., 2018). Researchers are currently concentrating on species like *Haematococcus*

pluvialis for astaxanthin (Li et al., 2011; Rammuni et al., 2019), *Murielopsis* sp. and *S. almeriensis* for lutein (Pagels et al., 2020), and *Dunaliella salina* for β-carotene (Pourkarimi et al., 2020; Wu et al., 2020; Xi et al., 2020). Nonetheless, *Chlorella vulgaris*, *Spirulina platensis*, *Haematococcus pluvialis*, and *Dunaliella salina* are the most researched species, according to Silva et al. (2020), who compiled the trends in the brightest pigments and microalgae sources over the previous ten years. Microalgae contain carotenoids such as diatoxanthin, diadinoxanthin, alloxanthin, and peridinin, which are important because they contain a variety of bioactive compounds. These substances have potential uses in several biotechnological fields and are advantageous to human health (Pistelli et al., 2021).

Terpenes are a diverse class of compounds with key ecological roles, including intraspecific communication, chemical defense, and protection against microbial contamination. Although generally classified as secondary metabolites, their isoprenoid precursors also contribute to primary metabolites like chlorophylls, carotenoids, and steroids. Algae, particularly red algae, produce various terpenes such as monoterpenes, sesquiterpenes, and diterpenes, which exhibit antimicrobial, anti-inflammatory, antioxidant, and anticancer properties. These characteristics make terpenes valuable for scientific and industrial applications (Liu et. al., 2024).

Microalgae such as cyanobacteria are indeed an important source of extracellular polysaccharides. They can be used as stabilizers in the food industry and as humectants in cosmetics and pharmaceuticals. Additionally, the human immune system is known to be stimulated by sulfated polysaccharides derived from microalgae (Fu et al., 2019).

Microalgae such as *Spirulina* and *Chlorella vulgaris* are rich in proteins. Studies have shown that the proteins in *Spirulina* can reduce inflammation and allergies, while the peptides in *Chlorella vulgaris* can protect against cell damage. In addition, these microalgae provide essential amino acids that mammals cannot synthesize (Barkia et al., 2019; Lordan et al., 2011).

Using biomolecules extracted from algae as active pharmaceutical ingredients plays a significant role in pharmacy. Most studies on this topic focus on these extracts' total phenolic content and antioxidant activity. Research has been conducted on the *in vitro* antioxidant activities of extracts and/or molecules derived from various *Chlorella* species, their protective effects against radical-induced oxidative stress in kidney cells, and the total phenolic content and antioxidant activity of *Ankistrodesmus* sp. (Ko et al., 2012; Chen et al.,2014; Nakashima et al., 2009; Jerez-Martel et al., 2017).

In a study by Manivannan et al. (2012), the authors assessed *Chlorella marina*'s *in vitro* antioxidant properties to identify safe and inexpensive new antioxidant sources. They prepared algal extracts using methanol, diethyl ether, and hexane solvents and tested their total phenolic content, antioxidant activities, deoxyribose radical scavenging activities, and reducing power. Their results indicated that the methanol extracts of *C. marina* might possess potential antioxidant effects (Manivannan et al., 2012).

Shanab et al. (2012) evaluated the antioxidant and anticancer activities of aqueous extracts from 9 microalgae species, including 8 cyanobacteria and 1 green alga (*Chlorella vulgaris*). The extracts were first evaluated for their total phenolic content, secondary metabolites such as terpenoids and alkaloids, and phycobiliprotein pigments like phycocyanin. Then, the antioxidant activities of the algal extracts were assessed. Finally, the effects of the extracts on the proliferation of HepG2 and EACC cancer cells were evaluated by calculating cell viability percentages. They found that *C. vulgaris* exhibited anticancer activity (Shanab et al., 2012).

Stress responses and tolerance mechanisms in microalgae

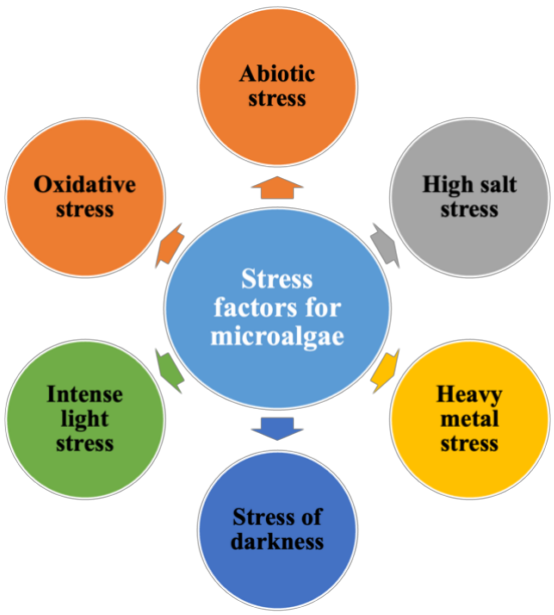

Figure 1. Stress factors for microalgae

Factors such as abiotic stress, high salt stress, oxidative stress, intense light stress, darkening stress and heavy metal stress can cause stress in microalgae (Figure 1). Stress factors can cause changes in the physiological and biochemical processes of microalgae and affect growth, photosynthesis, cellular ultrastructure, protein content and fatty acid composition. These stress factors can also trigger

the production of reactive oxygen species (ROS), which cause the oxidation of proteins, lipids and peptides and stimulate the antioxidant system (Xiao et al., 2023; Singh et al., 2018).

Responses of microalgae to abiotic stress

Microalgae demonstrate high tolerance to abiotic stressors and produce valuable metabolites. Exposure to nutrient deficiency, intense light, extreme temperatures, high salinity, or heavy metals can stimulate lipid and by-product biosynthesis (Paliwal et al., 2017; Chen et al., 2017). Nutrient deficiencies, particularly in nitrogen, phosphorus, and metal ions, are known to enhance lipid accumulation (Chen et al., 2011; Fernandes et al., 2013; Pancha et al., 2014). One well-studied species, *Chlorella protothecoides*, produces significant lutein and fatty acids suitable for biodiesel (Campenni' et al., 2013). While continuous stress promotes lipid or carbohydrate accumulation, balancing it with growth rate is crucial to maintaining productivity and reducing biofuel costs (Pancha et al., 2015).

Under stress, microalgae produce polyunsaturated fatty acids and adapt by modifying their membrane composition and accumulating compatible solutes. Salt stress, for instance, enhances carotenoid synthesis, likely due to increased reactive oxygen species (Li et al., 2009). Salt-tolerant species like *Dunaliella salina* produce osmoprotective solutes such as sucrose, glycerol, and betaine, aiding survival under extreme salinity (El Arroussi et al., 2015).

Responses of microalgae to high salt stress

Microalgae species adapt to extreme salinity through metabolic changes (Gebser & Pohnert, 2013; Paliwal et al., 2017). Elevated salt levels inhibit growth in freshwater algae such as *Chlorella vulgaris*, *Chlorella salina*, *Chlorella emersonii* (Talebi et al., 2013) and *Scenedesmus opoliensis* (Demetriou et al., 2007). In *Chlamydomonas*, high salt stress slows cell division, reduces size, and induces palmelloid formation, a transitional stage where cells lose flagella, secrete exopolysaccharides, and cluster together (Hema et al., 2007; Khona et al., 2016). *Chlorella* and *Dunaliella* respond differently to salt stress. *Chlorella* relies on osmoregulation through organic solutes and inorganic ion accumulation, while *Dunaliella*, lacking a rigid cell wall, rapidly adjusts turgor pressure by modulating intracellular ion and glycerol concentrations (Shetty et al., 2019; Kaçka & Dönmez, 2008).

Responses of microalgae to heavy metal stress

Recent studies have examined heavy metal stress in microalgae such as *Chlorella*, *Scenedesmus*, cyanobacteria, and *Chlamydomonas reinhardtii*, revealing species-dependent toxicological responses (Geng et al., 2022; Pradhan et al., 2019; Gu et al., 2020; Míguez et al., 2021). Industrial wastewater contains over 40 heavy metals, including Cu, Zn, Pb, Cd, and Hg, which persist in nature due to their non-biodegradable nature (Zamani et al., 2020). Microalgae absorb heavy metals through specialized surface interactions (Hamed et al., 2017) but exhibit stress symptoms such as slow growth, reduced pigments, and abnormal morphology. Metal ion uptake triggers reactive oxygen species (ROS) accumulation, which, if uncontrolled, disrupts cellular redox balance, damages biomolecules, and can cause cell death (Sun et al., 2018). The extent of damage depends on metal type, concentration, and environmental conditions.

Responses of microalgae to dark and intense light stress

Microalgae, as phototrophic organisms, rely on light for survival and reproduction. Changes in the light regime significantly impact chlorophyll concentration, photosynthesis, and productivity. Prolonged darkness inhibits proteins involved in nitrogen assimilation while stimulating glycolysis and fatty acid synthesis, redirecting cellular carbon and nitrogen to lipid biosynthesis (Bai et al., 2016). Light intensity also affects biomass and nutrient composition. High light increases neutral lipids like TAGs while reducing polar lipids due to oxidative damage (He et al., 2015; Breuer et al., 2013; Carvalho & Malcata, 2005). TAG accumulation rates vary across species such as *Chlorella* sp., *Monoraphidium* sp., *Scenedesmus obliquus*, *Pavlova lutheri*, and *Nannochloropsis gaditana* (Mitra et al., 2015).

Responses of microalgae to oxidative stress

Reactive oxygen species (ROS) are pro-oxidants that trigger oxidative stress. They accumulate from abiotic, anthropogenic, and biological sources, including photosynthesis and enzymatic reactions (Kehrer, 2000). In aerobic organisms, ROS include superoxide anions ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and hydroxyl radicals ($HO\cdot$). Photosynthetic organisms are highly exposed to ROS due to oxygen depletion in the electron transport chain (Chokshi et al., 2017; Gill & Tuteja, 2010; Rezayian et al., 2019). Elevated ROS levels damage nucleic acids, proteins, and lipids, leading to metabolic disorders and potentially cell death (Kehrer, 2000; Gill & Tuteja, 2010).

Anti-cancer activities of microalgae

Most microalgae species are rich in carotenoids, antioxidants known for their antitumor effects (Fleischauer et al., 2003). Many studies have shown that microalgae extracts have various anticancer, antiviral, antimicrobial, antibacterial and anti-inflammatory activities and properties. These algae-derived substances affect various cellular mechanisms such as cytotoxicity, suppression of tumor cell invasion and enhancement of apoptosis of cancer cells (Lee et al., 2013; Farooqi et al., 2012). Extensive research in the field of cell and molecular biology has shown significant and natural antitumor activity of algae compounds (Talero et al., 2015; Kumar et al., 2013). For example, fucoxanthin, a carotenoid found in microalgae, diatoms and brown algae, has shown remarkable cancer properties by inhibiting the growth of malignant cells, activating tumor suppressor genes and disrupting cell cycles while protecting tumor cell apoptosis (Takahashi et al., 2015; Peng et al., 2011). It has also been demonstrated that bioactive substances from microalgae, including lipids, carbohydrates, and phycobiliproteins, have apoptotic and antiproliferative effects on a variety of cancer types (Talero et al., 2015). In a previous study, fucoidan, a sulfated polysaccharide extracted from various microalgae such as *Fucus vesiculosus*, *Sargassum henslowianam*, *Cladosiphon fucoidan* and *Coccophora longsdorfii*, was shown to inhibits angiogenesis and metastasis in human lymphoma, melanoma, colon cancer, breast cancer, lung cancer and human promyeloid leukemia cells by reducing kinase activity and activating caspase-3/7 (Deniz et al., 2017). Microalgae are also rich in docosahexaenoic acid (DHA), a compound known to induce cytotoxicity and upregulate lipid peroxidation. It exhibits antitumor properties due to its effect on the cell nucleus and mitochondria and responds to the resulting stress factors with structural or functional changes that lead to apoptosis (Siddiq & Dembitsky, 2008). In another study, cyanobacterial extracts, which share certain bioactive compounds with microalgae, have shown strong antiproliferative effects and induced DNA damage in cancer cell lines, including colon cancer (Andeden et al., 2018). These findings support the potential anticancer role of microalgal secondary metabolites in breast cancer treatment.

The role of microalgae in breast cancer

Various species of microalgae produce carcinogenic bioactive compounds due to their natural origin such as carbohydrates, peptides, carotenoids, polyphenols and fatty acids, their rapid growth cycle, their ability to survive in a hostile environment, their low toxicity, their diverse bioactivities, their ability to control cellular, subcellular and molecular checkpoints involved in cancer development and progression, as well as their ability to induce autophagy and apoptosis, inhibit telomerase and protein kinases, and these compounds inhibit breast cancer cell proliferation, induce apoptosis and modulate key signaling pathways involved in cancer progression. In addition, the mechanisms of action of these bioactive compounds and their potential synergistic effects with conventional cancer therapies are being investigated. These microalgae offer a promising avenue for the development of alternative and complementary therapies for breast cancer. *In vivo* studies with these microalgae have shown a potent anti-angiogenesis effect on solid tumors as well as a reduction in tumor volume. These bioactive compounds of microalgae have also been investigated in clinical studies on various types of cancer, making them good candidates for the development of antitumor drugs.

In a study investigating the cytotoxic effect and apoptosis mechanism of ethanol extracts from *Chaetoceros calcitrans* on human breast cell lines, it was found that this extract inhibited cell growth in MCF-7 cells by apoptosis induction without cell cycle arrest. It was also observed that this extract induced apoptosis in MCF-7 cells by modulating CDK2, MDM2, p21Cip1, cyclin A2, Bax and Bcl-2 and showed an increase in Bax/Bcl-2 ratio, which activates caspase 7 and activates caspase-dependent pathways (Ebrahimi et al., 2013).

In a study investigating the cytotoxic effect of SRD3 against MCF-7 cell lines *in vitro*, it was found that four different solvent extracts (methanol, ethyl acetate, chloroform and hexane) of *Chlorella* sp. caused the death of MCF-7 cells, although differently for each extract. In addition, the methanol extract was shown to be non-toxic to the control cells, so this extract can be used in the pharmaceutical industry as a good source for the treatment of cancer cells (Sigamani et al., 2019).

Microalgae are known for their bioactive compounds with potential applications such as antimicrobial, anti-aging and anticancer activities. In a study by Akbarizare et al. (2019), the anticancer potential of saponins extracted from *Spirulina platensis* was investigated. After 24-hour treatment with 0.02-2 mg/ml saponin extracted from *S. platensis*, the cytotoxic activity changed in a concentration-dependent manner. The toxicity of saponins was determined as IC50=0.22 mg/ml in MDA-MB-123 cells, while the IC50 value in MCF-7 cells was 0.4 mg/ml. Nowadays, marine microalgae are considered a relatively new and rich source of bioactive compounds used in the nutraceutical and pharmaceutical sectors. In the study conducted by Wali et al. (2020), which investigated the anticancer effect of *Nannochloropsis oculata* extract in

MDA-MB-231 breast cancer cells, it was reported that the viability of the cells decreased depending on the extract concentration and time (400 µg/ml in 24 hours, 300 µg/ml in 48 hours and 200 µg/ml in 72 hours). In addition, it was observed in light microscopy images that the number of cells decreased with increasing concentration in the cells treated with the extract.

In a study by Salem et al. (2020), it was found that the methanol extract of *Chlorella vulgaris*, a type of green algae, showed strong cytotoxic activity against the breast cancer cell line MCF-7 (IC50=15.53 µg/ml).

Nowadays, the main objective of many studies is to screen sources of biologically active compounds that can treat cancer. In a study investigating the anticancer activities of methanol extracts from *Spirulina maxima*, *Chlorella salina*, *Nannochloropsis oceanica* and *Nannochloropsis oculata*, it was reported that the extract from *Spirulina maxima* showed promising activity against breast cancer by causing 75.50±1.76% cytotoxicity at a concentration of 200 µg/ml in MCF-7 cells. This was followed by the extract of *N. oceanica* (46.86±8.15% cytotoxicity) at the same concentration (Elkhateeb et al., 2020). Microalgae are a rich source of polyunsaturated fatty acids. In the study, the cytotoxic effect of the *Chlorella* sp. S14 strain, which has the potential to produce polyunsaturated fatty acids (PUFAs), was investigated on some cancer cells. While the PUFA-rich extract showed no cytotoxic effect on normal cells, the viability of cells from MCF-7 (31.58%) and A549 (62.56%) treated with this extract was significantly reduced. These results demonstrate the potential of PUFA-rich extracts from *Chlorella* sp. S14 to reduce the viability of A549 and MCF-7 cells (Vilakazi et al., 2021).

The most prevalent malignant malignancy in women globally is breast cancer. Conventional medicine has been challenged by drug resistance, toxicity, and the incapacity of present therapies to completely treat breast cancer. As a result, complementary alternative medicine has become popular due to its safety and efficacy. Alateyah et al. (2022) investigated the effects of methanol extract (T1) of *Haematococcus pluvialis* (*H. pulvialis*), a freshwater green microalgae species, on cell growth and migration/invasion in MDA-MB-231 MK cell line and fibroblast control cells. They reported that T1 significantly suppressed the growth of MDA-MB-231 MK cells, inhibited migration and invasion, and induced apoptosis. According to their findings, T1 inhibited invasion and induced apoptosis through the p53/Bax/Bcl2 signaling pathway, which is how it causes cancer. Microalgae-derived bioactive chemicals have been shown to have anti-inflammatory, anti-bacterial, anti-cancer, and antioxidant properties. Basha et al. (2024) performed extractions with three different solvents, namely methanol, acetone and hexane, from the microalgae species *Acutodesmus obliquus* (CN01) and *Desmodesmus perforates* (SP04) isolated and propagated from freshwater. Methanol extracts of *Acutodesmus obliquus* (CN01) and *Desmodesmus perforates* (SP04) showed antiproliferative effects against MCF-7 ranging from 87±1.1271% to 73±0.2744% and 82±0.0236% to 73±0.0423%, respectively.

Soha et al. (2024) investigated how *Spirulina* affects the phosphoinositide 3-kinases/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, which is important in cancer progression. To this end, a breast cancer model was created using female rats stimulated with 7,12-dimethylbenzanthracene (DMBA), and the antitumor, antioxidant and anti-inflammatory activities of *Spirulina* about breast cancer were evaluated using methods such as comprehensive. The study concluded that *Spirulina* exhibited significant antitumor activity against DMBA-induced breast cancer in female rats and has potential as a therapeutic agent in cancer treatment. *Spirulina* was also shown to possess potent antioxidant properties that contribute to the improvement of oxidative stress markers in the treated rats. This suggests that *Spirulina* may help to alleviate cancer-related oxidative damage. These studies suggest that microalgae extracts have apoptotic and antiproliferative properties on breast cancer cells, which may facilitate the creation of novel medications. However, further research is needed to fully elucidate their mechanisms and clinical applicability in anti-cancer strategies.

Conclusions

Despite the promising potential of microalgae extracts, further research is needed to fully understand their mechanisms and optimize their use in the clinical setting. The integration of these natural compounds into cancer therapy could revolutionize treatment approaches, especially for patients resistant to conventional drugs. All these studies suggest that microalgae extracts can be further investigated as a natural dietary supplement or adjunct therapy in the treatment of breast cancer and additional studies are needed to confirm their efficacy and mechanisms of action.

Author contributions

Solange Kolie: Literature review, figure/table organization, manuscript writing. Pınar Altın-Çelik: Conceptualization, data curation, figure/table organization, critical revision of the manuscript. Hamiyet Dönmez-Altuntaş: Supervision, conceptualization, draft preparation, reference management. Muazzez Derya-Andeden: Conceptualization, manuscript editing, final approval of the version to be published.

Declaration of interests

The authors declare that there is no conflict of interest.

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