Review Article

Microalgal Nanocarrier Drug Delivery in Cancer Therapy

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ABSTRACT

A suitable treatment plan is needed for cancer, a common medical condition. Chemotherapy also radiation are the two majorly common therapeutic modalities for the treatment of cancer; yet, serious side effects have been linked to these therapies. Radiation, for instance, can negatively impact a patient's immune system function. By offering cutting-edge corrective remedies, these adverse effects may be reduced. Microalgae also contain various types of bioactive molecules, including carotenoids, different kinds of polysaccharides, vitamins, sterols, fibers, minerals, etc. Considerable advancement in the creation of anti-malignant medications may be made possible by the vast amount of unused biomass found in microalgae and their excellent diversity of chemical components. Previously, this property of microalgal biodiversity was used for profit to produce dietary supplements and gelling agents. However, recently, several studies aimed at examining the possible anti-carcinogenic activity of microalgal extracts came to the majority of conclusions that they could induce programmed cancer cell death on either caspase-dependent or independent routes. Diatoms are unicellular photosynthetic creatures that are highly productive and have short growth cycles. They are important for the biogeochemical cycling of nitrogen, carbon, and silica. The bio-silica of diatoms has the potential to be a successful medication administration for targeted cancer remedial treatment because of its, biodegradability, bio-compatibility, nano-porosity, and substantial surface area. In this review work, we have talked about the many microphytal species that have athwart tumor activity and the tumor cell lines that have been modified using microalgal extracts that have been found to have an inhibitory effect on cell cycle and proliferation.

Keywords: Chemotherapy, diatoms, treatment, microalgae, tumor, microphyte.

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INTRODUCTION

The second leading cause of death worldwide is cancer. Additionally, it was responsible for 8.8 million fatalities in 2015. Thus, cancer was the cause of almost 1 in 6 fatalities. Uncontrolled cellular proliferation in malignant tumors is associated with significant pathologic alterations[1]. Uncontrollable tumors are presently y more than 200 dissimilar forms are displayed, as well as numerous malignancies that can spread to other organs and cause lethal metastat tumorsurs. The elimination of cancer has received a lot of attention due to its high level of impact [2]. Chemotherapy, which uses medications that can either kill cancerous cells or at least slow their growth, is frequently used as the initial line of treatment for cancer [3]. These medications are linked by toxicity, which can range from a minor reaction to a serious sickness that poses a life-threatening threat [4]. Hair loss and appetite loss were among the many chemotherapy medications adverse effects. As a result, various sources should be examined for potential anticancer drugs [5].

In general, algae are the primary producer of several natural anticancer amalgams or their metabolites. The biological effects of phytochemicals obtained from plants have been the focus of many studies, whereas microalgae-derived phytochemicals have received very less attention[6]. Phytochemicals with more potential biological activity are generated from microalgae than those with a terrestrial origin (plant phytochemicals). Compared to many other plant species, microalgae exhibit a variety of phenolic classes that are highly unique (medicinal plants, fruits, and vegetables)[7]. In comparison to some plants, microalgae have a higher concentration of chlorophyll and carotenoids. The eukaryotic microbes are thought to be a nice source of proteins and various nutrients[8]. Additionally, these bacteria create a wide variety of bioactive substances that may be sources of immunomodulatory molecules, anti-microbial, anti-inflammatory, and anti-cancer in addition to having other health-promoting benefits[9]. The phytonutrient parts of microalgae, particularly the peripheral metabolites, which are extraordinary sources of bioactive chemicals, are generally the foundation for the pharmacological activities of these organisms[10].

Peptides have a significant potential for application in pharmaceuticals, although they have not been extensively

studied as a class of chemicals[11]. Peptides are small, under 3 kDa molecular weight amino acid chains that typically have 2 to 20 units. Bioactive peptides play key roles in development regulation, cell signaling, and defense response in plants.

Plant-derived proteins can also be made in a lab by the catalytic breakdown of withdrawn proteins or by maceration (‘in the gastrointestinal system’) of proteins from eaten algal biomass[12 13]. The application of carbon compounds, one of the many beneficial by-products produced by microalgae, is in medicine, cosmetics, and pharmaceuticals. The presence of lipids, proteins, polysaccharides, vitamins, and antioxidants are only a few of the other components found in microalgae.[14 15] Microalgae improve the host's defense by boostingthe activity of natural killer cells, stimulating the immune system, and reducing the proliferation of cancer cells. The prevention of carcinogenesis was therefore thought to be in part due to microalgae. We have made an effort to cover the profitable aspect of microalgae bio-products in our review because they can essentially be used as anticancer medicines[16 17].

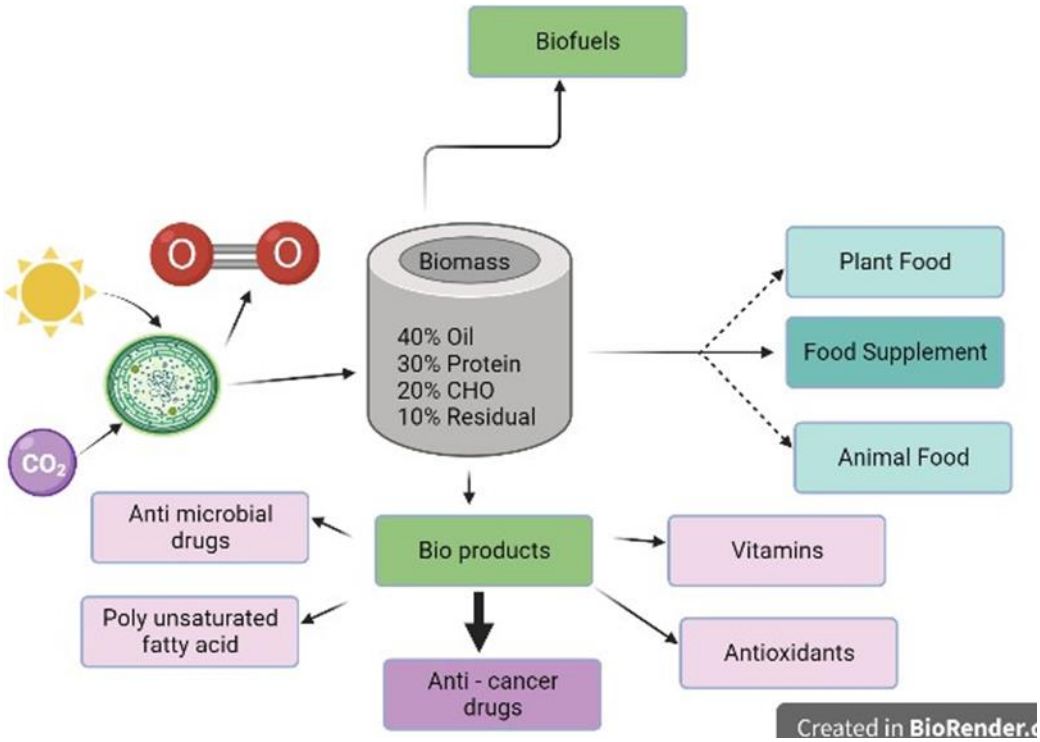

Figure 1: The majorly used microalgal-derived compounds; microalgal biomass is a viable origin for biofuel & biologically active goods.

Microalgae and its Versatile Health Benefits

A diverse category of photosynthetic microbes known as microalgae, whose biochemical compositions range greatly due to their evolutionary and phylogenetic variety[18 19]. In reaction to changes in their environment, these bacteria can biosynthesize, collect, and generate a broad variety of primary and secondary metabolites, many of which are extremely important compounds with industrial uses and positive health effects[20].

Although different populations have used microalgae as a food source for thousands of years, mercantile abuse of this resource only began in the last few decades, when there was concern over a potential shortage of protein due to the world's rapid population growth[21 22].For hundreds of years, people have used microalgae as food or nutritional supplements[23]. Around AD 1300, the ‘Aztecs’ employed the cyanobacterium spirulina (*‘Arthrospira maxima’*, *‘Arthrospira platensis’*) from ‘Lake Texcoco (Mexico)’. The blue-green masses that the local fisherman collected from the lakes and turned into the dry cake known as "tecuitlatl" were reported by ‘Spanish chroniclers’[24]. The people of ‘Chad’ have been regularly obtaining and utilizing spirulina, also known as "dihé," from ‘Lake Kossorom’.Nostoc, a type of filamentous cyanobacteria, has also long been consumed as food[25]. The ‘*N.Punctiforme*’,‘ *N. flagelliforme’* and ‘*N. commune’* also called as "fa cai" and "lake plum," are traditionally eaten in ‘China’, ‘South America’,etc[26 27].

Algae are divided into four taxonomic groupings in the Protista kingdom based on their color (red, brown, blue, and green)[28 29]. Microalgae are essentially composed of various ratios of lipids, carbohydrates, proteins, and nucleic acids; these ratios can vary depending on the species and growing circumstances. Additionally, they include carbohydrates, vitamins, minerals, and colours[30 31]. For instance, an examination of the cells of marine microalgae (*Nannochloropsis*) revealed the pigment, amino acids, and omega-3 fatty acid contents of the microalgae.[32 33 34]

Table 1: Two main sources of Microalgae[34]

Freshwater Algae	Marine Algae
The ten primary phyla of freshwater algae can be distinguished microscopically. In addition, other minor phyla have little impact on the freshwater environment, including *'Eustigmatophyta'* (three species),*'Prasinophyta'* (13 species), *'Glaucophyta'* (two species each), *'Haptophyta'* (five species), and *'Raphidophyta'*. A taxonomical range of microalgae can generally be determinedfrom the large species diversity of fresh water and terrestrial algae.	The unique beneficial genes and metabolites come from this key primary source. More than 30,000 distinct microalgae species have been identified todate. Eukaryotic species like diatoms and prokaryotic organisms are included in the heterogeneous marine microalgae.

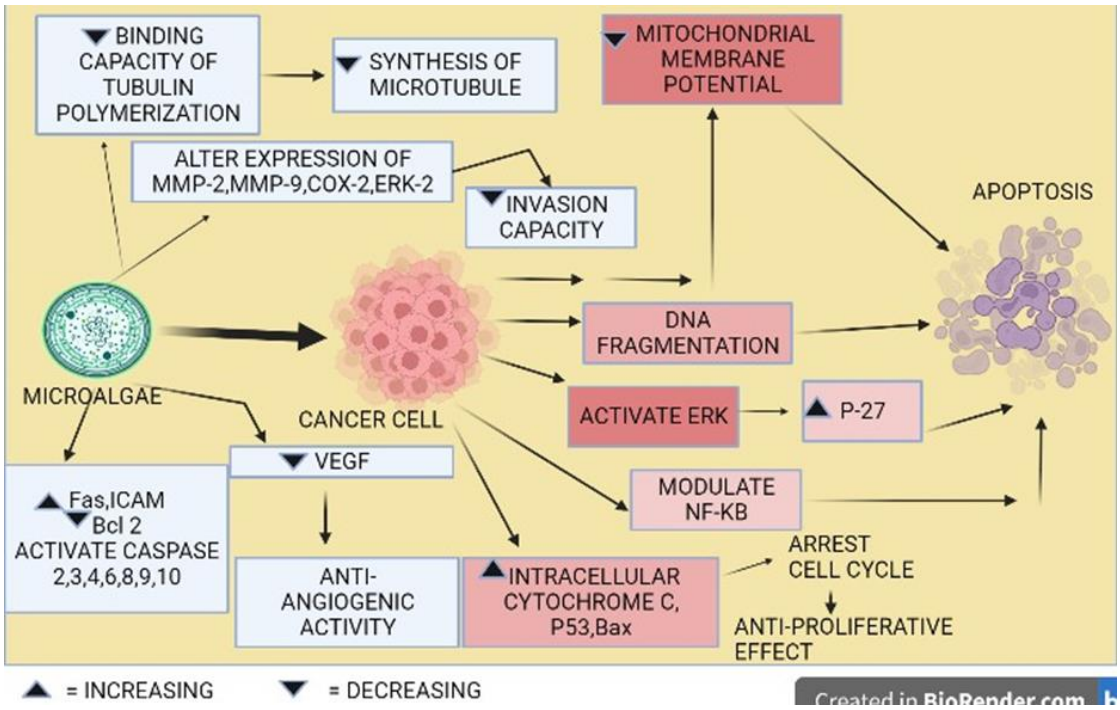

Figure 2: The potential cell mechanism(s) underlying microalgal anti-tumor activity and the potential function of the involved molecules.

Table 2: Types of microalgae, their phytoconstituents, and anti-cancer property[4]

Microalgae	Phytoconstituents	Anti-cancer property
Chondrus crispus Brown and Red algae	Beta-carotene	Prevents cell cycle arrest and apoptosis from occurring, as well as the development of numeroushuman colon cancer cell lines. Decreases the important cell cycle regulator cyclin A
Cystoseira sp.	Terpenoids	Extremely effective anti-platelet aggregation and anti-tumor action
Red algae	Phycoerythrin and phycocyanin	In 'HepG2' and 'A549' cells, cell proliferation is inhibited by inhibiting the tumor cell cycle, triggering tumor cell death, and activating autophagy.
Halimeda sp.	Catechin, flavonoids, phloro tannins, etc	Regulation of oxidative stress-related pathways. Inhibition of cell cycle progression and alteration of enzymes that scavenge reactive oxygen species (ROS).
Turbinaria conoides	Fucoidan, alginic acid	Stimulation of cytotoxic natural killer cells andmacrophages. The aptitude of polysaccharides to accumulate poisonsand heavy metals in the gut and modify them into less hazardous compounds.
Laminaria japonica, Sargassum wightii and most Red algae	Sulfated galectins, Glycosaminoglycan andFucoidan	Selective inhibition of tumor angiogenesis
Porphyra sp.	Porphyrin	'RAW264'-induced activation of NF-B in mouse macrophages results in a reduction of NO generation.
Sargassum sp. and otherbrown seaweeds and dinoflagellates.	Fucoxanthin	Melanoma cells' motility is weakened

Anticancer Activity of Microalgae

The antitumor capabilities of various algal resources have recently been revealed to influence several cellular pathways, including cellular cyto-toxication, downregulating tumorcell invasion, and enhancing cancer cell death.[35 36 37 38]Numerous cellular and molecular studies have revealed that chemicals produced from algae have powerful natural anti- malignant properties[39, 40]. Fucoxanthin, found in microalgae, diatoms, and brown seaweeds, is another illustration of this. It has powerful anticancer properties by inhibiting the growth of malignant cells, activating genes that fight cancer, and stopping cell cycles, but it does notaffect the apoptosis of tumor cells[41, 42]. A new, successful tumor therapy for humans may become more apparent as data about anticancer resources obtained from algae become more accumulated.[43-45]

Oncogene and Oncogenic Therapy: An Overview

Cancer is a distinct set of diseases brought on by aberrant cell development as a result of specific flaws. The human body's regular cell life cycle is rigorously controlled by several systems that tell the cells when to divide, grow, differentiate, or die[47-50]. Due to genetic flaws, cancer cells can avoid these controls and continue to grow uncontrollably.

Multiple variables, including genetic abnormalities, environmental conditions, specific viral infections, and occasionally no obvious cause, contribute to the development of cancer. Cancer can start in any area of the body and eventually spread across the entire body (metastasis). A gene with the capacity to cause cancer is known as an oncogene. These genes are frequently expressed at high levels or altered in tumor cells.[51-53] When crucial processes are distorted and dysfunctional, the majority of normal cells will die quickly andon their own accord (apoptosis). Cells intended for apoptosis may instead survive and proliferate as a result of activated oncogenes.[54, 55] The majority of oncogenes had their roots in proto-oncogenes, which were typically found in genes involved in proliferation, cell growth, or apoptosis suppression. Oncogenes are normal genes that promote cell development that is up-regulated through mutation ('gain-of-function mutation'), which predisposes the cell to cancer.[56, 57] Cancer is typically brought on by a combination of several oncogenes, altered genes that control apoptosis or tumor suppression, and other factors.An advanced kind of cancer treatment known as oncogenic therapy targets particular cancer-causing proteins and biological pathways. To stop cancer cells from growing uncontrollably, it uses drugs that change how they work.[58-60]

Colorectal cancer

Colorectal cancer risk factors include smoking, drinking alcohol, having inflammatory bowel disease, and having a family history of the illness.[61] The majority of colorectal malignancies, fortunately, start as little precancerous (adenomatous or serrated) polyps. These polyps typically grow slowly until they are huge or cancerous and do not show symptoms.[62 63] As a result, it is possible to identify and remove pre-cancerous polyps before they turn cancerous. Although there are many various types of colorectal polyps, it is believed that adenomas and sessile serrated lesions, which are premalignant cysts, are where most cancers are considered to start. A polyp that is discovered during a colonoscopy is often removed, if it is possible. Following removal during colonoscopies, polyps are analyzed by a pathologist to see if they have malignant or precancerous cells.

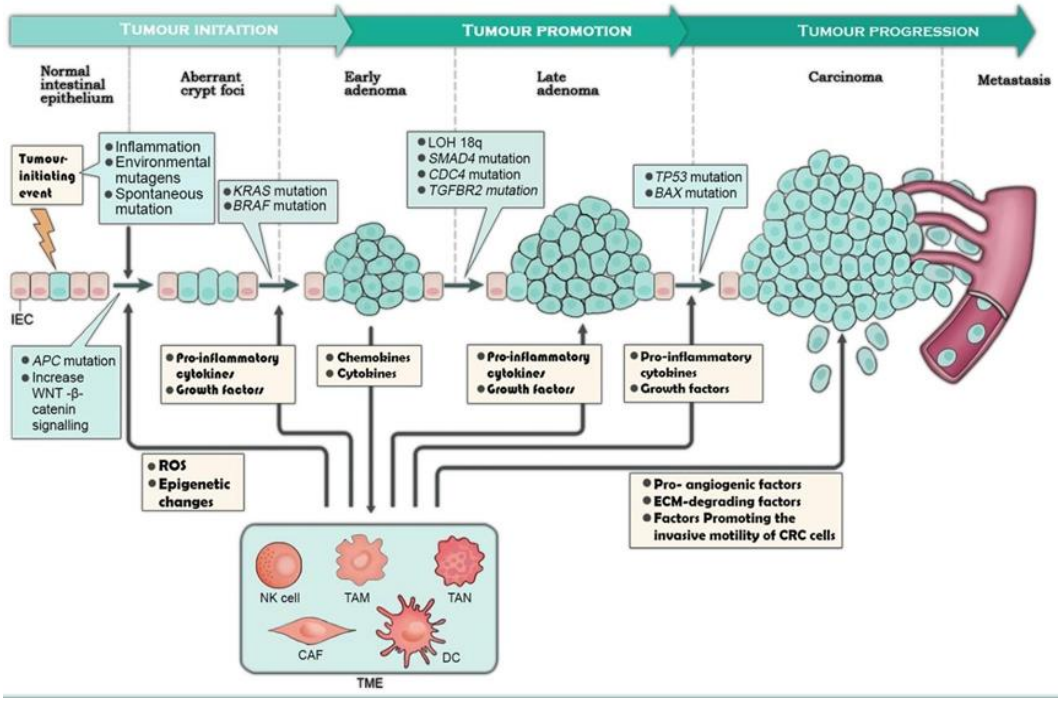

Figure 3: "The chromosomal instability", "microsatellite instability" and "CpG IslandMethylator Phenotype" molecular pathways have all been found.

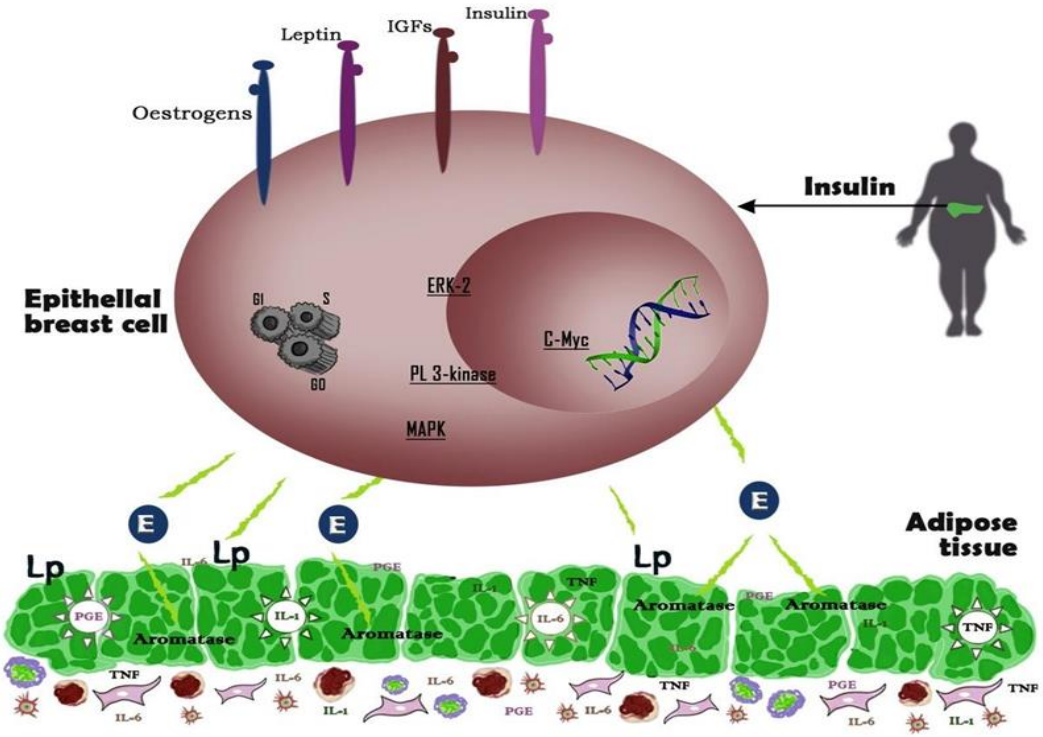

Figure 4: Paracrine and endocrine factors originating from adipose tissue regulate the increasing breast cancer cells through molecular processes. The mitogenic response in 'breast epithelial cells is synergistically induced in obesity by increased 'insulin' and 'IGF-I serum levels that interact with 'estrogen signaling pathways'. Adipocytes function as the peripheral location of estrogen aromatization and a paracrine source of many adipokines and inflammatory mediators. Leptin is one of the adipokines that can affect a variety of second intracellular messengers involved in the survival and proliferation of breast cancer cells.

Table 3: Principal types of genes involved in LC and signaling pathways[68]

Cell Indicating Passage	"Adenocarcinoma Genes involved (%)"	"Squamous Carcinoma Genes involved (%)"	"Small Cell Carcinoma Genes involved (%)"
"TP53"	"50 P53, MDM2"	"80 TP53"	"80-90 TP53"
"RAS/RAF"	"25 KRAS, NF1, BRAF, NRAS"	"22 NF1, KRAS, HRAS, NRAS, RASA1, BRAF"	
"PI3K/AKT"	"10-12 PIK3CA, PTEN, AKT1"	"59 PIK3CA, PTEN, AKT1-3, TSC1-2"	"10 PTEN"
"MYC"	"30 MYC"		'16-30 MYC, MYCN, MYCL'
"RTK"	'50 EGFR, ALK, RET, ERBB2, ROS, MET'	"27 EGFR, FGFR1-3, ERBB2/3, DDR2"	"6 FGFR1"
"RB1/CDKNA2"	"15-20 CDKNA2"	"79 CDKNA2, RB1"	"100 RB1, CCNE1"
"Epigenetic regulation"	"22 SMARCA4, ARID1A, SETD2"	"20 MLL2"	"19 EP300, MLL, CREBBP"
"Response to oxidative stress"	"10 KEAP 1"	"KEAP1, CUL3, NRF2"	

Breast cancer

The disorder is known as breast cancer characterized used by uncontrolled cell growth in the breast. Lobules, connective tissue, and ducts are the three primary components of a breast. Milk-producing glands are called lobules and are delivered to the nipple by tubes called ducts. The surrounding and unifying tissue is called connective tissue, where the majority of breast tumors start. While HER2 and ER are the two most often changed pathways in breast cancer, it is now well acknowledged that many other signaling pathways play a role in the disease' etiology. A total of 1,243 mRNAs were examined, and 854 (68.7%) of them were found in breast cancer.[64, 65] Between benign and cancerous tissues, 395 mRNAs showed statistically significant differences (fold change >2).

'33 mRNAs and 105 mRNAs', respectively, are only expressed in normal breast tissues and breast cancer tissues, respectively, of this group of mRNAs. Out of 131 proteins and phosphoproteins, '89' (68%) were found in cancerous tissues, and 57 proteins significantly distinguished tumors from normal tissues. Interestingly, only 3 genes ('CDK6, Vimentin, and SLUG') showed reductions in both protein and mRNA.

Pleural cancer

Two pliable organs in our chest called the lungs allow us to breathe in O_2 and exhaust CO_2. When we inhale tobacco smoke, which is full of "cancer-causing chemicals," changes in the lung tissue begin to occur almost immediately (carcinogens). The first damage may be able to be repaired by our body, but with each additional exposure, the healthy cells that line our lungs are gradually eliminated. Cells become dysfunctional as a result of damage over time, which could ultimately result in the growth of cancer. There are two main forms of pleural cancer, "small cell LC", which is more uncommon, and has a faster growth rate and a higher likelihood of developing metastases that were present at the time of diagnosis, and "non- small cell LC", which is more prevalent but has a slower growth rate.[40]More than 7,000 compounds, including over 70 recognized carcinogens, including nitrosamine ketones and 'polycyclic aromatic hydrocarbons' (PAH), which induce genetic changes by forming a complex with DNA, are found in tobacco smoke. The metabolism of the aforementioned carcinogens is activated, and 'glutathione-S-transferases', 'CYP family enzymes' and'cytochrome P450 all participate in this synthesis (GSTs).[67] [68] The aforementioned enzymes' roles have been modified in numerous LC signaling pathways. The majority of them are controlled by oncogenes, which cause the cells to proliferate uncontrollably and avoid apoptosis.

Contribution of Microalgae in Anti-Cancer Therapy

In the chloroplasts of brown seaweeds, there is a carotenoid called fucoxanthin. A drug sensitivity test was used to assess the antitumor effects of fucoxanthin and its metabolite, "fucoxanthin", on "20" tissue samples taken from surgically removed 'clinical colorectal cancer specimens and six 'colorectal cancer cell lines (CD-DST). At dosages of '20 M', "fucoxanthin" and "fucoxanthin" lowered the "T/C" (%) of the "HCT116", "Caco-2", "DLD-1" cell lines and "WiDrs". Fucoxanthinol likewise decreased the "T/C" (%) of 'SW620' cells, but neither carotenoid had any effect on the 'T/C' (%) of 'Colo205' cells. In particular, the 'T/C' (%) of 'Caco-2' and 'WiDr' cells was significantly reduced to 1.40.2 and 12.00.3%, respectively, after being treated with 20 M fucoxanthinol for 24 h. Additionally, in tissue samples from those who had colorectal cancer, 'fucoxanthin and fucoxanthinol' reduced the 'T/C' (%). Hence it would be suggested that the chemotherapeutic drugs fucoxanthin and fucoxanthinol can be useful resources for the treatment of colorectal cancer.[69]

For targeted drug delivery and fluorescence imaging-guided treatment of breast cancer lung metastases, '*Spirulina platensis*' may be used as a general carrier. To create the DOX-loaded SP '(SP@DOX)', which has an extremely high drug loading efficiency and PH-responsive drug sustained release, the chemotherapeutic doxorubicin (DOX) is simply added to '*S. platensis*' (SP). Because of the abundance of chlorophyll, 'SP@DOX' has outstanding in vivo tracking and real-time monitoring fluorescence imaging capabilities. The unsent carriers can finally be biologically broken down by renal clearance without significant harm.[70] [71] Treatment options for patients depend on the presence of 'HER2' receptors, which are proteins produced by the 'HER2' gene. Breast tumors that are triple negative and hormone receptor-positive are classified as 'HER2'-negative. The 'HER2' subtype has a new classification called 'HER2'-low. It defines a new subtype of breast cancer that is not 'HER2'-positive but does have some 'HER2' proteins on the cell surface. Enhertu is approved for 'HER2'-low breast cancer patients who have already had chemotherapy for metastatic disease or whose cancer reappeared during or within six months after finishing adjuvant therapy.[72] [73]

With '74 g' of "PUFAs" per kg of collected microalgae, "*Tetraselmis suecica*", marine green microalgae in the '*Chlorophyceae*' family, is particularly rich in biomolecules. When tested in the lab on the human pleural adenocarcinoma cell line "A549", its crude extract demonstrated significant antioxidant and cell-repairing activities. [74]The capacity of "A549" and 'H460' lung cancer cells to form colonies has also been shown to be suppressed by an extract from a combination of microalgae when given in doses of 5 g/L1.In addition, '*Chlorella vulgaris*' extract at a concentration of '200 g mL-1' significantly suppressed the proliferation and cell migration of the lung cancer cells "H1299", "A549", and "H1437". Human lung mucoepidermoid carcinoma "NCI-H292" cells were selectively affected by the ethanolic extracts of *'D. dichotoma', 'P. gymnospora'* and '*H. musciformis'*. Other than microalgae, the lung tumor, along with any adjacent lymph nodes in the chest, are removed while the surgery. A border or margin of healthy lung tissue must be present near the tumor when it is removed.[75] For NSCLC, the following surgical procedures could be used:

Lobectomy: An complete lung lobe is removed during a lobectomy. Even when the lung tumor is relatively small, it is now believed to be the most effective kind of surgery.

Segmentectomy: A segmentectomy involves the surgeon removing the lung tissue where the cancer first appeared.

Diatom-Based Nanocarrier Drug Delivery in Cancer Therapy

Minerals and secondary metabolites such as proteins, flavonoids, sterols, esters, acyl lipids, ester, and saturated and unsaturated fatty acids are abundant in diatoms. According to reports, these bioactive substances are effective anti-cancer, anti-bacterial agents, and anti-oxidant[76-80]. Due to their little growth cycles and high

production, diatoms are unicellular photosynthetic organisms that play a significant role in the biogeochemical circulation of silica, carbon, and nitrogen.[81] As it has a large surface area, bio-compatibility, nano-porosity, and biodegradability, the biosilica of diatoms has the potential to be an effective drug delivery system for targeted cancer therapy. A diatoms-based technologymay be suitable for use as a secure nanocarrier in nanomedicine applications because *in vivo* investigations on animal models have not revealed any discernible signs of tissue damage.[82-85]

Table 4: A list of the bioactive substances with anticancer effects on various cell lines that were obtained from various species of diatoms

Diatoms	Anticancer Compounds	Target cells
'Synedra cause	Chrysolaminaran	"Human colon cancer cells (HT-29)" "Colon cell line (DLD-1)"
	Nonyl 8-acetoxy-6- methyl octanoate (NAMO, fatty alcohol ester)	Human promyelocytic leukemia (HL-60). Human lung carcinoma (A549) Mouse melanoma (B16F10)
'Cocconeis scutellum'	Fraction 3 (eicosapentaenoic acid (EPA), diethyl ether extract)	"Breast carcinoma (BT20)" "Human normal lymphocytes"
'Chaetoceros calcitrans'	'AcOEt extract'	"Breast adenocarcinoma (MDA-MB-231)"
'Skeletonema Marino	Monoacylglycerides (MAGs)	"Colon cancer cell line (HCT-116)" "MePR-2B normal cells"

CONCLUSION AND FUTURE ASPECTS

It is clear from the recent review that microalgae represent an exciting & successful research topic with a promising future. It offers details about microalgae and the bioactive substances found in them that have the potential to treat cancer. An efficient anti- tumorogenic and anti-proliferative action has been demonstrated by several biomolecule types that have been isolated and described from microalgal origin. As a result, '*U. pinnatifida', 'S. horneri', and 'H. elongata'* gathered during the peak Fx production period can be useful as strong sources of Fx. The molecular processes underpinning brown algae and Fx's cancer prevention in individuals with "colorectal cancer" (CRC) and 'CRC' animal models will need to be clarified through subsequent in vitro investigations, which will serve as a crucial foundation. There aren't many published studies on how taking FX directly combats CRC in humans. IBD, diabetes, obesity, inflammation, metabolic syndrome, hereditary factors, and oxidation are proposed as major risk factors causing colorectal carcinogenesis.

Advanced biological and molecular studies are still required to fully understand the function, effectiveness, and characterization of these anti-cancerous chemicals obtained from algal sources. Furthermore, in-depth studies should be conducted on the bioactive components of microalgae to assess their potential usefulness against a variety of cancers, whether in-vitro or in vivo.

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