Review

Algae-Derived Bioactive Compounds with Anti-Lung Cancer Potential

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Abstract: Lung cancer is one of the major causes of death worldwide. Natural molecules with anti-lung cancer potential are of a great interest and considered as very promising alternative to substitute or enhance the efficiency of the conventional drugs. Recently, algae as source of high value-added compounds are considered as very promising source of these bioactive molecules. These are secondary metabolites that consist mainly of derivatives of peptides, carbohydrates, and lipids with various structures. Accordingly, various mechanisms by which different algae molecules demonstrate attenuation of tumor angiogenesis were stated and discussed. The mode of action of the algae bioactives is closely related to their nature and chemical structure. Furthermore, this literature review considers the synergistic effect between microalgae bioactives and conventional drugs and discuss the economic feasibility of producing microalgae bioactives at large scale to conclude with some future perspectives related to algae-based drug discovery.

Keywords: bioactives; drug discovery; marine algae; mode of action; molecular target; lung cancer

1. Introduction

Cancer is a critical worldwide public health challenge and specifically lung cancer is the leading cause of cancer-related deaths [1,2]. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) represent the two main types of Lung cancers with NSCLC occurring most commonly with a frequency of 85%. It was previously described that the 5 years survival rate of NSCLC and SCLC is 18% and 6%, respectively [3]. The three major histologic subtypes of NSCLC include adenocarcinomas, squamous cell carcinoma and large cell lung cancer. Adenocarcinoma, accounts for 40% of all lung cancers as is considered as the most common histological variant identified in non-smokers. This cancer type is frequent especially in females less than 60 years old [4]. Unfortunately, conventional treatment approaches including surgery radiotherapy and chemotherapy showed limited success rate.

Therefore, it is essential to identify alternative treatments to regress the development of lung cancer. Several research works are being carried out to discover drugs against cancer from natural origins such as plants and succeeded to identify over 195,000 bioactives with known quantitative interactions [5]. These compounds were tested on clinical level and recent studies done on 453 cancer patients showed that 77% of patients complement the conventional treatment with specific herbal medicines to reduce the symptoms related to cancer by improving the immune system, or even

eliminate the cancer directly [6]. As an example, a study done by the cancer national research institute proved that high dose of Vitamin A increases the number of germinal centers to enhance the maturity of the antibodies in tumor and lymph tissues which may be beneficial to patients with NSCLC.

In addition to plants, many widely described chemotherapeutic agents from microorganism such as cyanobacteria and microalgae have been discovered by in vitro assays [3]. Indeed, an estimate of 72,500 algal species have been identified, out of which the majority are of marine origin [7]. Several algae-based compounds, such as polysaccharides, steroids, fatty acids, carotenoids, halogenated compounds, and peptides, have exhibited a large number of biological properties including anticancer activity. These bioactive molecules bind to diverse sites, suppressing cell divisions, or inducing apoptosis via activation of specific cellular pathways [8].

Furthermore, previous investigation demonstrated that cancer cell killing efficiency of chemotherapeutic drugs was achieved with a very low dose once combined with Chinese herbs [9]. Furthermore, active compounds from natural sources showing reduced side-effects are of great interest due to their cytotoxic and chemosensitizing activities in addition to their synergistic interactions.

The increasing interest on using microalgae as natural, safe and renewable source of nutraceuticals and pharmaceuticals to fight cancer has led to rise in the research activities and related publications in this field. However, the focus was on specific health applications and a few numbers of publications was related to anti-lung cancer investigations. The current review article presented for the first time, to the best of our knowledge, a deep description of micro algae high-value compounds active against lung cancer considered as a big health challenge worldwide. Additionally, the mode of action for particular molecules will be described and discussed. Furthermore, this review paper considers the synergistic effect between microalgae bioactives and conventional drugs and conclude with discussing the economic feasibility of producing microalgae bioactives and presenting some future perspectives related to algae-based drug discovery.

2. Molecular Origin and Signaling Pathways Associated to Lung Cancer

The pathogenesis of human cancer is associated with multiple molecular abnormalities which lead to acquisition of cellular features, including enhanced angiogenesis, replicative immortality, cell death resistance, continuous proliferative signaling, inactivation of growth suppressors, and induction of invasion and metastasis [10]. Lung cancer is induced by genetic and epigenetic alterations including mutations, inhibition of tumor suppressor genes and overexpression of growth promoting oncogenes [11]. Commonly stimulated oncogenes in lung cancer are EGFR, ERBB2, MYC, KRAS, MET, CCND1, CDK4, MET, EML4-ALK fusion, and BCL2 [12]. Among these stimulators, EGFR also known as ErbB-1was the first receptor tyrosine kinase (RTK) identified and the first one linked to cancer. Furthermore, this receptor is the most intensively studied among all RTKs [13]. EGFR is overexpressed in 50–90% of NSCLCs, therefore, tyrosine kinase inhibitors namely, gefitinib and erlotinib, and monoclonal antibody cetuximab were developed to target EGFR signaling [12].

Furthermore, the lack of sensitivity of NSCLC cell lines to EGFR inhibitors was associated with persistent activity of ERK or Akt kinase pathways [14]. In addition, mutations of the KRAS oncogene have been suggested to contribute to the lack of sensitivity of EGFR tyrosine kinase inhibitors in NSCLC [15]. Another proposed mechanism that has been suggested to contribute to the resistance of EGFR inhibitors is the amplification of the Met proto-oncogene [16]. Impairment of EGFR tyrosine kinase inhibitors mediated apoptosis pathways (Bcl2 like 11/BIM deletion polymorphism) are other mechanisms that contribute to resistance of EGFR targeted drugs [17].

3. Photosynthetic Microorganisms as a Natural and Renewable Source of Anti-Lung Cancer Agents

Marine flora comprises of brown, blue, green, blue-green and red-algae. Among them, primarily, brown algae were used as a source of secondary metabolites with multiple biological activities. Marine microalgae, phytoplankton, are considered as an important constituent in the marine food chain [18,19].

They are attracting enormous attention and have been producing molecules which are chemically and pharmacologically novel with diverse biological efficacies [20]. These valuable molecules belong to different classes of algae such as microalgae, macroalgae and cyanobacteria and the current literature review focuses on biomolecules that are active against lung cancer.

3.1. Macroalgae

Marine macroalgae, designated as seaweeds is most dominant in the marine flora with a frequency of 90%. The seaweeds represent also 50% of the universal photosynthesis quota [21]. Seaweeds have been used in traditional medicine for more than 2000 years in China [22]. Due to their ability to fight numerous diseases such as gall stones, stomach ailments, eczema, cancer, renal disorders, scabies, psoriasis, asthma, arteriosclerosis, heart disease, lung diseases, and ulcers, seaweeds have attracted the attention of the scientific community in the last three decades [23]. The pharmaceutical potential of those molecules was amply investigated for drug discovery. Consequently, several high-value compounds (HVC) were identified like carotenoid, polysaccharides, fatty acids, glycoproteins, haloforms, halogenated alkanes, alkenes, alcohols, aldehydes, hydroquinones, ketones, phlorotannins, pigments, lectins, alkaloids, terpenoids, sterols, and some heterocyclic and phenolic compounds. Many of these HVC are in clinical or preclinical trials.

3.2. Microalgae

Microalgae are autotrophic microorganisms that consume CO_2, light, and inorganic nutrients to produce biomass, rich in primary metabolites such as lipids, carbohydrates, proteins, and pigments. In addition, microalgae can produce HVC such as polysaccharides, poly-unsaturated fatty acids (PUFAs), carotenoids (lutein, zeaxanthin, and astaxanthin), and vitamins with very high nutraceutical and pharmaceutical potentials [24]. For example, *Tetraselmis suecica*, a marine green microalgae belonging to the class Chlorophyceae, is enriched with biomolecules with an amount of 74 g of PUFAs per kg of microalgae harvested [25]. Its crude extract showed strong antioxidant and cell repairing activity in vitro in the human lung adenocarcinoma cell line A549. It has also been demonstrated that extract from a heterogeneous mixture of microalgae inhibited the colony forming ability of A549 and H460 lung cancer cells at a dose of 5 µg µL^{-1} [26]. Moreover, the proliferation and cell migration of H1299, A549, and H1437 lung cancer cells were markedly inhibited by *Chlorella vulgaris* extract with a dose of 200 µg mL^{-1} [27]. Varying the polarity of the solvents used for the extraction will help to dissolve and extract most of the biomolecules that are selectively active against specific type of cancer cells. Ethanolic extracts of *H. musciformis*, *P. gymnospora*, and *D. dichotoma* showed selectivity towards NCI-H292 cells (human lung mucoepidermoid carcinoma) 22.0 ± 3.5 µg mL^{-1}, whereas, the dichloromethane extract, chloroform extract and methanolic extracts of *D. dichotoma* were active against HEp-2 (human larynx epidermoid carcinoma) cells [28].

3.3. Cyanobacteria

Blue green algae (cyanobacteria), a cyanophyta, possess different mechanisms to produce various cyclic nitrogenous compounds that have potent biological activities. For example, *Lyngbya majuscula* produces several molecules such as obyanamide, hectochlorin, lyngbyastatin 3, and apratoxin with proven cytotoxic activities [20]. Similarly, *Nostoc* species are also known to generate compounds like cryptophycin whose analogues are very effective against cancer (Hela cells) [29]. Deniz et al [30], emphasized the use of phycocyanins from *Spirulina platensis* against A549 lung cancer cell line with an IC50 value of 29.41 µg mL^{-1} after 24 h of incubation [30,31].

4. Bioactive Compounds from Algae

HVC in algae differ in terms of their chemical properties. Phenolics and carotenoids are the most studied microalgal phytochemicals. Guedes et al [28] showed a selective activity of algae extracts towards NCI-H292 lung cancer cells [28]. Ethanol extracts of *H. musciformis* and *P. gymnospora* presented

anti-proliferative activity with IC50 of 22.0 ± 3.5 µg mL^{-1} and 15.9 ± 2.8 µg mL^{-1}, respectively. However, for *Dictyota dichotoma*, the anticancer capacity was observed using both ethanol and chloroform extracts with IC50 of 25.2 ± 1.1 µg mL^{-1} and 22.0 ± 3.5 µg mL^{-1}, respectively. Several chemical components were identified as active against lung cancer such as: Polysaccharides, sulfate polysaccharides, terpenoids, and peptides. Tables 1 and 2 group several examples of macroalgae and microalgae bioactives respectively, with their origins, targets and mode of action. All anticancer investigations should be performed using the American Cancer Institute (NCI) protocol, which considers a plant crude extract and pure substances as interesting if it showed IC50 less than 30 µg mL^{-1} and 4 µg mL^{-1}, respectively [32].

Table 1. Macroalgae bioactive molecules with biological source and activity against lung cancer cells.

Algae Species	Active Molecule	Lung Cancer Cells	Dose IC50	Inhibition Pathways	Ref.
U. pinnatifid algae	Fucoidan	Human lung cancer A549 cells	50, 100, 200 µg mL^{-1}	↓ procaspase 3 PARP cleavage Caspase-9 activation ↓ procaspase 3 ↓ Bcl-2, ↑ Bax	[33]
F. vesiculosus	Fucoidan	lung cancer A549 cells	50–400 µg mL^{-1}	inhibited the MMP-2 and MMP-9 protein expression, cell migration, and invasion activities of LLC cells	[34]
Bryopsis	Kahalalide F	lung cancer A549 cells	2.5 µg L^{-1}	Targets the lysosomes,	[35]
Hypnea musciformis	Chloroform extract	NCI-H292 (human lung mucoepidermoid carcinoma)	15.0 ± 1.3 µg mL^{-1}	-	[28]
	Ethanol extract	NCI-H292	22.0 ± 3.5 µg mL^{-1}	-	[28]
Gracilariopsis lemaneiformis	Polysaccharide	NSCLC cell line, A549	50 µg mL^{-1}	-	[36]
Sargassum fusiforme	Ploysaccharide	lung adenocarcinoma SPC-A-1 cells and its xenograft model	-	inhibit VEGF-A-related angiogenesis and proliferation	[37]
Sargassum macrocarpum	Tuberatolide B (TTB, C27H34O4)	(A549 and H1299)	-	promotes ROS, mediated inhibition of STAT3 signaling, decreased the expression of Bcl2, increases the cleavage of caspase-3 and PARP, enhances the percentage of annexin V, positive apoptotic cells, induces ROS generation, induces DNA Damage, induces the phosphorylation of Chk2 and H2AX.	[38]
Plocamium cartilagineum	halogenated monoterpene 1 (5E,7Z)-3 48-trichloro-7-dichloromethyl-3-methyl-157-octatriene)	(NCI-H460)	4 µg mL^{-1}	-	[39]
Codium decorticatum	glycoprotein	A549 lung cancer	40 ± 0.41 µg mL^{-1}	Induction of apoptosis	[40]
Gracilaria edulis	phytol, a diterpene	A549 lung cancer	24.5 ± 19.1 µg mL^{-1} at 48 h	-	[41]

-: not determined; Ref.: Reference; ROS: Reactive oxygen species.

**Table 2.** Microalgae bioactive molecules with biological source and activity against lung cancer cells.

Algae Species	Active Molecule	Lung Cancer Cells	Dose IC50	Inhibition Pathways	Ref.
Haematococcus sp.	Astaxanthin	NSCLC	5–25 µg mL^{-1}	↓ MKK1/2-ERK1/2 inducing cytotoxicity against cancer	[42]
Chlorella zofingiensis	Lycopene	A549	3–5 mM	↓ mRNA and protein levels of cyclin E	[43–45]
Dunaliella salina	Beta-carotene	A549	25–100 µg mL^{-1}	↓cell proliferation, induce apoptosis and cell cycle G0/G1 arrest	[46]
Tetraselmis; Nannochloropsis	EPA and DHA	A549 H1299	EPA = 6.05 µM 50% inhibition	Generate PGE3 through COX-2 enzyme ↓ Of Akt phosphorylation by PGE3.	[47,48]
Chlorella Vulgaris	Polyphenols, Flavonoid	H1299, A549, and H1437	13.40 and 0.46 (µg Gallic acid/g lyophilized extract), 3.18 µg quercetin/g lyophilized extract	Affects migration of cells, inhibits metastasis	[27]
Lyngbya sp.	Phycoerythrin	A549	100–200 µg mL^{-1}	Cell arrest at G0/G1 phase, ↓ cell viability and mitochondrial membrane potential, an increment in lactate dehydrogenase release	[49]
Arthrospira platensis, Oscillatoria tenuise	Phycocyanin	A549	26.82 µg mL^{-1}	Cell apoptosis/blebbing necrosis,	[30,50]
Lyngbya majuscule, Lyngbya sordida	Alotmide A, Aurilide	H-460 NCI–H460	-	Cell apoptosis	[51]
Leptolyngbya	Coibamide	NCI–H460	LC50 < 23 nM	Inhibits cell proliferation through novel mechanism	[52]
Caldora penicillata	Laucysteinamide A, Curacin.	H-460	11 uM,	Anti-tubulin formation	[42]
Gymnodinium	GA3P, d-galactan sulfate	NCI-H23 NCI-H226 NCI-H522 NCI-H460 A54 DMS273 DMS11	2.8 2.2 1.3 3.8 11 2.0 2.7	Inhibits topo I and topo II	[53]
P. tricornutum	Nonyl 8-acetoxy-6-methyloctanoate (NAMO)	A549	35% inhibition at 50 µg mL^{-1}	p53 and caspace-3 mediated cell apoptotic pathway	[54]

-: Not Determined; Ref.: Reference.

4.1. Derivatives of Carbohydrates

4.1.1. Polysaccharides

Polysaccharides (PS) are polymers of simple sugar (monosaccharide) allied by glycosidic bonds (Figure 1). They are considered as the major algae component (reaching up to 76% of the dry weight) since they play a key role in the cell wall structure as well as in physiological functions. Several marine algae PS were subjected for in vitro and in vivo investigations for their anticancer potential [55,56]. The PS bioactivity is closely dependent on their physicochemical properties [36]. These properties depend strongly on the nature of the algae that produces it. Kang et al [36] succeeded recently to identify a neutral polysaccharide from *Gracilariopsis lemaneiformis* with a linear structure of repeated disaccharide agarobiose units consisting of 3,6-anhydro-L-galactose and D-galactose. Such polysaccharides showed high activity against A549 lung cancer cell line (Table 1).
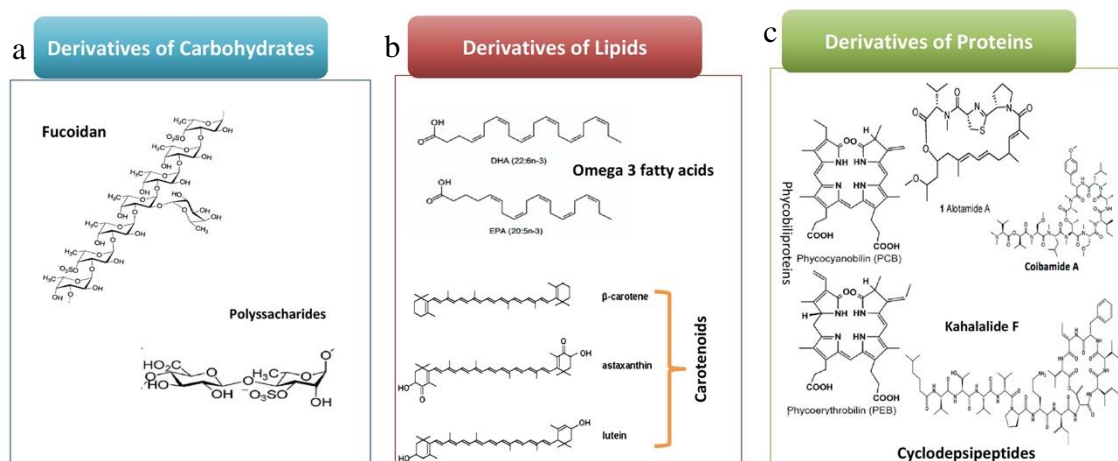
Figure 1. Chemical Structure of the algae bioactives with against lung cancer potential (**a**) derivatives of carbohydrates; (**b**) derivatives of lipids; and (**c**) derivatives of proteins.

4.1.2. Fucoidan

Fucoidans are sulfated polysaccharides generally produced by brown algae such as: *Sargassum thunbergi* [57], *Ascophyllum nodosum* [58], *Viz fucusvesiculosus* [59], *Laminaria japonica* [60], *Fucus evanescens*, and *Laminaria cichorioides* [61]. It was stated that algae fucoidans present high anticancer activity against several cancer types, including lung cancer, via targeting the key apoptotic molecules. Previous study demonstrated that fucoidans inhibit lung cancer through Smurf2 dependent ubiquitin degradation of TGFβ receptors [36]. It was also reported that prophylactic administration of fucoidans suppress lung cancer metastasis by inhibiting MMPs and VEGF [57]. Besides that, fucoidans have the ability to present a synergistic effect towards the anticancer agents currently in use [41]. This has emphasized the need for further research by combining such polysaccharides with the existing medicines to improve the efficacy of conventional drugs. Atashrazm et al [62] evidenced also its beneficial effects as polysaccharides can prevent from the toxic effect associated to the conventional therapies. The chemical structure of the fucoidan is present in the Figure 1.

4.2. Derivatives of Protein

4.2.1. Phycobiliprotein

Phycobiliproteins are composed of protein covalently linked to chromophore called phycobilins (Figure 1). Accordingly, they are considered as strong fluorescent markers. These proteins are water soluble and present antioxidant properties [49,63]. Phycocyanin and phycoerythrin are the most widely known phycobiliproteins that have been produced commercially to be used as natural food colorant. Phycocyanin which is a blue colored phycobiliprotein produced essentially from *Arthrospira* sp., reportedly showed anticancer properties against A549 lung cancer cells [30]. Previous study mentioned the use of phycocyanin individually and/or in combination with other agents to obtain anticancer effects against lung cancer [40,41]. Phycoerythrin (pink colored protein pigment) produced by a marine *Lyngbya* showed apoptotic activity against A549 human lung carcinoma cells [64].

4.2.2. Glycoprotein

Glycoprotein consists of proteins bound to carbohydrates. Very recently, Senthilkumar and Jayanthi [40] successfully isolated, purified and characterized a glycoprotein of size 48KDa from *Codium decorticatum* using HPLC, IR, NMR, and Circular Dichroism (CD). Carbohydrates representing 36.24% of the glycoprotein consist of: Rhamnose, galactose, glucose, and mannose with a mole ratio of 38:30:26:6. Using FT-IR and NMR spectra, the authors proved that sugars are attached to the protein via (1→4)-linked β-galactose residues and β-linked glucose residues. The investigation of the anticancer

activity of this glycoprotein expressed interesting activity against A549 lung cancer cells with IC50 of ~40 g mL^{-1} after 48 h of incubation. Such activity is time and dose dependent. Using fluorescence microscopy, these authors proved that glycoproteins induce apoptosis.

4.2.3. The Cyclo Depsipeptides

- Kahalalides F

The Kahalalides consist of series of depsipeptide isolated from *Bryopsis pennata* [65]. Among them, the Kahalalide F, which contains 13 amino acids and 5-methylhexanoic acid at its N-terminus, was described as highly active against solid tumors including lung cancer (Figure 1). A significant in vitro activity was recorded against human non-small cell lung cancer cells (A549) with an IC50 of 2.5 µg mL^{-1} [65]. Furthermore, patient treated ex vivo with 0.01–1 µM of Kahalalide F showed a total inhibition of the non-small-cell lung cancer. The investigation of chemical properties of this molecule for drug discovery currently reached phase II trials by PharmaMar [66]. The stereochemistry of the Kahalalide F was assessed by several researchers but only through total synthesis that Lopez-Macia et al. [67] succeeded to firmly identify it and suggested that the cyclized and linear side chains play a critical role in the biological activity of the drug [65].

- Other cyclo depsipeptide from cyanobacteria

Several cyclo depsipeptides, chains of 50 or less amino acids, have been isolated from blue green algae such as Coibamide A, Alotmide A, Veraguamide A [68]. Coibamide A was isolated from cyanobacterium *Leptolyngbya sp*. The chemical structure was determined using NMR and mass spectroscopy. The excessive number of N and O methylation and the abundance of alkyl amino constituents make the structure very complicated. Such molecule showed cytotoxicity against NCIH-460 lung cancer cells. Alotmide A, a cyclic depsipeptide isolated from *Lyngbya majuscula* and *Lyngbya sordida* showed cytotoxicity against H-460 human lung cancer cells [51]. Similar action was exhibited by Palmyramide A and Dolastatin 16 on the same cell line [69]. Finally, Veraguamide A, a cyclic peptide from *Oscillatoria margaritifera* showed cytotoxicity against cancer cells with LD50 equal to 141 nM [70].

4.3. Derivatives of Lipids

4.3.1. Carotenoids

Carotenoids are the most diverse and widespread lipophilic colored compounds in nature [71,72]. The major carotenoids found in microalgae are astaxanthin, β-carotene, lutein, lycopene, and canthaxanthin (Figure 1). Carotenoids can be over produced in algae culture by exposing it to strong or continuous light from 50 to over 1250 µmol photon m^{-2} s^{-1} [73]. High temperatures and modification of the growth media favors their production [74]. Zhang et al [42] modeled that light attenuation, temperature, and lower nitrogen sources were optimal for astaxanthin production. Similarly, lycopene inhibited human lung cancer cells (NCI-H226) proliferation and suppressed insulin-like growth factor-I stimulated growth which are the major autocrine/paracrine regulators of mammary and endometrial cancer cell growth [43]. Analogously, astaxanthin, produced commonly by *Haematococcus* sp. [30], a non-provitamin A carotenoid, has recently gained attention by inhibiting cell viability and proliferation of two NSCLC, A549 and H1703 [75]. Hence, microalgal carotenoids possess substantial potential against lung carcinomas.

4.3.2. Omega Fatty Acids

Fatty acids are a group of secondary metabolites synthesized by Claisen condensation reactions between acetyl-CoA and malonyl-CoA with the action of fatty acid synthases. Marine microalgae such as *Isochrysis*, *Tetraselmis*, *Chaetoceros*, *Thalassiosira*, and *Nannochloropsis* are known with high ability to produce polyunsaturated fatty acids (PUFAs) with multiple health benefits [76,77]. These molecules

exert anticancer actions against lung and gastrointestinal carcinomas [78]. Its implication in lung cancer is shown by in vivo studies demonstrating slow growth of lung cancer in mice when fed with eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) rich food [47,79]. The anti-proliferative effect of DHA and EPA on A549 lung cancer cell lines was confirmed by different in vitro assays suggesting their potential therapeutic role [80].

4.4. Tuberatolide B (TTB, C27H34O4)

Tuberatolide B was isolated for the first time from the Korean *Sargassum macrocarpum* and identified as diastereomeric meroterpenoid that acts as a Farnesoid X receptor (FXR) antagonist [81]. Recently, Choi et al [38] proved that TTB induced the ROS production leading to STAT3 inhibition, DNA damage, and apoptotic cell death. Therefore, TTB suppresses cancer progression by promoting ROS-mediated inhibition of STAT3 signaling.

5. Anticancer Mode of Action and Putative Targets

Knowledge of mechanism by which various molecules exert their effects is important to design drugs for treating cancer and to improve the lifestyle of those at risks. There are various mechanisms by which different molecules demonstrate attenuation of tumor angiogenesis [82], promotion of cell cycle arrest [83,84], induction of apoptosis [36,85], or necrosis and immuno stimulation [86]. The mechanism by which algae bioactives function is mainly based on the nature and chemical properties of the algae bioactives. Atashrazm et al [62] stated that fucoidan fights lung cancer via delaying cancer development, eliminating cancer cells, and presenting synergistic effect with the anticancer chemotherapeutic agents, simultaneously.

Algae bioactives trigger apoptosis via several pathways. Very recently, Kang et al [36] proved that *Gracilariopsis lemaneiformis* PS stimulates apoptosis via Fas/FasL pathway. However, the *Sargassum fusiforme* PS decreased the expression of CD31, VEGF-A and tumor microvessel density [37]. In addition, it inhibits the expression of VEGF-A in tumor cells and its receptor VEGFR2 in human umbilical vein endothelial cells. Accordingly, PS of *S. fusiforme* are considered an alternative anti-lung cancer drug.

Choi et al. [38] proved that tuberatolide B inhibits lung cancer growth via the histone H2AX protein, which is important in the DNA damage response (DDR) pathway. The formation of γH2AX foci on double stranded DNA activates the DDR pathway. Tuberatolide enhances DNA damage by inducing γH2AX foci formation and the phosphorylation of DNA damage-related proteins such as Chk2 and H2AX. Furthermore, Tuberatolide decreases the expression of BCL2 and increases the cleavage of caspase 3 and PARP and increases the percentage of annexin V-positive apoptotic cells. An important determinant of cellular response to DNA damage is the level of intracellular reactive oxygen species (ROS); Tuberatolide B induces the formation of ROS, which could act as a cellular toxicant.

Although significant advances have been made during the last 24 years in the purification, identification and biological and chemical characterization of depsipeptide, their mode of action is not completely understood. The putative mode of action of the microalgae bioactives is presented in the Figure 2. It was stated that PI3K/Akt signaling pathway coupled to ErbB3 receptors could be the target [87]. There are no clinical reports related to potential ErbB3 inhibiting drugs, Accordingly, Kahalalide F would be considered as a promising candidate for inhibition of ErbB3 receptors in tumor cells [88].

Several postulates have been made to explain the action of omegas against cancer cells. Apoptosis, the process of programmed cell death is controlled by caspases [89]. EPA and DHA are known to increase caspases specifically 3 and 9, that induce apoptosis of cancer cells [90]. It is reported that DHA stimulates autophagy via p53-mediated AMPK/mTOR signaling [91]. Auto phagosomes have been induced upon treatment of A549 cells with DHA or EPA. Furthermore, it was stated that DHA reduced the expression of COX-2 and suppressed the formation of pro inflammatory lipid mediator, prostaglandin E2, leading to anti-proliferative effect. It was ultimately proved that omega3 fatty acids reduced the COX2 expression by downregulating NF-κB [92]. Additionally, several other factors such

as: Ras transcription factors and protein kinases were considered as potential targets of omega3 fatty acids mediated tumor inhibition [78,93].
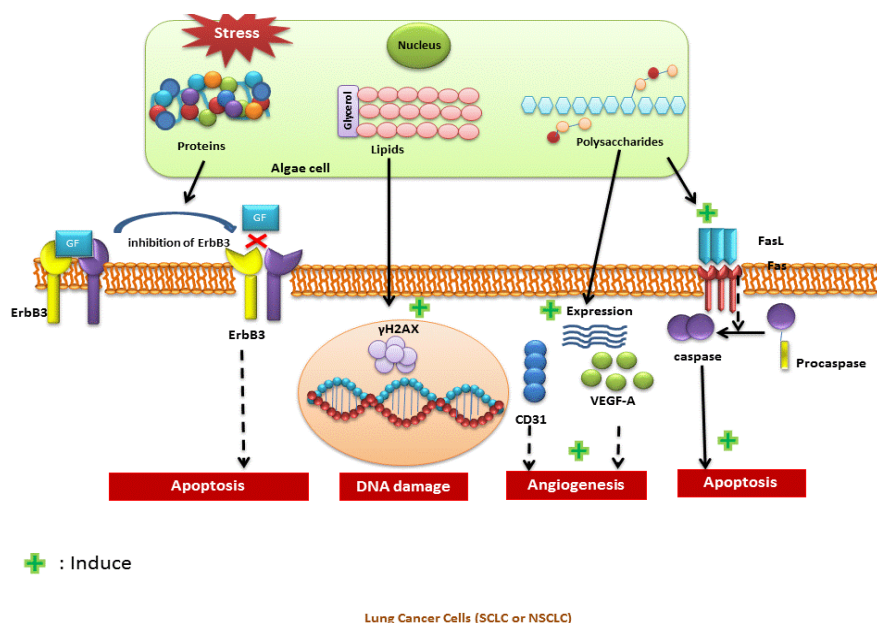
Figure 2. Examples of Mode of action of the major photosynthetic bioactives against lung cancer.

The anticancer activity of carotenoid derivatives is mediated by the activation of several receptors and augmentation of carcinogen-metabolizing enzymes [94]. Whereas, phycocyanin can inhibit the proliferation of the tumor cells via arrest cell cycle at the G0/G1 phase and block DNA synthesis [95]. It was seen that phycocyanin molecules triggered apoptosis by targeting cellular proteins via intrinsic and extrinsic pathways. Several molecules responsible of inducing apoptosis such as: CDK-4, TNF, caspase-3, were identified as molecular targets of phycocyanin [96].

6. Potential to Combine Natural Products with Existing Drug Regimens in the Treatment of Lung Cancer

The use of natural products in combination with conventional chemotherapeutic agents like cisplatin has the potential to enhance the therapeutic effectiveness of common chemotherapy agents through cancer. Hence, the synergistic enhancement of cisplatin therapy would be a beneficial strategy to overcome the severe toxic side effects and drug resistance of cisplatin. In line with such concept [97], some of the compounds isolated from algae can also be used as co-adjuvants to improve the efficiency of the drugs currently used as therapeutics. Indeed, the pre-treatment of HepG2 cells with fucoxanthin allowed to improve the therapeutic effect of cisplatin [98]. Additionally, the conjugation of λ-carrageenan [99], Cf-PLS [100], and porphyran [101] compounds with 5-FU drug enhanced its antitumor activity. Furthermore, Psammaplin A, a phenolic compound containing a sulfur bridge accruing naturally in monomers or dimers, is produced by microalgae and cyanobacteria. Charkie [102] demonstrated that, can enhance the activity of camptothecin (a DNA damage inducing drug) against different kind of cancers including Bap1-null lung cancer via inhibiting the histone deacetylase (HDAC) responsible of tumourigenesis and angiogenesis.

7. Economic Feasibility and Challenges in Using Microalgae for Lung Cancer

It is evident from our review that microalgae have high potential as a source of anti-lung cancer molecules, however it still needs to be extensively investigated further, in vitro and in vivo [103]. Although microalgae present high potential for producing pharmaceuticals and nutraceuticals with high antioxidant and anticancer activities, some limitations and challenges need to be addressed

carefully especially before moving from laboratory to pilot and industrial scale [104]. Some challenges are related to the upstream part leading the biomass production and here we present as example the selection of the most suitable cultivation system for producing biomass enriched with high value products and contamination free. This normally requires the use of photobioreactors which present high cost comparatively to the open raceway pond which is considered as the most common and economically feasible way to produce microalgae biomass. On the other hand, studies have proven that the production of HVC from algae can be enhanced by various physicochemical stresses [105–107]. Thus, the optimization of the best conditions for producing microalgae biomass enriched with high-value products requires more energy and cost [108].

Additionally, the downstream processing of the microalgae biomass to extract the high-value products is still unviable and needs a lot of optimizations of the different steps. New low-cost harvesting technology is required to make the whole process sustainable since harvesting is considered as a major challenge as it is requiring almost 30% of the total cost of the pharmaceuticals production process. Different initiatives are recently developed but still they didn't meet the viability [109–112]. Furthermore, the extraction process that is efficient, safe for the molecules, economically feasible and environmentally friendly is far from being a reality. For that, a lot of optimizations are urgently required. Some initiatives targeting a cost-effective process to extract the microalgae bioactives are also existing but still they did not meet the sustainability required [113]. Finally, microalgae bioactives are very promising as pharmaceuticals and efficient drugs against lung cancer however a lot of optimizations are required to make the up and down stream processing steps viable and economically feasible. For the time being, including microalgae biomass enriched with high value products in the human diets could be a very good option to enhance the immune system and improve the human health.

8. Future Perspective

Cancer is a serious problem constituting the second most threatening disease after cardiac complications [114]. Microalgae emerged as a vast, and largely untapped potential repository of natural compounds. It is not only used as functional foods but also have a long history of use in Asian countries in treatment of cancer. Many crude or partially purified molecules especially polysaccharides have been tested for their antitumor activities.

Different Genus such as *Chlorella*, *Cladophoropsis*, *Codium*, *Dunaliella*, *Enteromorpha*, *Helimenda*, *Udocea,* and *Ulva* were previously reported to be able to produce HVC which exhibit Bioactive properties against cancer [40,43,44,46,114]. Strains isolated from desert harsh environment are poorly investigated for their potential repository of anticancerous natural compounds. Hence, further examination of local isolated algal species is necessary to truly investigate this great resource and highlight the importance of using this natural molecule to complement the existing medicines and provide similar results with lesser or no side effects. In the future, with achieving a viable and economically feasible production of marine microalga biomass, microalgae bioactives will represent the most promising natural alternative for chemical drugs with higher recovery rates and lesser side effects.

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