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Algae Potent Source for Cancer Therapy, Current Updates and Knowledge

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ABSTRACT

Although cancer treatments are able to successfully kill cancerous cells, their effectiveness is mostly limited to a few harmful side effects. As a result, antioxidant supplementation, which reduces reactive species levels and mitigates persistent oxidative damage, is frequently required to alleviate these side effects. As a result, it has the potential to prevent cancer cells from growing while simultaneously protecting healthy cells. Additionally, antioxidant supplementation, either by itself or in conjunction with chemotherapeutics, prevents chemoresistance by enhancing the response to chemotherapy drugs, improves cancer patients' quality of life, and reduces side effects. Phytochemical and dietary antioxidants from various sources have been shown to be effective in treating chemo and radiation therapy-induced toxicities and increasing treatment efficacy in preclinical and clinical studies. Algae, both microscopic and macro, may be considered an alternative natural source of antioxidants in this context. Green growth have cell reinforcements from different gatherings, which can be taken advantage of in the drug business. Algal antioxidant research and application are still in their infancy, despite their nutritional benefits. Twenty-three antioxidants from microalgae are discussed in detail in this review article, along with their potential mechanism of action in cancer cells and application in cancer therapy. Antioxidants derived from seaweeds, particularly those

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that are edible, are also discussed.

Keywords: algae, antioxidant, cancer therapy, reactive species, dietary supplements, cancer.

INTRODUCTION

The main force behind maintaining cell metabolism and viability is oxygen, which is necessary for aerobic life. Since oxygen's paramagnetic properties encourage the formation of partially oxidized high-reactive components, or reactive oxygen species (ROS), simultaneously (Francenia Santos-Sánchez et al., 2019). However the digestion of oxygen produces ROS in residing creatures as side-effects, they impact cell flagging and redox homeostasis. When the cell comes into contact with either endogenous or exogenous sources, ROS levels can sometimes rise, resulting in oxidative stress. In such an express, the ROS level arrives at a poisonous limit, and it figures out how to beat the cancer prevention agent arrangement of the cell, in this way escapes to end and stay in the cell (Raza and co., 2017). Negative oxidative stress is the result of these reactive oxygen species (ROS), which alters cellular signaling pathways, initiates genomic instability, or activates immunosuppression, resulting in carcinogenesis (Morry et al., 2017). Disease cells are more delicate to remedial medications that produce unnecessary measures of ROS or debilitate ROS rummaging limit of cells, which incites apoptosis (Mut-Salud et al., 2015).

Chemotherapy is still the most common form of cancer treatment out of a wide range of options. However tranquilizes utilized in chemotherapy can effectively take out quickly developing harmful tissues, these medications can influence the mucous layers of different organs. As a result, cancer patients experience a number of side effects, including anaphylaxis, a different kind of cytopenia, toxicity to the liver, heart, nephron, and ear, as well as nausea, vomiting, pain, diarrhea, alopecia, anorexia, cachexia, mucous membrane inflammation, and asthenia (Oun et al. 2018). Antioxidant supplements are frequently prescribed to alleviate

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these side effects without affecting the effectiveness of the treatment (Ambrosone et al., 2019). To manage the side effects of their treatments, cancer patients frequently take supplements of vitamins and minerals, natural products made from plants, or herbal remedies. The most widely recognized suggested cell reinforcements are nutrients, polyphenols, and carotenoids. Vegetables and fruits that can be eaten are a great source of a variety of antioxidant phytochemicals with varying levels of antioxidant power. It has been suggested that eating more than 400 grams of fruits and vegetables daily can help prevent certain types of cancer (Miller and Snyder, 2012; Chester et al., 2019; Olivas-Aguirre and Wall-Medrano, 2020).

Microalgae can be an excellent alternative source of antioxidant compounds in addition to these plant products. Microalgae are in many cases considered a jackpot of high worth chemically significant metabolites, similar to carotenoids, polyphenols, unsaturated fats, phycobiliproteins, nutrients, which are the results of guard systems of microalgae against stress factors (Chu, 2013). In addition to their in vitro and in vivo anticancer properties, these bioactive compounds have been shown to have antioxidant properties. For instance, microalgal tetraterpenoids are a decent wellspring of cell reinforcements and furthermore have shown promising antitumor action in various cell lines. Microalgal antioxidants are a good source of nutraceuticals for human health because their activity is comparable to or even greater than that of antioxidants of plant or animal origin (Sansone and Brunet, 2019). Due to their diverse and extensive range of metabolites, rapid growth rate, ability to adapt to seasonal changes, lack of need for cultivable land or fresh water, and, most importantly, lack of impact on food crops, microalgae are increasingly being looked at for pharmaceutical applications (Khan et al., 2018). Astaxanthin and DHA, which are metabolites of microalgae, are popular supplements. Spirulina and chlorella are the two healthy foods that are consumed the most frequently in the form of powder, tablets, or capsules. Tetraselmis, which is consumed as an antioxidant supplement, is currently joining the race. Nutraceuticals can also

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be found in food products that have been enriched with microalgae (Koyande et al., 2019). Seaweeds are also a good source of molecules that protect against free radicals. Fucoidans, phlorotannin, laminarin, and terpenoids are among these bioactives that have been extensively studied for their antioxidant properties (Gupta and Abu-Ghannam, 2011). Additionally, many Asian nations, including China, Indonesia, Japan, Korea, Malaysia, Thailand, and the Philippines, are the most important producers and consumers of high-quality edible seaweeds containing these antioxidants (Ferdouse et al., 2018).

However, it has been hypothesized that the antioxidant phytochemicals in these algae play a chemo-preventive role in normal cells by inhibiting aberrant cell proliferation, metastasis, and angiogenesis, preventing ROS-mediated genomic instability, and suppressing oxidative stress caused by radiation or chemotherapy. Antioxidants can also play a therapeutic role when used in conjunction with chemotherapeutic agents. They have the potential to increase tumor cell oxidative stress, disable transcription factors, activate signaling pathways related to apoptosis, and impede signaling pathways related to cell proliferation (Chikara et al., 2018). However, there are still some disagreements regarding the use of antioxidants in cancer treatment. This audit explains receptive species as well as oxidative pressure, and their jobs in disease advancement. Then, at that point, the characterization and method of activity of cancer prevention agents have been made sense of momentarily. Finally, a few well-known antioxidants from microalgae and seaweed are discussed, along with their potential applications in cancer treatment.

REACTIVE SPECIES AND OXIDATIVE STRESS

Free revolutionaries contain at least one unpaired electrons in their molecules' furthest shell, which makes them strikingly receptive and more temperamental. They can potentially harm cells and are formed in our bodies naturally as byproducts of biological processes or from external sources. Shrivastava et al., 2019). Free

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revolutionaries are connected with responsive oxygen species (ROS), receptive nitrogen species (RNS), receptive sulfur species (RSS), responsive carbonyl species (RCS), and receptive selenium species (RSeS) (Sies et al., 2017). Our bodies continually produce these reactive species from both endogenous and exogenous sources. Intracellular organelles like peroxisomes and mitochondria, as well as extracellular components like inflammatory cells like macrophages, eosinophils, and neutrophils, are examples of endogenous sources. High ionizing radiation, environmental toxins (pollution, allergens, toxic metals like cadmium, lead, mercury, iron, arsenic, and pesticides), microorganisms, certain drugs, cigarette smoke, alcohol, and dietary xenobiotics are examples of exogenous sources (Pizzino et al., 2017).

ROS are extensively studied among these reactive species. ROS is produced in the cytosol by solvent cell parts and cytosolic chemicals, on layers of mitochondria, in the peroxisomes, in the endoplasmic reticulum, on the plasma film of the broken cells, and in the lysosomes (Di Meo et al., 2016). However, there are two types of ROS: The superoxide anion, nitric oxide, hydroperoxyl, and peroxyl radicals, as well as the hydroxyl radical, are examples of one type of radical. Non-radical ROS, which lack an unpaired electron but retain their chemical reactivity and the ability to change into radical ROS (such as singlet oxygen, ozone, hydrogen peroxide, and hypochlorous acid, Chahal et al., 2018). ROS can act as secondary messengers in cell signaling, stimulating various signal transduction pathways that involve gene activation or cellular growth and thus contributing significantly to a variety of cellular processes (Klaunig and Wang, 2018).

ROS responding with nitric oxide brings about RNS and RSS, with thiols (Corpas and Barroso, 2015; Mut-Salud and others, 2015; Sies et al., 2017). Nitric oxide (NO•), nitrogen dioxide radical (NO2•), peroxynitrite (HNO3), and other nitrogen oxides make up RNS, or oxidants that contain nitrogen. Additionally, responsive sulfur species (RSS) are sulfur-containing particles, which

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incorporate hydrogen sulfide (H2S), thiols (RSH), persulfides (RSSH), polysulfides, S-nitrosothiols (RSNO), hydrogen polysulfides, and sulfenic acids (RSOH), that play fundamental parts in the guideline of cell frameworks (Xu et al., 2019).

The concept of oxidative stress as a concept in redox biology was first discussed in 1985 in the book "Oxidative Stress." According to Di Meo et al., oxidative stress (OS) occurs when there is a disparity between the biological system in cells' generation of RS and its detoxification. 2016). “An imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage” is what Helmut Sie defines as oxidative stress. Oxidative stress can have two different effects, which are categorized based on their intensity as oxidative stress and oxidative distress. Addressing specific targets for redox signaling, which is necessary for maintaining normal physiology and is known as oxidative eustress, is possible with low exposure to reactive species or oxidants. Through the expression of antioxidant proteins and compounds, the base level of OS boosts the defense system, resulting in health benefits. Conflictingly, over the top oxidant or RS challenge prompts disturbed redox flagging, causing harmful impact, as macromolecular harm in intracellular organelles, inactivation of redox administrative proteins, or strange cell multiplication and demise, which is named as oxidative misery (Niki, 2016; Go and Jones, 2017; Sies, 2020) (Figure 1). Nutritional, postprandial, photooxidative, radiation-induced, reductive, and nitroxidative, nitrosative, and nitrative oxidative stress are examples of different types of oxidative stress that are mostly determined by the generation source (Sies, 2019).

EFFECT ON CANCER CELLS

Operating system can assume a significant part in all periods of the oncogenic cycle (commencement, advancement, and movement), by actuating different record factors, including atomic component (NF-κB), Atomic variable erythroid 2- related factor 2 (Nrf2), hypoxia-inducible element (HIF-1α), activator protein (AP),

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growth protein (p53), β-catenin/Wnt flagging pathway, which helps in balancing the outflow of resistant and provocative related qualities and accordingly sets off carcinogenesis (Saed et al., 2017). Plus, ROS capabilities bidirectionally in malignant growth. It can be beneficial or harmful to cancer. A variety of cancer signaling pathways, including MAPK/AP-1/NF-B, associated with cancer metastasis and angiogenesis, can contribute to the development of cancer. ROS can also activate NF-B, AP-1, HIF-1a, growth factors, inflammatory cytokines, and chemokines to cause inflammation. Conversely, antitumorigenic signaling is triggered when ROS levels rise, which promotes cancer cell death caused by oxidative stress (Reczek and Chandel, 2017; Kashyap and other, 2019). To enable pro-tumorigenic cell signaling without triggering cell death, cancer cells must always maintain an elevated ROS level. Additionally, tumor cells stimulate the ROS scavenging mechanism in order to keep ROS levels below the cytotoxic threshold (Ilghami et al., 2020).

Cell Proliferation and Survival

The regulation of mitogen-activated protein kinase, protein kinase D (PKD) signaling pathways, transcription factors like AP, NF-B, and HIF-1, as well as the negative regulation of phosphatases and protein tyrosine phosphatase 1B (PTP1B), epigenetic alterations in transcription factors and tumor suppressors, Nrf2 and p53, as well as by down-regulating the expression of E-cad 2017; Moloney and Cotter, 2018).

Genetic Instability

ROS frequently go about as middle people of DNA harm. ROS-interacting modifications, such as inter- and intra-strand bindings or DNA-protein crosslinks, which alter gene expression, are frequently produced when ROS accumulate cells through overproduction. ROS cause DNA harm through oxidizing nucleoside bases and structure DNA sores, for example, the arrangement of 8-oxo guanine, that create DNA twofold strand breaks (DSBs), if unrepaired. Degradation, strand breaks, and

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mitochondrial DNA lesions are all caused by ROS accumulation. Moreover, expanded ROS through the enactment of oncogenes impacts the replication stress. ROS can oxidize dNTPs, which can alter the activity of polymerase, break down replication forks, and form DSBs, all of which contribute to genomic instability. Additionally, ROS cause proteins associated with the cell cycle checkpoint to be activated, resulting in cell cycle arrest. Most importantly, these chromosomal changes cause genetic instability and, ultimately, cancer (De Sá Junior et al., 2017; Srinivas et al., 2019).

Cell Death

Expanded ROS cause cell cycle capture, senescence, and apoptosis. Through either intrinsic or extrinsic pathways, elevated intracellular ROS production induces apoptosis. Besides, ROS trigger apoptosis by inactivating or upgrading the ubiquitination of against apoptotic protein, Bcl-2, and by diminishing the degrees of apoptosis controller, Bax, and Terrible. Then again, ROS can kill disease cells through autophagy, a successful safeguard against operating system harm. ROS can inhibit the negative regulator of autophagy (TORC1) and inactivate genes related to autophagy. Necrosis is accelerated by ROS produced by NOXs or in the electron transport chain of mitochondria. Besides, growth silencer protein p53 causes cell demise through ferroptosis (relies upon intracellular iron) which is actuated by expanded ROS level (Perillo et al., 2020).

Angiogenesis and Metastasis

In metastasis, growth cells are coursed from the essential site to different spots in the body by means of blood and lymph. ROS can cause metastasis by initiating hypoxia-interceded MMPs (lattice metalloproteinases) and cathepsin articulation. Numerous tumor progression pathways and metastasis signaling pathways may be stimulated or altered by an elevated ROS level, activating the MMP enzymes. ROS can contribute to tumor migration if they are produced by signaling kinases that are modulated by integrin

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assembly and activated growth factor receptors. Cell invasion is caused by FAK (cell motility controlling protein) activation, which is mediated by ROS. Cofilin, an actin-binding protein, can also be activated by ROS, facilitating cell migration.
In any case, metastasis can be prompted by ROS by different systems additionally, as proteolytic debasement of glycosaminoglycan (GAG) and other ECM parts. By inhibiting prolyl hydroxylases (PHDs) and, consequently, VEGF (primary pro-angiogenic factor) activation, an elevated level of ROS can stabilize HIF, rendering angiogenesis and tumor progression impossible (Galadari et al., 2017; Kashyap and other, 2019).

Chemoresistance

Chemoresistance is an essential driver of therapy inadequacy in malignant growth. A transporter protein known as P-glycoprotein is a multidrug resistance protein that is responsible for the efflux or removal of multiple anticancer drugs from cancer cells. This protein can be upregulated by ROS, which results in chemoresistance and prevents cell death (Galadari et al., 2017).
Antioxidants Halliwell et al. were the first to define an antioxidant, in 1989 as "any substance that, present in low focuses contrasted with oxidizable substrates (sugars, lipids, proteins or nucleic acids), essentially delays or restrains the oxidation of the referenced substrates" (Halliwell et al., 1992). Antioxidants are molecules that combat oxidant activity, hence the name "antioxidant." Cell reinforcements can be characterized as, synthetic substances that can restrain or extinguish free revolutionaries, that are shaped as normal side-effects in the body during the natural cycle, and hence hindering oxidative harm (Chahal et al., 2018; Khurana and other, 2018).

Endogenous antioxidants are antioxidants that are produced in the body through metabolism. Exogenous antioxidants, which are found in foods and supplements, can also be incorporated into the body. Moreover, there is additionally one more gathering of cell reinforcements that can be created artificially, which are generally

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Seaweeds as a Potential Source of Antioxidants

Seaweed are a significant piece of Asian cooking and are rich in chemically significant bioactive mixtures. Carotenoids, polyphenols, phycobilin (phycoerythrin and phycocyanin), sulfated polysaccharides, and vitamins A and C make up the majority of seaweed antioxidants (Cornish and Garbary, 2011). Sulfated polysaccharides and polyphenols from kelp are not like microalgae. The seaweed or macroalgal sulfated polysaccharides with antioxidant and anticancer activity that have received the most research are the carrageenans, fucoidans, ulvan, and porphyran. Additionally, non-sulfated polysaccharides like alginic acid and laminarin, which are found in macroalgae, have antioxidative and antitumor properties (Venugopal, 2019). On account of polyphenolic compounds, the presence of phlorotannins, tetraphloretol, fucophlorethol, eckol, difucol, fucodiphlorethol, phloroglucinol, diphlorethol have been

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accounted for from macroalgae (Mekinić et al., 2019). Phlorotannins, one of the antioxidant-rich phenolic compounds, are prevalent in brown algae and other macroalgae (Montero et al., 2017). According to Fleita et al., fatty acids from *Laurencia papillosa* (a red alga), sulfated polysaccharides from *Pterocladia capillacea*, meroterpenoids like sargachromanol, sargahydroquinoic, and sargaquinoic acid from Sargassum serratifolium, and sesquiterpenoids (isozonarol) from Dictyopteris 2015; Kumagai and other, 2018; Omar and co., 2018; Lim et al., 2019). Other than these, a scope of eatable ocean growth with antioxidative properties is consumed universally.

CONCLUSION

There have been a number of in vitro and in vivo studies on antioxidant therapies over the past few decades. These studies have shown that daily consumption of a specific dosage of antioxidant nutraceuticals has a negative correlation with cancer risk and increases treatment efficacy. However, randomized clinical trials have shown mixed results, which is considered a real problem for the widespread use of antioxidant supplements in cancer treatment. The dose, synergy, bioavailability of the antioxidants used, the health status of the patients, the type of cancer they have, their lifestyle, their tendency to take supplements, and the length of time the studies were conducted can all influence these inconsistent results. Consequently, more controlled and obvious clinical preliminaries with fresher methodologies should be directed to achieve a protected and viable cell reinforcement supplement framework in malignant growth treatment. In a similar vein, extensive research is required to investigate novel algae-derived antioxidant molecules. Priority should be given to purification methods and in vivo studies. The actual antioxidant compounds in several organic and aqueous extracts that have already demonstrated in vitro antioxidant and anticancer activities, as well as their mechanism of action on the cellular system and their capacity to enhance chemotherapeutic drugs, require additional research.

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