

Research & Reviews: Journal of Pharmaceutics and Nanotechnology

The Role of Algae in Pharmaceutical Development

Aditya T^{1*}, Bitu G¹ and Mercy Eleanor G²

¹KIIT School of Biotechnology, Kalinga Institute of Industrial Technology University, Bhubaneswar, India

²Vignan Institute of Pharmaceutical Technology, Jawaharlal Nehru Technological University Kakinada, Andhra Pradesh, India

Review Article

Received: 21/08/2016
Revised: 30/08/2016
Accepted: 06/09/2016

*For Correspondence

Aditya T, KIIT School of Biotechnology, Kalinga Institute of Industrial Technology University, Bhubaneswar, India

Keywords: Microalgae, lectins, Antioxidants, Bioactive compounds, Nutraceuticals

E-mail: adityacharan@gmail.com

ABSTRACT

Marine algae have received growing attention as sources of bioactive metabolites and considered for the pharmaceutical industry in drug development. Algae have many convincing properties to make it stand out in front of synthetic drugs. This review focuses specifically on the potentials, properties, medicinal uses, applications of algal molecules. This also focuses on the future aspects and challenges of algae in the pharmaceutical and nutraceutical area.

INTRODUCTION

Algae are a very simple chlorophyll-containing organism composed of one or group of cells together in colonies which are basically not much related to each other making it polyphyletic in nature^[1-4]. Natural products from algae have been widely explored, since long time, for human use as food and as medical treatments. Many chemicals and products from algae have economic importance and are broadly used as it is a good source of fibre, minerals, antioxidants, vitamins, pigments, steroids, lectins, halogenated compounds, polysaccharides, proteins, polyunsaturated fatty acids and other lipids; thus, they are even consumed in many countries^[5-8]. Algae are a rich and varied source of pharmacologically active natural products and nutraceuticals. Currently these products are very valuable in the market. Many products are now being commercialized such as carotenoids, phycobilins, fatty acids, polysaccharides, vitamins, and biologically active molecules for use in human and animal health^[9-16]. Even marine algae which are categorized into micro/macro algae are being very beneficial to the pharmaceutical industries. Marine algae are potential sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical requirements^[17-22]. Many studies are now being carried out on the chemicals which are being extracted from marine algae for human benefits and welfare. After biofuel many researchers are working on production of biologic drugs by coaxing therapeutic pharmaceuticals to replace expensive drugs^[18,19].

Algae as a Source of Pharmaceuticals

The global market of pharmaceutical industries is on a huge rise. In India 70% to 80% of the market is dominated by pharmaceutical industries, the market size is growing every year. Algae always had the potential to be beneficial to mankind; especially the use of cyanobacteria (blue-green algae), for antibiotics and pharmacologically active compounds has received ever increasing interest. Large ranges of products are being derived from algae which include; Antimicrobials, Antivirals, Therapeutic proteins, drugs, Antifungals and many more^[23-28].

Mostly the bases of these are dependent on the properties of algae such as the antioxidant properties, anticancer activity, and antiviral properties^[29,30]

- **Antioxidant properties:** The most powerful water soluble antioxidants found in algae are polyphenols, phycobiliproteins and vitamins. Antioxidants help in the inhibition of cancer growth by causing regression of premalignant lesions^[31-36]. A study has found out that many algal species have helped in prevention of oxidative damage by the process of scavenging free radicals and active oxygen which helps in cancer prevention. Antioxidants are the key to fight out various diseases including chronic disorders, cardiovascular diseases, and inflammations. Polyphenols found mostly in marine algae are having good antioxidant properties, also known as phlorotannins. The sulphate polysaccharides which are isolated from marine algae release radical scavenging activities^[37-41]. Several methods of extraction are designed out by researchers for this. Filamentous green algae have great antioxidant properties. Seaweeds contain a wide variety of bioactive compounds, which has this property and is very well used commercially worldwide^[42-47].

- **Anticancer activity:** Mostly marine algae are involved in this as it has wide range of properties. They have good antibiotic properties which are inhibiting many dangerous diseases. Oral cancers can be treated by the use of algae which exhibits antioxidant properties such as β - carotenes, floral compounds of algae are being used as therapeutics for cancer. This section is under vigorous study by researchers and people from pharmaceutical industries^[48-55].

Aqueous extracts of algae show anticancer activities, cyanobacteria *S. platensis* shows the highest antioxidants which leads to anticancer efficiency, phyllobili proteins are another example, sargassum species^[56-60].

Antiviral properties: When limitations arose on vaccines it led way to many synthetic antiviral compounds for the treatment of active herpetic infections, but this was too unsuccessful^[61,62]. Researches then found out the antiviral property in brown algae, as it has a wide spectrum of activity which completely inhibits virus. This discovery has led to antiviral chemotherapy^[63-66]. Algal polysaccharides are derived which are used against particular viruses;

- Carragen from red algae used against Influenza virus, DENV, HSV-1, HSV-2, HPV, HRV, HIV
- Galactan from Red algae, *Callophyllis variegata*, *Agardhiella tenera* used against HSV-1, HSV-2, HIV-1, HIV-2, DENV, HAV
- Alginate from Brown algae against HIV, IAV, HBV
- Nostaflan from Blue-green alga, *Nostoc flagelliforme* against HSV-1, HSV-2, influenza A virus, human cytomegalovirus
- Fucan from Brown algae, *Ascophyllum nodosum*, *Macrocystis pyrifera* against HIV, IAV, HBV^[67-76]

Algae as nutraceuticals

The current value of algal nutraceuticals is very high in the market. Though the expansion of strains is very small, basic nutraceuticals from algae include food supplements, dietary supplements, value-added processed foods as well as non-food supplements such as tablets, and soft gels^[77-82]. The major products derived from algae are Omega 3 polyunsaturated fatty acids (PUFA), β -Carotene, Astaxanthin, Carotenoids etc.

- **Carotenoids:** Microalgae is being widely used for nutraceutical supplements, species of *Chlorella*, *Dunaliella*, *Haematococcus*, *Spirulina*, *Aphanizomenon*, are widely evaluated by researchers for its potential. It generally depends on the protein content of the species which determines its credibility towards nutraceutical development. Extracts of *Chlorella*, *Spirulina* have good antioxidant, anti-inflammatory, anti-tumor properties. *Haematococcus* has many vitamins in it which makes it more interesting towards nutraceutical development. *Aphanizomenon* plays a huge role in cholesterol controlling, stimulation of liver functions and also is a cure for many dermatological problems^[83,84].
- **Astaxanthin:** Natural Algae Astaxanthin Association (NAXA), is playing a major role in determining the benefits and value of astaxanthin. It is laying stress on differences between natural algal astaxanthin and other synthetic sources. Astaxanthins are built from carbon precursors, its high lipid soluble pigment, it's basically an antioxidant with slightly low activity but has good free radical terminating of each carotenoid. Astaxanthins are used as food supplements^[85-90].
- **Omega 3 polyunsaturated fatty acids:** PUFA is very important for body metabolism in humans. Chlorophytes, Bryophyta algae are used for the extraction of these healthy and essential fatty acids. N-6 PUFA is a diet

rich fatty acid which is derived from the above. The fatty acid content in algae makes it a well-known bioactive compound which is very useful in the pharmaceutical industry.

Algal Drugs

Algae could be used to make complex, targeted cancer drugs, their photosynthetic organelles, chloroplasts make it more helpful. Researches and scientists are working vigorously on genetically engineered tiny algae. These are helpful in killing harmful cancer cells, leading to tumour treatments. This is a major outbreak in the development of cancer drug therapy. Algae have a great ability of folding proteins into complex three dimensional structures. In San Diego human antibodies were successfully produced by algae, human therapeutic drugs, such as human vascular endothelial growth factor, were used to treat patients suffering from pulmonary emphysema [71-77].

Laboratories were interested in fusion of algal proteins which help in antibody formation, these was produced in the chloroplast of algae (Figure 1).



Figure 1: Algal engineered anti-cancer therapy.

Microalgae play a big role in development of anti-cancer drugs; a compound named cryptophycin has been isolated from the blue green algae which is a strong component for an anti-cancer drug development. They even produce alkaloidal neurotoxins such as saxitoxin and polyketide, having anti-inflammatory and anti-cancer properties [83-88].

Whereas, Macro algae contain alkaloids giving way to anti-cancer drugs

Medicinal uses of algae/algal drugs

Different types of algae have different medicinal properties making them unique from other. They are used for various treatments and below is a small list of such algae and their medicinal cures [91-96];

- *Enteromorpha*: It can be used to treat hemorrhoids, parasitic disease, goiter, coughing and bronchitis; fever reduction capacity and ease pain.
- *Acetabularia*: This can be used to treat urinary diseases and edema.
- *Laminaria*: It can be used for thyroid problems and urinary diseases.
- *Sargassum*: It can be used to treat cervical lymphadenitis, edema; diminishes inflammation; induces urination; contains both iodine and potassium
- *Gelidium*: can be used to extract agar
- *Corallina*: It can be used as pesticides
- *Grateloupia*: Blood sugar lowering capability

- *Gloeopeltis*: Treatment for tonsils, goitre.

Applications and future of algal drugs

Algal drugs are having many applications which make it a new boon for the future in drug and pharmaceutical sectors. The applications include;

- High value oils
- Cosmetics
- Colorants
- Waste water treatment
- Food supplements
- Personalized drugs
- Fertilizers
- In forensic medicines

So, as scientists are looking for cheaper biological drugs, green algae have been the upcoming trend, and looking at the above applications it's becoming friendlier. Seeing the ability of bioactive compound production, especially by green algae is a boon to the pharmaceutical research^[96-100].

CONCLUSION

The confirmation of scientists towards algal products has increased its sustainability in drug development field. The therapeutic drugs prepared from algae which exist on both sunlight and carbon dioxide in the air will be manufactured at one-thousandth of today's costs, which makes it cheaper. Yet the development of these drugs has few drawbacks which is creating hindrance. Many strains are really commercially useful. Using of bioreactors has been common and is being widely promoted.

Seeing the above studies and the on-going researches one can believe in the future and the improvement of algal drugs.

REFERENCES

1. Christaki E, et al. Phycobiliproteins: A New Perspective in Natural Pigments Derived from Microalgae. *J Oceanogr Mar Res.* 2016; 4:e114.
2. Fábio A.E. Torresa, et al. New drugs with antiprotozoal activity from marine algae: a review. *Rev. bras. Farmacogn.* 2014; 24: 3.
3. Harsha K, et al. Algae as future drugs. *Asian Journal of Pharmaceutical and Clinical Research.* 2014; 5:4.
4. Montasser MS, et al. A Novel Eco-friendly Method of Using Red Algae (*Laurencia papillosa*) to Synthesize Gold Nanoparticles. *J Nanomed Nanotechnol.* 2016; 7: 383.
5. Mehta P, et al. Growth and Tolerability of Healthy Term Infants Fed a New Formula Supplemented with DHA from *Schizochytrium* sp Microalgae. *J Vasc Med Surg.* 2016; 4:267.
6. Muraleedhara Kurup G and Mariya Jose G (2016) In Vitro Antioxidant Properties of Edible Marine Algae *Sargassum swartzii*, *Ulva fasciata* and *Chaetomorpha antennina* of Kerala Coast. *J Pharma Reports* 2016; 1: 112.
7. Oramary. Feeding Common Carp Fish (*Cyprinus carpio*) on Natural Foods (Algae, Phytoplankton, Zooplankton and Others) on Tigris River in Mosul Dam /Duhok, Kurdistan Region of Iraq. *J Aquac Res Development.* 2016; 7: 413.
8. L Pérez. Biofuels from Microalgae, A Promising Alternative. *Pharm Anal Chem.* 2016; 2: e103.
9. El-Sharony TF, et al. Effect of Foliar Application with Algae and Plant Extracts on Growth, Yield and Fruit Quality of Fruitful Mango Trees Cv. Fagri Kalan. *Horticulture* 2015; 2: 162.
10. Ramirez-Merida LG, et al. Microalgae as Nanofactory for Production of Antimicrobial Molecules. *J Nanomedic Nanotechnol.* 2015; S6-004.

11. Abdolsamad, et al. The effect of Silver nanoparticles [AgNPs] on chlorophyll A and β -carotene content [as two natural antioxidants] in the microalgae *Chlorella vulgaris*. 2015; JEES.
12. Stoyneva-Gärtner MP and Uzunov BA. An Ethno biological Glance on Globalization Impact on the Traditional Use of Algae and Fungi as Food in Bulgaria. *J Nutr Food Sci*. 2015; 5: 413.
13. Rumki Nandi, et al. Surfactant Assistant Enhancement of Bioremediation Rate for Hexavalent Chromium by Water Algae. *Biochem Physiol*. 2014; 4: 173.
14. Suantika G, et al. Performance of Zero Water Discharge (ZWD) System with Nitrifying Bacteria and Microalgae *Chaetoceros calcitrans* Components in Super Intensive White Shrimp (*Litopenaeus vannamei*) Culture. *J Aquac Res Development*. 2015; 6: 9.
15. Swapnil Sanmukh, et al. Bioactive Compounds Derived from Microalgae Showing Antimicrobial Activities. *J Aquac Res Development*. 2014; 5:224.
16. Bastian Steudel. Microalgae in Ecology: Ecosystem Functioning Experiments. *Oceanography*. 2014; 2: 122.
17. Rehder D (2014) Vanadate-Dependent Peroxidases in Macroalgae: Function, Applications, and Environmental Impact. *Oceanography* 2014; 2: 121.
18. Suryanarayanan TS and Johnson JA (2014) Fungal Endosymbionts of Macroalgae: Need for Enquiries into Diversity and Technological Potential. *Oceanography* 2014; 2: 119.
19. Raja R, Shanmugam H, Ganesan V and Carvalho IS (2014) Biomass from Microalgae: An Overview. *Oceanography* 2014; 2: 118.
20. Gede Suantika, et al. The Use of Indigenous Probiotic *Halomonas aquamarina* and *Shewanella* algae for White Shrimp (*Litopenaeus vannamei* Boone) Hatchery Productivity in Zero Water Discharge System. *J Aquac Res Development*. 2013; 4:194.
21. Gisela Jakob, et al. Surveying a Diverse Pool of Microalgae as a Bioresource for Future Biotechnological Applications. *J Pet Environ Biotechnol*. 2013; 4: 153
22. Evan Stephens, et al. Algae Fuels as an Alternative to Petroleum. *J Pet Environ Biotechnol*. 2013, 4:148
23. Budiyo and TD.Kusworo. Microalgae for Stabilizing Biogas Production from Cassava Starch Wastewater. *Int J Waste Resources*. 2012.
24. Abbas H. Sulaymon, et al. Column Biosorption of Lead, Cadmium, Copper, and Arsenic ions onto Algae. *J Bioprocess Biotechniq*. 2013; 3: 128.
25. Silva M, et al. Chemical Study and Biological Activity Evaluation of Two Azorean Macroalgae: *Ulva rigida* and *Gelidium microdon*. *Oceanography*. 2013; 1: 102.
26. Vikas Tomar. Raman Spectroscopy of Algae: A Review. *J Nanomed Nanotechnol*. 2012; 3:131
27. Dessy Ariyanti, et al. Feasibility of Using Microalgae for Biocement Production through Biocementation. *J Bioprocess Biotechniq*. 2012; 2:111.
28. Mostafa M El-Sheekh, et al. Biodegradation of Phenolic and Polycyclic Aromatic Compounds by Some Algae and Cyanobacteria. *J Bioremed Biodegrad*. 2012; 3:133.
29. Da-Kui Zhang, et al. Prognostic Value of Lymph Node Number and Ratio Staging System in Stage Rectal Cancer Following Neoadjuvant Radiochemotherapy. *J Cancer Sci Ther*. 2016; 8.7: 185.
30. Vallejo-Benítez Ana, et al. Myxofibrosarcoma Following Chemotherapy and Radiotherapy for Hodgkin's Lymphoma: Case Study and Review. *J Clin Case Rep*. 2016; 6: 816.
31. Ichihara H, et al. Negatively Charged Cell Membranes-Targeted Highly Selective Chemotherapy with Cationic Hybrid Liposomes against Colorectal Cancer In Vitro and In Vivo. *J Carcinog Mutagen*. 2016; 7: 267.
32. Prakash S Bisen. Nutritional Therapy as a Potent Alternate to Chemotherapy against Cancer. *J Cancer Sci Ther*. 2016; 8.6: 168.
33. Alessandro Pastorino, et al. Cisplatin-related Atrial Fibrillation during PEB Chemotherapy for Testicular Seminoma: A Case Report. *J Health Med Inform*. 2016.
34. Mahmoud AS, et al. *Corchorus Olitorius* Linn: A Rich Source of ω -3-Fatty Acids. *Pharm Anal Acta*. 2015; 7: 486.
35. Igor Brandão and Rafael Longhi. Trans Fatty Acids, does Exist Safety Dosage?. *J Obes Weight Loss Ther*. 2016; 6: 312.
36. Liu L, et al. A Review of Fatty Acids and Genetic Characterization of Safflower (*Carthamus tinctorius* L.) Seed Oil. *Organic Chem Curr Res*. 2016.

37. Enass Yossef Osman. Effects of Celecoxib or Omega-3 Fatty Acids Alone and in Combination with Risperidone on the Behavior and Brain Biochemistry Using Amphetamine-Induced Model of Schizophrenia in Rats. *J Pharma Reports*. 2016; 1: 116.
38. Dhan Lord Fortela, et al. Microbial Lipid Accumulation Capability of Activated Sludge Feeding on Short Chain Fatty Acids as Carbon Sources through Fed-Batch Cultivation. *J Bioprocess Biotech*. 2016; 6:275.
39. José Alberto Ariza-Ortega, et al. Effect of Long Time Electric Field Treatment on the Spatial Configuration of Fatty Acids in Crude Avocado (*Persea americana* Mill var. Hass) Oil. *Journal of Botanical Science*.
40. Tawfik A. Saleh. Nanomaterials for Pharmaceuticals Determination. *Bioenergetics*. 2016.
41. Samah Abo E Abass, et al. Development and Validation of Spectrophotometric and Pre-column Derivatization HPLC Method for Determination of Famotidine in Pharmaceuticals by Reaction with Sodium Nitroprusside; Application to Combined Tablets. *Pharm Anal Acta*. 2015; 7: 476
42. Yasir Mehmood*. Challenges Fases by MNCs in Pakistan Due To Unethical Practice of National Pharmaceuticals. *RRJHCP*.
43. Blaga Mutafova, et al. Microbial Transformations of Plant Origin Compounds as a Step in Preparation of Highly Valuable Pharmaceuticals. *J Drug Metab Toxicol*. 2015.
44. Ali SM, et al. Bioequivalence Study of Pegylated Doxorubicin Hydrochloride Liposome (PEGADRIA) and DOXIL[®] in Ovarian Cancer Patients: Physicochemical Characterization and Pre-clinical Studies. *J Nanomed Nanotechnol*. 2016; 7: 361
45. A Heidari. A Chemotherapeutic and Biospectroscopic Investigation of the Interaction of Double Standard DNA/RNA Binding Molecules with Cadmium Oxide (CdO) and Rhodium (III) Oxide (Rh₂O₃) Nanoparticles as Anti Cancer Drugs for Cancer Cells Treatment. *Chemotherapy (Los Angel)*. 2016; 5: e129
46. Surendra R Punganuru, et al. Colchicine-Based Hybrid Anticancer Drugs to Combat Tumor Heterogeneity. *Med Chem (Los Angeles)*. 2016; 6: 165
47. Aykut Özgür and Yusuf Tutar. Heat Shock Proteins: An Important Targets for Development of Next Generation Cancer Drugs. *Journal of Pharmacy and Pharmaceutical Sciences*. 2016.
48. Murari Bhandari, et al. Traditional Ayurvedic medicines: Pathway to develop anti-cancer drugs. *J Mol Pharm Org Process Res*. 2015; 3:130
49. Liu JJ, et al. Systems Pharmacology for the Study of Anticancer Drugs: Promises and Challenges. *Clin Pharmacol Biopharm*. 2015; 4:140
50. Ashish Chauhan and Rajat Tyagi. Herbal Anti-Cancer Drugs: A Better Way to Cure the Disease. *Pharm Anal Acta*. 2015; 6: e176
51. Hartley C Atkinson, et al. A Pharmacokinetic Analysis of a Novel Fixed Dose Oral Combination of Paracetamol and Ibuprofen, with Emphasis on Food Effect. *J Bioequiv Availab*.
52. Ateeq Ahmad, et al. Nanosomal Paclitaxel Lipid Suspension Demonstrates Higher Response Rates Compared to Paclitaxel in Patients with Metastatic Breast Cancer. *J Cancer Sci Ther*. 2015; 7.4: 116-120.
53. Yerasi N, et al. Evaluation of Frog as an Animal Model to Study the Fraction of Oral Dose Absorbed in Humans. *J Bioequiv Availab*. 2015.
54. Suman Garlapati and Shanthi Priyanka. Cradles of Signals for Pharmacovigilance Process. *J Pharmacovigil*. 2015; 3:e126
55. Suprita A Tawde. Particulate Matter in Injectables: Main cause for Recalls. *J Pharmacovigil*. 2015; 3:e128
56. Saifuddin Sheikh, et al. A New Topical Formulation of Minoxidil and Finasteride Improves Hair Growth in Men with Androgenetic Alopecia. *J Clin Exp Dermatol Res*. 2015; 6: 253
57. Eugene Lipov. With War-Related Post Traumatic Stress Disorder Being Resistant to Pharmaceuticals is it Time to Give Stellate Ganglion Block (SGB) a Shot?. *J Trauma Treat*. 2015; S4-020
58. Todd A Anderson, et al. Using Conventional HPLC to Study the Interaction of Pharmaceuticals and Personal Care Products (PPCPs) with Plants. *Pharm Anal Acta*. 2015; 6: 414
59. Amouzgar P and Salamatinia B. A Short Review on Presence of Pharmaceuticals in Water Bodies and the Potential of Chitosan and Chitosan Derivatives for Elimination of Pharmaceuticals. *J Mol Genet Med*. 2015; S4: 001
60. Seiji Kojima, et al. Broadband Terahertz Time-Domain and Low-Frequency Raman Spectroscopy of Crystalline and Glassy Pharmaceuticals. *Pharm Anal Acta*. 2015; 6: 401

61. Amruta Sumedh Mandpe, et al. Correlation of Disease Knowledge with Adherence to Drug Therapy, Blood Sugar Levels and Complications Associated with Disease among Type 2 Diabetic Patients. *J Diabetes Metab.* 2014; 5:369
62. Shiv Prasad Kosta, et al. Bio-Logical Human Tissue Based Electronic Circuits - An Alternate to Drug Therapy for Sick-Man (A Perspective Visionary Concept). *J Bioeng Biomed Sci.* 2013; 3:127
63. Michael P Keith. Overview of Drug Therapy for Spondyloarthritis. *Rheumatology (Sunnyvale).* 2013; 3:119
64. Gauze-Gnagne C, et al. Evaluation of the Anti-oxidant Effect of Spirulina on Marathon Runners in Cote Divoire. *J Nutr Food Sci.* 2015, 5: 392
65. Jia Cai Xian and Zhang Mei Ping. Study on the Methods of β -Carotene Extraction of *Spirulina platensis*. *Journal of Botanical Sciences.* 2015
66. Nematzadeh GH, et al. Evaluating Effect of Di-potassium Hydrogen Phosphate (K_2HPO_4) on Accumulation of Some Secondary Metabolites in *Spirulina* cyst. *J Ecosyst Ecogr.* 2015; 5: 155
67. Kollimalai Sakthivel and Kandasamy Kathiresan. Cholesterol Degradation Effect Analyzed using Marine Cyanobacterial Species *Spirulina subsalsa*. *J Microb Biochem Technol.* 2015; 7: 120-123
68. Mark McCarty. Low-Glycotoxin Diets and Spirulina may have Potential for Slowing the Growth and Spread of Rage-expressing Cancers. *J Integr Oncol.* 2015; 4:129
69. Anantharajappa Kumudha and Ravi Sarada. Effect of Different Extraction Methods on Vitamin B12 from Blue Green Algae, *Spirulina Platensis*. *Pharm Anal Acta.* 2015; 6: 337
70. Ghosh R and Mitra A. Suitability of Green Macroalgae *Enteromorpha intestinalis* as a Feed Form *Macrobrachium rosenbergii*. *J Fisheries Livest Prod.* 2015; 3:138
71. Rehder D. Vanadate-Dependent Peroxidases in Macroalgae: Function, Applications, and Environmental Impact. *Oceanography.* 2014; 2:121.
72. Suryanarayanan TS and Johnson JA. Fungal Endosymbionts of Macroalgae: Need for Enquiries into Diversity and Technological Potential. *Oceanography.* 2015; 2:119
73. Singh M, et al. Drug Delivery System for Controlled Cancer Therapy Using Physico-Chemically Stabilized Bioconjugated Gold Nanoparticles Synthesized from Marine Macroalgae, *Padina Gymnospora*. *J Nanomed Nanotechol.* 2014; S5:009.
74. Silva M, et al. Chemical Study and Biological Activity Evaluation of Two Azorean Macroalgae: *Ulva rigida* and *Gelidium microdon*. *Oceanography.* 2013; 1:102
75. Visconti GL, et al. Determination by UPLC/MS-MS of Coenzyme Q10 (CoQ10) in Plasma of Healthy Volunteers before and after Oral Intake of Food Supplements Containing CoQ10. *J Anal Bioanal Tech.* 2015; S13:011
76. Basystiuk YI and Kostiv IY. Getting Hydrated Magnesium Chloride from Magnesium Chloride Solutions of Potassium Sulfate Fertilizers Production. *J Chem Eng Process Technol.* 2016; 7:291.
77. Montoya-Gonzalez AH, et al. Isolation of *Trichoderma* Spp. from Desert Soil, Biocontrol Potential Evaluation and Liquid Culture Production of *Conidia* Using Agricultural Fertilizers. *J Fertil Pestic.* 2016; 7:163
78. Hamouda R, et al. Some Physical and Chemical Properties of Bio-fertilizers. *J Fertil Pestic.* 2016; 7:161.
79. Sane SA and Mehta SK. Isolation and Evaluation of Rock Phosphate Solubilizing Fungi as Potential Bio-fertilizer. *J Biofertil Biopestici.* 2015; 6:156.
80. Chandra KK. Growth, Fruit Yield and Disease Index of *Carica papaya* L. Inoculated with *Pseudomonas straita* and Inorganic Fertilizers. *J Biofertil Biopestici.* 2014; 5:146
81. Ofoegbu RU, et al. Bioremediation of Crude Oil Contaminated Soil Using Organic and Inorganic Fertilizers. *J Pet Environ Biotechnol.* 2014; 6:198
82. Mehta SK, et al. *Bacillus cereus* Mediated ϵ -Caprolactam Degradation: An Initiative for Waste Water Treatment of Nylon-6 Production Plant. *J Bioremed Biodeg.* 2014; 5:230.
83. Aajjane A, et al. Availability of Three Phosphorus Fertilizers to Corn Grown in Limed Acid-Producing Mine Tailings. *J Bioremed Biodeg.* 2014; 5:229.
84. Farfour SA and Al-Saman MA. Root-rot and Stem-canker Control in Faba Bean Plants by Using Some Biofertilizers Agents. *J Plant Pathol Microb.* 2014; 5:218.
85. Vinale F. Biopesticides and Biofertilizers Based on Fungal Secondary Metabolites. *J Biofertil Biopestici.* 2015; 5:e119.

86. Raja N. Biopesticides and Biofertilizers: Ecofriendly Sources for Sustainable Agriculture. *J Biofertil Biopestici*. 2014; 4:e112.
87. Paul N, et al. Evaluation of Biofertilizers in Cultured Rice. *J Biofertil Biopestici*. 2013; 4:133.
88. <http://www.oilgae.com/blog/2010/09/algae-as-a-source-of-pharmaceuticals-nutraceuticals.html>
89. Ali A. El Gamal. *Saudi Pharm J*. 2010; 18: 1–25.
90. Clay Dillow. USING GREEN ALGAE AS DRUG FACTORY COULD CUT PHARMA COSTS BY 1,000 TIMES. *Popular sciences*.
91. Jin-Ching Lee, et al. Marine algal natural products with anti-oxidative, anti-inflammatory, and anti-cancer properties. *Cancer Cell Int*. 2013; 13: 55.
92. Sanaa MM Shanab, et al. Aqueous extracts of microalgae exhibit antioxidant and anticancer activities. *Asian Pac J Trop Biomed*. 2012; 8: 608–615.
93. Kulikova O, et al. Effects of Antioxidants on the Viability of the Human Neuroblastoma SH-SY5Y Cell Culture under the Conditions of Heavy Metal Toxicity. *Biol Med (Aligarh)*. 2014; 8:305.
94. Zhang E, et al. Effects of Long-term Nitrogen and Organic Fertilization on Antioxidants Content of Tomato Fruits. *J Horticulture*. 2016; 3:172.
95. Cemile MS and Çigdem E. The Effects of Oxidative Stress and Some of the Popular Antioxidants on Reproductive System: A Mini Review. *J Nutr Food Sci*. 2016; 6:464.
96. Amer SAM, et al. Protective Role of Some Antioxidants on Arsenic Toxicity in Male Mice: Physiological and Histopathological Perspectives. *Biol Med (Aligarh)*. 2016; 8:266.
97. Niknam M, et al. Anti-Inflammatory Effects of Dietary Antioxidants in Patients with Coronary Artery Disease. *Endocrinol Metab Syndr*. 2015; 4:207.
98. Yadav RK and Srivastava SK. Effect of Arsenite and Arsenate on Lipid Peroxidation, Enzymatic and Non-Enzymatic Antioxidants in *Zea mays* Linn. *Biochem Physiol*. 2015; 4:186.
99. Paulis G, et al. Pentoxifylline Associated with Other Antioxidants (Multimodal Therapy) on Patients with Peyronie's Disease. Results of a Controlled Study. *Andrology*. 2014; 3:123.
100. Gebrehiwot KT, et al. Association of Total Levels of Serum Antioxidants with Periportal Fibrosis and Intensity of *Schistosoma mansoni* Infections in Cheretee, North East Ethiopia. *J Bacteriol Parasitol*. 2014; 6:220.