Current Advances in Biodiversity, Conservation, and Environmental Sciences

Algal Farming Systems

From Production to Application for a Sustainable Future




Editors
Jeyabalan Sangeetha
Devarajan Thangadurai

CRC Press
Taylor & Francis Group
APPLE ACADEMIC PRESS

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Edited by

Jeyabalan Sangeetha, PhD
Devarajan Thangadurai, PhD

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First edition published 2024

Apple Academic Press Inc.
1265 Goldenrod Circle, NE,
Palm Bay, FL 32905 USA

760 Laurentian Drive, Unit 19,
Burlington, ON L7N 0A4, CANADA

CRC Press
2385 NW Executive Center Drive,
Suite 320, Boca Raton FL 33431

4 Park Square, Milton Park,
Abingdon, Oxon, OX14 4RN UK

Library and Archives Canada Cataloguing in Publication

Title: Algal farming systems : from production to application for a sustainable future / edited by Jeyabalan Sangeetha, PhD, Devarajan Thangadurai, PhD.
Names: Sangeetha, Jeyabalan, editor. | Thangadurai, Devarajan, 1976- editor.
Series: Current advances in biodiversity, conservation, and environmental sciences (Series)
Description: First edition. | Series statement: Current advances in biodiversity, conservation, and environmental sciences | Includes bibliographical references and index.
Identifiers: Canadiana (print) 2023055492X | Canadiana (ebook) 20230554938 | ISBN 9781774916520 (hardcover) | ISBN 9781774916537 (softcover) | ISBN 9781032700359 (ebook)
Subjects: LCSH: Algae culture. | LCSH: Microalgae. | LCSH: Microalgae—Biotechnology. | LCSH: Algal biofuels. | LCSH: Algae products. | LCSH: Pharmaceutical industry.
Classification: LCC SH389 .A44 2024 | DDC 579.8—dc23

ISBN: 978-1-77491-652-0 (hbk)
ISBN: 978-1-77491-653-7 (pbk)
ISBN: 978-1-03270-035-9 (ebk)

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Current Advances in Biodiversity, Conservation and Environmental Sciences

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Nature is that entity composed of three main internally interactive components: biodiversity–human–environment. These are triangularly related aspects of life science, and the interdependency of these three reflects the crucial need of maintenance of equilibrium in their interaction. Both human and biodiversity are two interactive phases of environment that provide a necessary platform for interaction. Being part of biodiversity, human life is almost dependent on biodiversity and its products. This is the point where the human–biodiversity interaction fluctuates due to overexploitation of biodiversity, where humans take more than the basic needs of human life. Over the past few centuries, this fluctuation in interaction has caused dramatic depletion of biodiversity and thus a drastic change in environment. This has now boomeranged on human life significantly. This variation in the interaction triangle has already travelled the long path of time. Until now, conservationists and life scientists are thinking of restoring the equilibrium in the interaction triangle by taking innovative steps in conserving biodiversity and protecting the environment.

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
AFA	*Aphanizomenon flos-aquae*
AIV	avian influenza virus
ALA	α-linolenic acid
ALV-J	avian leukosis virus J
AML	acute myeloid leukemia
Ap	*Arthrospira platensis*
ARA	arachidonic acid
BFGF	basic fibroblast growth factor
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BIM	building information modeling
BOD	biological oxygen demand
CBL	*Cystoseira barbata* laminaran
CEH-MS	coupled enzymatic hydrolysis and membrane separation
CGF	chlorella growth factor
CMC	carboxymethyl cellulose/Critical micellar concentration
CNT	carbon nanotube
CO_2	carbon dioxide
COD	chemical oxygen demand
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CRGs	carrageenans
CSIR	Center of Scientific and Industrial Research
CVDs	cardiovascular diseases
DCLU	direct changes in land use
DENV	dengue virus
DHA	docosahexaenoic acid
DIT	di-iodothyronine
DM	diabetes mellitus
DMAPP	dimethyl allyl pyrophosphate
DSS	dextran sulfate sodium
DW	dry weight
EAA	essential amino acids

EAE	enzyme assisted extraction
EFA	essential fatty acids
EGFR	epidermal growth factor receptor
EPA	eicosapentaenoic acid
EPS	exopolysaccharides
ERK	extracellular signal-regulated kinase
EU	European Union
FACS	fluorescence-activated cell sorting
FAO	Food and Agriculture Organization
FAS	fatty acid synthase gene
FC	free cholesterol
FL	Fogh and Lund
FP	flat panel
FSANZ	Food Standards Australia New Zealand
FSV	feline sarcoma virus
GAG	glycosaminoglycan
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GGPP	geranylgeranyl pyrophosphate
GIP	glucose-independent-insulinotropic polypeptide
GIS	geographic information system
GLP-1	glucagon-like-peptide-1
GLUT	glucose transporter
GMP	good manufacturing practices
GR	glutathione oxidoreductase
GSH	glutathione
HACCP	hazard analysis and critical control points
HBV	hepatitis B virus
HCMV	human cytomegalovirus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HME	high moisture extrusion
HPV	human papillomavirus
HSV	herpes simplex virus
ICAM	intercellular adhesion molecule
IHD	ischemic heart disease
IPP	isopentenyl pyrophosphate
JEV	Japanese encephalitis virus
LA	linoleic acid
LDLC	low-density lipopolysaccharide cholesterol

LEDs	light-emitting diodes
LK	leukotrienes
LMW	low molecular weight
LNCaP	lymph node carcinoma of the prostate cell line
LPS	lipopolysaccharide
MAAs	mycosporine-like amino acids
MAE	microwave-assisted extraction
MAPK	mitogen-activated protein kinase
MEF	mouse embryonic fibroblasts
MFE	membrane filtration extraction
MIPP	microalgae industrial production plant
MMP-1	matrix metalloproteases-1
MPPP	microalgae pilot production plant
MUFAs	monounsaturated fatty acids
NAXA	Natural Algae Astaxanthin Association
NDV	newcastle disease virus
NEAA	non-essential amino acids
NK	natural killer
NO	nitric oxide
NP	nanoparticles
NPK	nitrogen, phosphorus, and potassium
NRPS	non-ribosomal peptide synthase
NSAIDs	nonsteroidal anti-inflammatory drugs
NTA	nitrilotriacetic acid
O/W	oil in water
ORAC	oxygen radical absorbance capacity
OSE	organic solvent derived extraction
PARP	poly (ADP-ribose) polymerase
PBRs	photobioreactors
PC	polycarbonate
PCL	poly ε-caprolactone
PEF	pulsed electric field
PEG	polyethylene glycol
PG	prostaglandins
PGE2	prostaglandin E2
PLE	pressurized assisted extraction
PMBC	peripheral blood mononuclear cells
PSS	propylene glycol alginate sodium sulfate
PTLC	preparative thin layer chromatography

PUAs	polyunsaturated aldehydes
PUFA	polyunsaturated fatty acids
R&D	research and development
RAAS	renin-angiotensin-aldosterone-system
RDI	reference daily intake
ROS	reactive oxygen species
RP-HPLC	reversed-phase high performance liquid chromatography
RSV	respiratory syncytial virus
SA	spirulina algae
SCFAs	short-chain fatty acids
SFAs	saturated fatty acids
SFE	supercritical fluid extraction
SHRs	spontaneously hypersensitive rats
SOD	superoxide dismutase
SPs	sulfated polysaccharides
STDs	sexually transmitted diseases
SWE	subcritical water extraction
T3	triiodothyronine
T4	thyroxin
TBHQ	tert-butyl hydroquinone
TC	total cholesterol
TCGA	the cancer genome atlas
TE	trolox equivalent
TGs	triglycerides
TNF-α	tumor necrosis factor-alpha
TNF-β	tumor necrosis factor-beta
TSC	total serum cholesterol
TTB	tuberatolide B
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
TX	thromboxanes
UAE	ultrasound-assisted extraction
UNU	United Nations University
UV	ultraviolet
VEGF	vascular endothelial growth factor
VLDL	very-low-density lipoprotein
WHO	World Health Organization
WNV	West Nile virus
YFV	yellow fever virus

PREFACE

The potential renewable and sustainable energy resources are generally considered by three major features: cost, safety, and environmental impact. A country's economic growth and development depend increasingly on the sustainable utilization of reliable energy resources. Even though the potential of algal biomass has been recognized, still significant in-depth understanding is still needed in the field of algal production for various applications.

Mass production of microalgal biomass was primarily aimed at the extraction of nutritious food supplements and nutraceuticals. Marine algae have the potential ability to concurrently fuel vehicles and recycle carbon dioxide. Microalgal farming on a large scale is very limited in most developing countries due to several technological barriers and regulatory measures. A comprehensive mapping, characterization, up-scaling of the production volumes, and marketing strategies are the major aspects to boost and support the growth of algal farming. In the near future, World's blue bioeconomy will depend on the algal industry.

The farming of algal biomass on a large scale for various purposes is converting the production to a commercial scale. During this crucial stage, institutional framework supports and commercialization could kindle the development of the algal industry as a promising source of renewable fuels, high-value protein, and low-cost drugs. The assistance programs supported by local governments and international bodies need to focus more on algae production and commercialization. Such initiatives and support are imperative for emerging algal-based industries to encourage investments, build basic and advanced infrastructure, share technical experience, and create markets.

Algal Farming Systems: From Production to Application for a Sustainable Future consolidates the latest research in the field together with market potential and policy considerations. This book is dedicated to enthusiastic researchers, academicians, entrepreneurs, policymakers, and anyone interested in the status and future possibilities of algae commercialization. The book consists of four parts. Part I includes a chapter on phycotechnology and highlights the current trend and future scope of algal technology. Part II consists of three chapters and provides comprehensive information on algal culture conditions and cultivation strategies. Algal production, marketing strategies, and their commercialization are discussed in Part III. In Part IV, five chapters are extensively devoted to industrial applications of algae and focus mainly on nutraceutical, pharmaceutical, and cosmeceutical applications of microalgae and macroalgae. This section also highlights the green synthesis of nanoparticles from algae for various commercial applications.

The contributing authors have comprehensively illustrated the concepts. All the chapters in the present book were prepared and authenticated by eminent researchers and entrepreneurs of algal farming. We greatly appreciate all the people who have shared their valuable suggestions and guidance to complete this book.

—Editors

PART I
PHYCOTECHNOLOGY

CHAPTER 1

ALGAL TECHNOLOGY: CURRENT TREND AND FUTURE SCOPE

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ABSTRACT

Nature's produce has been the lone most productive source in the development of new pharmaceuticals and nutraceuticals. Interest for natural products has revived with great consideration in the last few decades. Their efficacy with the least toxicity to humans has increased their affinity in the research community. One such variant is algae which are known to produce a wide range of secondary metabolites of human interest. A few examples of secondary metabolites produced by algae include peptides, phenolic compounds, carotenoids, polysaccharides, unsaturated fatty acids, phycobiliprotein pigments etc. These compounds are demonstrated to possess biological activities like anticancer, antioxidant, antimicrobial against bacteria and virus. Moreover, many algal species are equipped with the potential to produce an enormous amount of target molecule viz. proteins, lipids, carbohydrates, pigments of commercial scale. Therefore, hyphenated extraction processes such as solvent derived extraction, enzyme-assisted extraction for secondary metabolites is under great consideration. Given the side effects and growing resistance towards the existing drugs, the potential of different algal species in nutraceuticals and pharmaceuticals are the need of the hour.

Algal Farming Systems: From Production to Application for a Sustainable Future.
Jeyabalan Sangeetha, Devarajan Thangadurai (Eds.)

1.1 INTRODUCTION

Nature's produce has been the lone most productive source in the development of new pharmaceuticals and nutraceuticals. It harbors the majority of the active ingredients used in these industries. This is the sole approach for drug discovery in bygones age before the advent of the proficient screening processes. Interestingly, natural products or their derivatives constitute more than 80% of drug compounds (Sneader, 1997). Arguably, this is still the fact that almost 50% of the drugs approved since 1994 are nature based (Newman and Cragg, 2007). Butler (2008) has reported 13 natural product based drugs that were approved between 2005 and 2007. Out of them, 5 constituted the first candidate for the new classes of drugs. Interest for natural products has revived with great consideration in the last few decades. Their efficacy with the least toxicity to humans has increased their affinity in the research community. One such variant is algae, the photosynthetic organisms adapted to survive in extreme and complex environments. Algae coincide with plants in the production of a wide range of secondary metabolites (Cardozo et al., 2007). The substances do not participate directly in the growth and development processes of the host organism. Interestingly, they possess a great array of activities because of that it proved to be a boon to mankind. The production of these metabolites is limited either towards the end of the growth phase or under stressed environmental conditions which leads to metabolic alteration. A few examples of secondary metabolites produced by algae include peptides, phenolic compounds, carotenoids, polysaccharides, unsaturated fatty acids, phycobiliprotein pigments etc., (Shalaby, 2011). Vis-à-vis, all these compounds are demonstrated to own biological activities like anticancer, antioxidant, antimicrobial against bacteria, virus (El-Baroty et al., 2007). Moreover, many algal species are equipped with the potential to produce an enormous amount of target molecule viz. proteins, lipids, carbohydrates, pigments of commercial scale (Priyadarshani and Rath, 2012). The key focus of this chapter is to apprehend the algal farming and extraction processes such as solvent derived extraction, enzyme-assisted extraction with special emphasis on secondary metabolites holding bioactivities. Given the side effects and growing resistance towards the existing drugs, the potential of different algal species in nutraceuticals and pharmaceuticals that includes antioxidant, anticancerous, antihypertensive are among the major highlights.

1.1.1 BASICS

Algae are plants like organisms inhabiting rivers, seas, ponds, and lakes. They can be broadly categorized into two types based on their size – macroalgae and microalgae. Macroalgae, very commonly known as seaweed, is a multicellular, marine organism that can be seen with naked eyes. They include brown, red, and green algae. Microalgae, the microscopic counterpart of macroalgae, are largely comprised of diatoms, dinoflagellates, and blue green algae or cyanobacteria. Additionally, based on their pigments, algae are classified into seven groups inhabiting either freshwater or marine ecosystems. They are euglenoids, golden-brown algae, fire algae, green algae, red algae, brown algae, and yellow-green algae. Being the primary producer of the ecosystems, organisms at different strata are highly dependent on algae (Hanson et al., 2010). This indicates that the energy requirements of the organisms of the food web are fulfilled by algae. Fascinatingly, the marine habitat which rarely disturbed and majorly remains unexplored is believed to be a reservoir of bioactive compounds. Hence, it is reasonable to contemplate that algae bear a wide range of secondary metabolites of great importance.

1.1.2 BACKGROUND

Post 1970, three areas of aquatic natural products have emerged namely chemical and physical ecology, toxins, and bio-products. So far more than 2100 compounds are identified. Considering the by-products it produces, pharmaceutical research has given major emphasis to the algal research. To survive the extreme environment, both marine and freshwater algae produce a plethora of compounds of structural and chemical diversity to strengthen their defense mechanism. The exploration of these compounds has revealed numerous prototypes for the discovery of novel components that jolted industries to use the best extraction techniques. Hence, there is a need to accelerate the process of extraction and identification of pure components of economical grade. Hence, both primary and secondary metabolisms are studied as a prelude for future pharmaceutical and economic advancement. The primary metabolism provides major intermediates for the synthesis of vital molecules whereas secondary metabolism is found to be more restricted. Body of literature provides countless works on algae but only a few studies describe about biosynthetic pathways. Majorly reports found to focus on the secondary metabolites containing structurally and chemically diverse groups. The diversity is the result of the modification and combination of secondary metabolites with different molecules of primary metabolism down the line. Majorly, the sectors influenced by algae are pharmaceuticals (Agyei and Danquah, 2011) and nutraceuticals (Chacón-Lee and González-Mariño, 2010). As a reservoir of biomolecules like lipids, bioactive peptides, algae has gained significant interest among the scientific community (Cavalier-Smith, 1999). Many of the isolated peptides are found to mimic hormones (Samarakoon and Jeon, 2012). This is an indication that the peptides could play an important role in the physiological system. For instance, their use to target specific cells or receptors gives a proclaim image of the mechanism (Fitzgerald and Murray, 2006; Kitts and Weiler, 2016). Moreover, many species have reached beyond nutritional properties and depicted activities similar to bio-proteins viz. antioxidants (Karawita et al., 2007), anticancer (Sheih et al., 2010), immune-modulatory (Morris et al., 2007). These factors collectively lead to a spike in the number of algal studies to uncover "yet to be known" novel molecules.

1.2 ALGAL FARMING

Several thousand tons of algae are farmed every year for nutraceuticals and pharmaceutical industries. The great demand owes to the wide range of bioactivities it performs/bioactive molecules it possesses. China is the largest producer of algae and supports approximately half of the production. The other half is farmed in India, Japan, United States, Taiwan, and Australia. A small stake of algal farming is devoted to foods of zooplanktons and rotifers. A few commonly farmed species are *Chlorella*, *Haematococcus*, *Spirulina*, *Dunaliella*. Often algae are used in the food industries due to the wide range of metabolites present in it. Later, the interest has been shifted to farming than wild harvest so that the desired molecules can be produced in a large scale. However, the algal toxins accumulated in the ecosystem poses an alarming threat for the other animals sharing the ecosystems (Baden, 1993). Hence, an efficient extraction procedure followed by separation of toxin residue is of prime importance (Keijola et al., 1988). This certainly allows us to framework the scenario for isolation of bioactive components that could be probably entering the drug industry. Hence, the analysis of the isolated bio-elements from the algae and their possible components would lead us to establish and platform for future therapeutic drugs (Spolaore et al., 2006).

Therefore it would benefit humanity by providing various pharmaceuticals and nutraceuticals.

1.2.1 BASIS OF ALGAL FARMING

Algal farming is undoubtedly the solution for large scale production of desired biomolecules. The process requires standard protocols and requirements beforehand. Suitable land topography, temperature range, and water bodies are a few examples that facilitate the accuracy of production. Some algae grow in brackish water, thus eliminates the requirement of freshwater. Many universities namely the University of California, University of Texas have the pilot plant (Murphy and Allen, 2011). It takes years for the establishment of a large scale algal production. With the advancement of technology and control over the process and harvesting, farmers reap benefits like cost effectiveness, improved production (Resurreccion et al., 2012). Further benefits could be obtained by using wastewater, residual nutrients, excess heat that resulted in effective farming (Yun et al., 1997; Zhou et al., 2012). Algal farming is commonly done in greenhouses, photobioreactors, ponds, and a hybrid system that combine the pond with photobioreactor. For example, *Dunaliella* requires deep saline ponds. On the other hand, *Spirulina* needs shallow water along with compressed air that allows the culture to move and remains on the surface to ensure proper sunlight absorbance. Then harvesting is done by filtering, centrifugation, or flocculation.

1.2.2 BASIC REQUIREMENTS

Algal farming is dependent on some basic prerequisites (Hochman and Zilberman, 2014). One major need is the high temperature that sustains the algal growth. Proper sunlight should reach the cells in order to carry out photosynthesis. Water requirement is large when farming involves a pond. Moreover, flat surface and clay soil is an important ingredient for setting up ponds. Yet another important constituent is the continuous supply of carbon dioxide required to continue the photosynthesis process. The culturing process is reliably begun in photobioreactors with a 1–2% amount of expected algae biomass. This is because adding a small algal culture in the large pond won't produce the desired result. These cultures were then transferred to the pond for large scale production.

1.2.3 APPROACH FOR ALGAE FARMING

Today algae farming is done in open raceways as they are cost effective to build and operate (James and Boriah, 2010). Areas with high temperatures, low rainfall rely on ponds that heighten productivity. However, outdoor ponds often lead to lower productivity due to temperature variation and contamination. One added difficulty is predators like rotifers, amoeba, fungi, zooplankton, etc. that devour on algae biomass leaving it for no use (Wang et al., 2013). To address these issues, research is going on to introduce an effective automated system. One of the modern concepts includes community gardens that are the new farming ground for algae (Gardiner et al., 2014). Even, shipping containers are revamped with controlled conditions for algae farming. They are cost effective with easy insulation and can be placed anywhere. Algae can also be harvested in pods, popularly known as podponics, often comes with led light and well controlled conditions that use less than 90% water than the greenhouses, zero pesticides, and fast harvesting rate (Juracsek, 2013). Broadly farming process involves photobioreactors and ponds (Figure 1.1). Photobioreactors are preferred for small scale farming and ponds are chosen for large scale biomass production. Photobioreactors are closed, self-contained system that flow water through tubes or plastic bags continuously to bath algae. They are exposed to light through the LED bulbs.

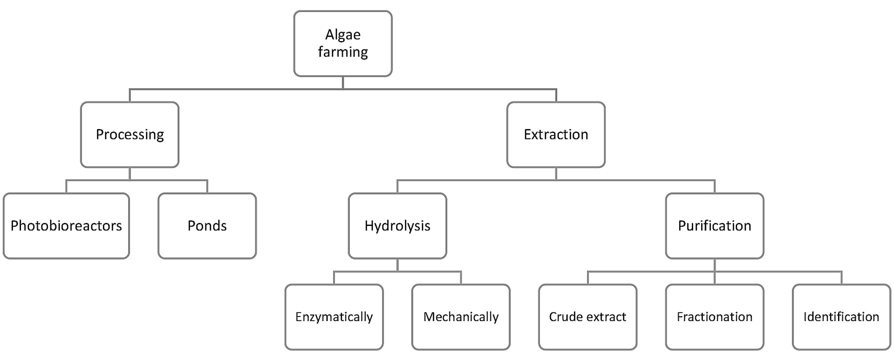

FIGURE 1.1 Generalized procedure of algae farming to identify novel compounds.

1.2.4 CHALLENGES FACED IN FARMING

Harvesting algae is not as easy as it seems. Several technological challenges need to be addressed. According to the estimation, everyday 20–40% of the biomass has to be harvested (Hannon et al., 2010; Vassilev and Vassileva, 2016). Moreover, the cultures have to be sufficiently concentrated. Chemical additives required for augmenting cell flocculation (Smith and Davis, 2012). However, its minimal and careful application is suggested to ensure no contaminants in the fuel produced. The biggest challenge is to finalize a cost effective, effective harvesting system. However, to retrieve the final products, biomass has to pass through the appropriate extraction procedures. The final oil obtained has to be further processed before use it.

One major technical issue into which scientists ponder is that gene mutation. The brief scenario is that the algal culture basically starts with one or a few cells which multiply and reaches billions in number at the end of the process. The main concept is about gene mutation which prevailed in due course of the multiplication process. It is obvious and questions the effectiveness and safeguard of nutrients and oil content. Moreover, proper screening is highly recommended before the introduction of algal cells in the pond as a single invasive species can substantially affect its productivity.

1.2.5 EXTRACTION

Standardizing new analytical methods are of concern in order to identify more and more ingredients from algae with pharmaceutical and nutraceuticals importance. Arizona Center for Algae Technology and Innovation, USA, actively grappled in the research of bioactivities of algae. Indeed, extraction and isolation are of prime importance when we deal with the biomolecules to ensure the safety and effectiveness of the end-products. Biological activities are highly dependent on confirmation which in turn relies on the surrounding environment (Cheng and Rossky, 1998). Hence, hyphenated techniques like supercritical CO_2, ultrasonic based extraction are preferred to ensure the usability of the final product. More emphasis is given for the extraction of algae biomolecules intended to be used as drugs or pharmaceuticals. Hence, the best possible extraction process is finalized based on important criteria. For example, the process should be efficient to draw all the important secondary metabolites, at the same time ensures no existence of toxic residues. Based on the potentiality, two extraction processes are dominating – organic solvent derived extraction (OSE) and enzyme-assisted extraction (EAE). EAE has superseded the other counterpart due to its higher yield potential and purity (Hahn et al., 2012) (Hardouin et al., 2016). Moreover, the major limitation associated with the OSE is the traces of toxic residue recovered with the target molecules.

Briefly, the processing of macroalgae involves 3 steps, i.e. preparation, hydrolysis, and purification (Hammed et al., 2013). As a part of the preparation step, algae are stored in the opaque vials to avoid degradation of UV-light sensitive molecules immediately after harvesting. While handling, algae are thoroughly washed to remove all the debris and associated shrubs. Then the samples are dried, and ground into a powder and processed for hydrolysis. However, the preparation is different in the case of microalgae. They are initially cultured in the lab that mimics its natural habitat followed by harvesting and isolating the target species. Then they are mass cultured in polycarbonate bottles for 14 days. The biomass is then isolated through centrifugation or filtration process. Like microalgae, they are powdered and processed for hydrolysis. The essential components present inside the algal cell are accessed through the enzymatic break down of the cell wall (Gerken et al., 2013). Mechanical techniques like ultrasound sonication and pulverization of lyophilic components are also in use. Commonly hydrolysis is done by three methods for recovering the biomolecules from the inner cell wall. They are as follows:

- Digestive enzymes from animals
- Proteolytic enzymes from microorganisms and plants
- Proteolytic microorganisms during fermentation

The physico-chemical character of protein should be scrutinized thoroughly while carrying out hydrolysis. Temperature and pH are the major factors which if not maintained under the suitable range would cause the degradation of proteins. The next step is the purification of the crude extract obtained from cells to identify the molecule. Currently, fractionation uses ultra-filtration and sodium-dodecyl gel electrophoresis. These enable the accurate separation of protein hydrolysates based on their molecular mass. Further purification is done using chromatographic techniques like ion-exchange, gel filtration, reverse-phase, etc. (Figure 1.2). Additionally, techniques like LC-MS and MS-MS are frequently being in use for characterizing the structure of the hydrolysates.

1.3 USE OF ALGAE IN PHARMACEUTICALS

The use of algae in treating medical conditions or as a preventive measure can be traced back to the ancient era. Their popularity in Asian countries was correlated to the activities pertaining to seas that have led to the discovery of beneficial characteristics of the algal community. They have well emerged

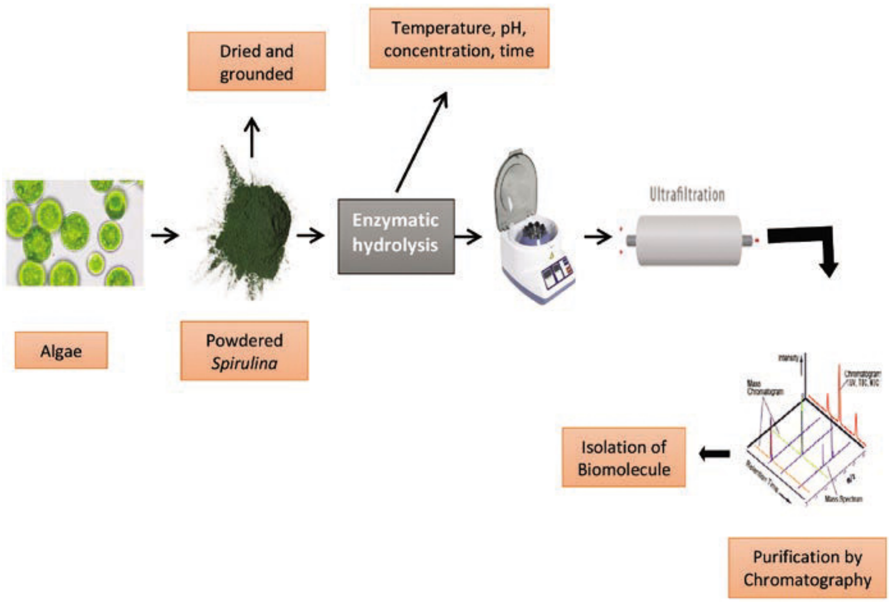

FIGURE 1.2 Isolation of bioactive molecules from algae using enzyme assisted extraction methodology.

Source: Modified from Selvamuthukumaran & Shi (2017).

as a phycocolloids, polysaccharides derived from seaweeds, which later paved the way for finding its associated bioactivities. However, their involvement in the drug industry is reported. Carrageenan, one of the major phycocolloid, is chiefly involved in cough syrup emulsions, and the makings of dental molds. Another phycocolloid, agar is used as an anticoagulant, binding agent for the tablets. Seldom, the algal based polysaccharides are used in non-habit forming laxatives too. Later, the algal industry has seen a significant expansion due to bioactivities like antiviral, anti-helminthic, antibiotics, anticancerous, anti-hypertensive, etc. For example, microalgae such as *Spirulina*, *Dunaliella*, and *Chlorella* are substantiated to possess bioactivities like antitumor, antimicrobial, anti-inflammatory, antiviral, anti-allergy, antioxidant, etc. (El-Baky and El-Baroty, 2013). Noaman et al. (2004) have further added to the efficiency of production by quoting the important factors like temperature of incubation, pH of the culture medium, incubation period, medium constituents, and light intensity that would form the base in the drug industries. The detailed insight into the major pharmacological values of algae is discussed in Table 1.1.

TABLE 1.1 Pharmacological Properties of the Biomolecules Isolated from Few Major Algae Species

Name of Algae	Classification	Bioactivity	Active Compound	References
Ecklonia cava	Brown macroalga	Antioxidant, anticancer, antihypertensive, anti-inflammatory, immunostimulant	Phenolic compounds, sulfated polysaccharides, galactofucan, fucoidan, phlorotannins, peptides	Heo et al. (2003); Ahn et al. (2008); Kim & Bae (2010); Kim & Himaya (2011); Ahn et al. (2015)
Scytosiphon lomentaria	Brown macroalga	Antioxidant	Phenolic compounds	Heo et al. (2003)
Ishige okamurae	Brown macroalga	Antioxidant, anti-inflammatory	Peptides, polyphenols, galactofucan, fucoidan	Heo & Jeon (2008); Kim et al. (2009)
Scytosiphon lomentaria	Brown macroalga	Antioxidant	Polysaccharides	Ahn et al. (2004)
Palmaria palmata	Red macroalga	Antioxidant	Phenolic content	Wang et al. (2010)
Spirulina platensis	Blue-green microalga	Antioxidant, anticancer, antihypertensive, increasing intestinal lactobacilli, reduces nephrotoxicity, lowers cholesterol	C-phycocyanin, peptides	Belay et al. (1993); Bhat & Madyastha (2000); Suetsuna & Chen (2001); Wergedahl et al. (2004); Wang et al. (2007)
Ulva fasciata	Green macroalga	Antioxidant	Sesquiterpene	Chakraborty & Paulraj (2010)
Laminaria japonica	Brown macroalga	Antioxidant	Fucoidan	Wang et al. (2008)
Cystoseira barbata	Brown macroalga	Antioxidant	Alginates	Sellimi et al. (2015)
Polysiphonia urceolata	Red macroalga	Antioxidant	Phenolic content	Duan et al. (2006)
Dunaliella salina	Green microalga	Antioxidant	β-carotene	Zhu & Jiang (2008)
Chlorella vulgaris	Green microalga	Anticancer, antihypertensive, immunomodulating	Peptides, glycoprotein peptide	Suetsuna & Chen (2001); Morris et al. (2007); Sheih et al. (2009); Chen et al. (2011)
Sargassum pallidum	Brown macroalga	Anticancer	Sulfated polysaccharides	Ye et al. (2008)

TABLE 1.1 *(Continued)*

Name of Algae	Classification	Bioactivity	Active Compound	References
Porphyra vietnamensis	Red macroalga	Anticancer	Porphyran	Venkatpurwar et al. (2011)
Saccharina japonica and *Undaria pinnatifida*	Brown macroalga	Anticancer	Fucoidan	Vishchuk et al. (2011)
Gelidium cartilegineum	Red macroalga	Antiviral	Polysaccharides	Gerber et al. (1958)
Cladosiphon okamuranus	Brown macroalga	Antiviral	Fucoidan	Hidari et al. (2008)
Gracilariopsis lemaneiformis	Red macroalga	Antihypertensive	Peptide	Cao et al. (2017)
Porphyra yezoensis	Red macroalga	Antihypertensive, anticoagulant, immunomodulating, anti-hyperlipidemic	Peptide, polysaccharide, sulfated polysaccharide	Yoshizawa et al. (1995); Tsuge et al. (2004); Qu et al. (2010)
Codium fragile	Green macroalga	Anticoagulant	Sulfated proteoglycans, polysaccharides, proteoglycans	Jurd et al. (1995); Athukorala et al. (2007)
Sargassum horneri	Brown macroalga	Anti-coagulant	polysaccharides, proteoglycans	Athukorala et al. (2007)
Codium pugniforme	Green macroalga	Anti-coagulant	Sulfated polysaccharides, proteoglycan	Matsubara et al. (2000)
Codium intricatum	Green macroalga	Anti-coagulant	Fibrinolytic enzymes	Matsubara et al. (1998)
Gracilaria sp.	Red macroalga	Anti-inflammatory	Peptides	Almeida et al. (2011); Chen et al. (2013)
Porphyridium sp.	Red microalga	Anti-inflammatory	Polysaccharides	Talyshinsky et al. (2002)

TABLE 1.1 *(Continued)*

Name of Algae	Classification	Bioactivity	Active Compound	References
Polyopes affinis	Red macroalga	Anti-inflammatory	Phenolic compounds	Lee et al. (2011)
Ulva sp.	Green macroalga	Anti-inflammatory	Sulfated polysaccharides	Jin et al. (2006); Margret et al. (2009)
Caulerpa mexicana	Green macroalga	Antinociceptive, Anti-inflammatory	Lectin, sulfated polysaccharides	Silva et al. (2011); Coura et al. (2012)
Ulva rigida	Green macroalga	Immunomodulating	Carrageenan, sulfated polysaccharides	Ogata et al. (1999); Leiro et al. (2007)
Digenea simplex	Red macroalga	Antihelminthic	Kainic acid	Moo-Puc et al. (2008)
Chondria armata	Red macroalga	Antihelminthic	Domonic acid	Higa & Kuniyoshi (2000)
Sargassum natans	Brown macroalga	Antihelminthic	Sulfated polysaccharides	Orhan et al. (2006)
Laurencia dendroidea	Red macroalga	Antihelminthic	Sesquiterpene	Veiga-Santos et al. (2010)
Undaria pinnatifida	Green macroalga	Differentiation of osteoblast cells, protection of gastric mucosa against regular acids, inhibit UV-B induced MMP-1	Fucoidan	Moon et al. (2008); Cho et al. (2009); Choi et al. (2010)
Ulva pertusa	Green macroalga	Anti-hyperlipidemic, sequestration of bile acids	Sulfated polysaccharide	Lahaye (1991); Pengzhan et al. (2003)
Fucus sp.	Brown algae	Anticancer	Fucoxanthin	Kotake-Nara et al. (2001)
Haematococcus pluvialis	Red microalga	Antioxidants	Astaxanthin	Capelli et al. (2013)

1.3.1 ANTIOXIDANT PROPERTIES

Antioxidants play a major role in the human system by keeping a check on the antioxidative reactions thus reducing the reactive oxygen species (ROS). The in-build antioxidants like catalase, glutathione peroxidase, superoxide dismutase, selenium, vitamin C often responsible for maintaining homeostasis (Ahn et al., 2004). However, conditions like environmental pollution, alcohol, high-fat diet, chemical smoke, ultraviolet radiation cause imbalances which often lead to an increase in ROS accumulation in the body tissues. ROS is a major underlying culprit behind several diseases like cancer, hypertension, diabetes mellitus, cardiovascular ailments, inflammatory conditions, neurodegenerative diseases, and aging (Valko et al., 2007). This could be reasoned since ROS attacks the major macromolecules, viz. carbohydrate, protein, lipids of our body. Many commercial antioxidants used in pharmaceutical industries namely butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and propyl gallate (PG) function to retard the rate of oxidation and peroxidation reactions. However, strict regulations are implemented on their use due to possible health hazards. Hence, an alternative that could address these issues needs to be introduced. In this regard, the research community has been galvanized towards natural resources. The marine algae provide the best solution which largely remains untouched. This is an environment of extreme environmental condition which increases ROS production in algae (Ngo et al., 2011). However, it is found that they efficiently quench the ROS and protect themselves from the oxidative damage (Guedes et al., 2011). The mechanism and the metabolites involved in the process presents an astonishing ray to combat the life threatening ailments. Secondary metabolites including peptide, polysaccharides, polyphenol compounds, carotenoids, etc. are responsible for these activities. Among all, the antioxidant property of algae is well studied (Heo et al., 2005, 2006; Kim et al., 2006; Karawita et al., 2007). It is established that covalent bonds in certain proteins are associated with antioxidant properties (Sheih et al., 2009). The antioxidant property of algae is substantiated by a large number of works found in the literature. A survey conducted about a decade earlier, has documented the prominent antioxidant properties of both micro and macroalgae employing DPPH, hydrogen peroxide, superoxide anion scavenging methods (Ngo et al., 2011). Another report evaluated the antioxidant activities of seven species, viz. *Ecklonia cava*, *Ishige okamurae*, *Sargassum fulvellum*, *Sargassum horneri*, *Sargassum coreanum*, *Sargassum thunbergii*, and *Scytosiphon lomentaria* of brown seaweed. The enzymatic extracts of the algae were reported to significantly reduce the DNA damage compared to the commercial antioxidants

(Heo et al., 2003). Among these, enzymatic extracts of *E. cava* have been reported to show the best antioxidant property with thermal stability. It is found that majorly hydrogen peroxide activity is affected by the enzymatic extracts of algal species (Heo and Jeon, 2008). The efficacy of protease extract over carbohydrase extract in displaying hydrogen peroxide scavenging activity is one of a kind result. In his work, Ahn et al. (2004) have established another brown alga *Scytosiphon lomentaria* with potent ROS scavenging activity. Similar work with *Palmaria palmata*, red algae, has reported antioxidant activity of proteases over carbohydrase against peroxyl radicals (Wang et al., 2010). An isolate of *Spirulina platensis*, C-Phycocyanin has effectually inhibited lipid peroxidation induced by CCl_4 in vivo condition with rat liver cells (Bhat and Madyastha, 2000). *Ulva fasciata*, a green alga, were also found to possess free radical scavenging activities due to sesquiterpenes (Chakraborty and Paulraj, 2010). Even blue-green algae *Spirulina platensis* has gained considerable attention for possessing a number of health benefits including antioxidant properties (Piero Estrada et al., 2001). While surveying through the literature it is majorly seen that algal peptides are ahead in the race. However, a review was looked to emphasize on the sulfated polysaccharides (SP) extracted from the marine algae (Wijesekara et al., 2011). Beyond their well-known functions, SPs of marine origin are also found to possess antioxidant properties that increase the thrust to unveil more aspects of it. SPs like fucoidan, alginates proves it all (Wang et al., 2008; Sellimi et al., 2015). Most of the polyphenols are extracted from micro and macroalgae and show the antioxidant property. Approximately 8000 different polyphenols belonging to 10 groups are identified to date. They are known to exist in variable conformations ranging from simple structures (e.g. phenolic acids) to complex groups (e.g. phlorotannins). Studies reported that antioxidant activities largely dependent on the polymerization of polyphenols. The less the complexity of polymerization the greater antioxidant potential is exhibited. The species *Polysiphonia urceolata*, a red alga, portrays the positive correlation between antioxidant capacity and the phenolic content it possesses (Duan et al., 2006). Other candidate carotenoids, the naturally occurring pigment, are known to possess antioxidant properties and regarded as an active component against cancer, cardiovascular ailments, and muscular degeneration too (Cooper et al., 2009). Vis-à-vis, many algal species are known reservoirs of carotenoids. For instance, the microalga *Dunaliella salina* can accumulate large amounts of β-carotene when cultivated under specific conditions (Zhu and Jiang, 2008). The statement is further substantiated by the work of Higuera-Ciapara et al. (2006) who have proved the antioxidant property of astaxanthin, a well-known carotenoid.

1.3.2 ANTICANCER/ANTI-TUMOR ACTIVITY

Cancer is one of the leading causes of death in both developed and developing nations (Ezzati et al., 2002). It is found that genetic cancers constitute about 10–15% of all the cases whereas the remaining 85–90% is grappled by the epigenetic factors. This includes alcohol, smoke, environmental pollution, fat-rich diet, sedentary lifestyles (Anand et al., 2008). The characteristic, uncontrolled cell division is often induced by the oxidative free radicals. Hence, knowledge and awareness about cancer-causing factors and their early diagnosis help to reduce the risks. However, the majority of the cases are detected at the progressive stage where the use of chemotherapy is the most promising approach available now in order to treat the disease (Sheih et al., 2010). However, reports on resistance development pose a great challenge to pharmaceutical industries. Hence, much attention is given to identify bioactive molecules from the natural sources that have intended to reduce morbidity and mortality. Marine based seaweeds and microalgae have been a reservoir of potent components to be added in the cancer treatment. For example, sulfated polysaccharides have actively reduced carcinogenesis in humans (Rocha De Souza et al., 2007). During multistage cancer, normal cells proceeds through three phases, i.e. initiation, promotion, and progression. The problem can be checked by the naturally occurring components which manipulate the cancer cells with no side effects. Hence, exploring and identifying novel natural bioactive components holds a ray of hope for future cancer treatment. Proteases derived from marine algae show significant health benefits. One such work conducted by Chen et al. (2011) has shown that proteases isolated from *Chlorella vulgaris* effectively inhibited the UV-b induced MMP-1 in skin fibroblast cells. The MMP 1 degrades collagen and resulted in photoaging (Ågren et al., 2015). *C. vulgaris* derived peptides have effectively downregulated the MMP1 and other players in the trophic pathway, viz. CYR61 and MCP-1 (Chen et al., 2011). Moreover, a glycoprotein (ARS-2) eluted with hot water from *C. vulgaris* was expressed by the toll like receptors 2 against the anti-tumor activity (Hasegawa et al., 2002). The scientists have explained that interleukin production in ARS-2 treated rat spleen cells was TLR 2 dependant and not TLR 4. Wang et al. (2007) have reported the anti-tumor activities of C-Phycocyanin (C-PC) isolated from *Spirulina platensis*. The scientists have expressed β-subunit of C-PC that have effectively inhibited the proliferation of four different cell lines and induced their apoptosis. The mechanism of action is linked with the interaction between C-PC/β with β-tubulin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Moreover, they resulted in the depolymerization of microtubules and actin-filaments. It is noted that the C-PC/β treatment has resulted in the cell cycle arrest at G_0/G_1 phase, upregulation of caspases mainly C-3 and C-8. The decrease in the level of GAPDH indicates cell cycle arrest thus suggesting C-PC/β as a promising anti-cancer candidate. Several reports claim the anti-proliferative actions of sulfated polysaccharides in vitro (Ye et al., 2008). They also possess anti-metastatic activity by blocking the interaction between cancer cells and their basement membrane (Parish et al., 1987). A report by Yamamoto et al. (1986) has documented the effectiveness of seaweeds in reducing the incidence of carcinogenesis when administered orally. In an in vitro study, Porphyran induced the death of cancer cells through apoptosis without affecting the growth of normal cells (Venkatpurwar et al., 2011). Another SP isolated from *Ecklonia cava* induced cell death in vitro and showed a potential antiproliferative effect in a human lymphoma cell line (Ahn et al., 2015). Fucoidan also shows anti cancerous activity which is closely related to the sulfated content of the same (Vishchuk et al., 2011). Often anti-cancerous property of algal components is seen to be associated with their antioxidant property. This is justified by the work of Lee et al. (2012) who have reported the positive correlation between ROS generation and cancer induction on metal exposure. Moreover, continuous production of ROS causes severe damage to the genomic DNA and often leads to carcinogenic conditions (Aykin-Burns et al., 2009). One major issue faced by drug industries is that many of the drugs associated with the ROS generation can be proclaimed through miRNAs expression (Fayyaz and Farooqi, 2013). Correlated to this, the upregulation of miRNA-34a was reported in the cells treated with ferric nitrilotriacetate. The involvement of ROS and miRNA became prominent in cancer when the downregulation of miRNA-34a by siRNA was reported in HeLa and MCF7 cells. Additionally, it is seen that representative of red, green, brown and blue-green algae shows anticancerous property (Khan et al., 2005; Kwon and Nam, 2007; Zandi et al., 2010; Ermakova et al., 2011). Hence, components of natural origin would help the drug industries to design prototypes for cancer treatment.

1.3.3 ANTIVIRAL PROPERTIES

Viral infections are age-old reality and have caused havoc to mankind with regard to their life. Influenza A and B are responsible for flue like conditions in human and have affected many lives. A report by Gerber et al. (1958) has demonstrated the antiviral potential of polysaccharides extracted from *Gelidium cartilagineum* that tested against virus infested embryonic eggs.

Polysaccharides with antiviral properties are found to be highly sulfated (Wijesekara et al., 2011). Moreover, molecular mass, sugar groups, are the vital factors that highly influence the antiviral properties. Simultaneously, the degree of sulphation and distribution of sulfate groups in the polysaccharides are directly correlated with antiviral activity. It is reported that low sulfate content polysaccharides are inactive against the virus (Damonte et al., 2004; Adhikari et al., 2006). The SPs have actively inhibited the replication and growth of flavivirus, togavirus, orthpoxvirus, herpesvirus, etc. (Witvrouw and De Clercq, 1997). Acquired immunodeficiency syndrome caused by HIV-1 has affected millions of lives and the most deadly condition next to cancer. The first generation of anti-AIDS treatment has severely failed with only a 50% success rate (Artan et al., 2008). The major reason for failure is the resistance development in the virus. Moreover, the virus changes its confirmation quickly that makes it more difficult to design a drug against it. Therefore, launching a new generation of potent drugs that actively retard the growth of the virus is a need of the hour (Singh et al., 2005). This can be addressed by exploring natural bioactive agents and their derivatives as a new line of therapeutics against the disease with no side-effects. Sulfated polysaccharides extracted from *Mimosa scabrella* were reported with anti-viral activity and have negatively affected yellow fever virus, HIV, and flavivirus both in vivo and in vitro testing (Talarico et al., 2005). To date, no specific licensed vaccine is available for the dengue virus. However, yellow fever virus belonging to the same family Flaviviridae has a vaccine. Over time, we have discussed the phenomenon of "resistance development." Hence, finding a vaccine candidate from the natural resources would be an appropriate solution. Hidari et al. (2008) have demonstrated that Fucoidan, SP isolated from *Cladosiphon okamuranus*, has efficiently impeded dengue virus type 2 infection. Their detailed investigation has revealed that fucoidan interacts directly with the enveloped glycoprotein of dengue virus 2 particles. This proves the effectiveness of this against dengue virus type 2. This leaves us with the hope that unveiling other SP molecules from algae will eventually control other types of dengue virus. Another study has thrown light into the efficacy of SP molecules isolated from several algae against the herpes simplex virus I and II (Harden et al., 2010). The SPs were found very effective at the first hour of viral infection however after that their effect has diluted. Moreover, macroalgal sulfonic polysaccharides are frequently used in the vaginal antiviral formulation. Their use is promoted for being safe without inferring with the normal function of vagina lining cells and the bacterial flora (Béress et al., 1993). The major challenge is the selection of the most promising antiviral

SP compound from the whole reservoir. Low cost, safety, least toxicity, and broad spectrum properties are the advantages of SPs that make it a favorable drug candidate with further studies required to approve the best one. The resistance development of the pathogenic microorganisms against the available antibiotics is a major concern that leaves mankind in vain. This raises the need to identify new antibiotics of natural origin as they are least toxic to humans. Among all, marine derived antimicrobial peptides offer promising results with broad spectrum antimicrobial activities. No such antibiotics are in use currently. But they can make up a novel future drug line against the pathogenic microorganisms. For example, the Covid-19 pandemic against which the whole world is battling is a virus borne disease. Though a vaccine is a need of the hour but resistance development with time is an expected phenomenon. Hence, to deal with such difficulty finding out a novel natural solution would be the best cure. Recently, Council of Scientific and Industrial Research (CSIR), India, has announced its upcoming drug trial schedule with phytopharmaceutical ACQH against covid-19. Moreover, favipiravir, another plant based drug, entering the clinical trial is an indication of future prospects of algal based biomolecules in curbing the deadly disease.

1.3.4 ANTI-HYPERTENSIVE

Cardiovascular diseases are among the high-risk factors affecting and claiming millions of lives every year (Kearney et al., 2005). Their incidence is more likely connected with pre-existing conditions like high blood pressure, hypertension, and aging which resulted in ROS accumulation (Archer et al., 2008). Hypertension often leads to other medical complications like stroke, arteriosclerosis, myocardial infarction later. This a major cause of death in the developed as well as developing nations. These conditions are often managed by a strict diet and lifestyle management that keep a check in the blood pressure. Nevertheless, natural resources with ACE-1 inhibitory potential can bring new hope in the pharmaceutical for treating the condition (Wilson et al., 2011). Blood volume and its pressure in humans are maintained by the Renin-angiotensin-aldosterone system (Fitzgerald et al., 2011). Angiotensin I gets readily converted to Angiotensin II by Angiotensin I converting enzyme (Zhao and Xu, 2008). Moreover, the enzyme is also known to inactivate the vasodilator bradykinin. Angiotensin II is the vasoconstrictive molecule. Hence, targeting ACE-I with biomolecules of natural origin would immensely help (Riordan, 2003). Renin is another candidate whose blockage can give the drug industry suitable results as they catalyze the formation of Angiotensin I from Angiotensinogen. Interestingly, the association of ACE in the degradation of neuropeptides like substance P, neurotensin, encephalin, which ensure the proper functioning of the cardiovascular system, provides a suitable target in drug development. The drug industry depends on synthetic molecules to treat hypertension. Majorly, chemically synthesized drugs like captopril, alcacepril, enalapril, lisinopril are in use to treat cardiovascular disease. Aliskerin, a renin inhibitor, was discovered almost a decade ago but it was banned due to harmful effects. The naturally occurring ACE inhibitor has been isolated from snake venom. However, it reported numerous side effects like cough, skin rash, angioneurotic edema, taste disturbance. Henceforth, the greater interest is devoted to finding novel components from the algal community that can inhibit the ACE-I without posing a negative effect on human health. The foundation of the natural ace-I inhibitor was laid almost four decades ago (Oshima et al., 1979). The first inhibitor peptide was reported from the food protein hydrolyzed by the digestive proteases. Later on, the efficacy of marine organisms in the treatment of mild hypertension patients by inhibiting ACE-I converting enzymes was testified (Lee et al., 2005; Guang and Phillips, 2009). Gradually, ACE inhibitory peptides are isolated and reported from algae (Suetsuna and Chen, 2001; Cao et al., 2017). The peptides work either by binding to the active site or to the inhibitor site which eventually alters the structure of the substrate. This doesn't allow enzymes to bind to the substrate molecule and thus inhibit the ACE-I enzyme. It is seen that some peptides opt for the non-competitive mechanism (Qian et a., 2007). Algal peptides have efficiently acted as ACE-I inhibitor and that is well understood (Samarakoon and Jeon, 2012; Cao et al., 2017). The efficacy of the anti-hypertensive effect of seven different brown algae namely *Ecklonia cava*, *Ishige okamurae*, *Sargassum fulvellum*, *Sargassum horneri*, *Sargassum coreanum*, *Sargassum thunbergii*, and *Scytosiphon lomentaria* was tested. Among all, *Ecklonia cava* has shown the best ACE inhibitory activity (Heo et al., 2003). Chao et al. (2000) have compared the potential of ACE inhibitory enzymes derived from green and brown algae. Results indicated that brown algae are superior to green algae. In a study by Sheih et al. (2009) ACE-I inhibitory activity was analyzed for the peptide isolated from the *C. vulgaris* protein waste. It was hendecapeptide and found to exhibit high ACE-I inhibitory activity with additional benefits of pH and heat stability against GI tracks enzymes. This provides a suitable example of waste utility. *Porphyra yezoensis*, edible red algae, has significantly inhibited ACE-I in a hypertensive rat (Qu et al.,