ejpmr, 2024, 11(4), 308-321

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

EXPLORING MARINE SEAWEED-DERIVED PHYTOCONSTITUENTS AS POTENTIAL THERAPEUTIC AGENTS AGAINST MYCOBACTERIUM TUBERCULOSIS: A REVIEW

Rashith A.[1]*, Dr. Sathiya Balan G.[2], Keerthana T.[1], Dr. Venkata Rathina Kumar T.[3]

[1]M.Pharm, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.

[2]Assistant Professor, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.

[3]Professor and HOD, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.

***Corresponding Author: Rashith A.**

M.Pharm, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.

Article Received on 19/02/2024 **Article Revised on 10/03/2024** **Article Accepted on 31/03/2024**

ABSTRACT

Globally, 7.5 million individuals were diagnosed with tuberculosis (TB). TB is an infectious pulmonary ailment instigated by *Mycobacterium tuberculosis*. This surge exceeded pre-COVID levels (7.1 million in 2019) by 16%, and surpassed 2023 figures by 28%. Although drugs like Rifampicin, pyrazinamide, Isoniazid, Ethambutal and streptomycin are used as first line drugs were used in the treatment and control of tuberculosis progression, cause hepatic disorder and drug resistance may occurs. Natural source such and plants and marine organisms possess various secondary metabolites acts against mycobacterium *in vitro*. The secondary metabolites act by various mechanisms to supress the growth of mycobacterium and also enhance the immunity. But yet to evaluated in humans and have to be standardised properly to ensure the safety and efficacy of the natural sources. This review will focus on the various marine seaweed derived phytoconstituents in recent year shown a promising activity against *Mycobacterium tuberculosis.* More research is required to get new moiety in the treatment of tuberculosis.

KEYWORDS: *Mycobacterium tuberculosis*, Seaweed, GC-MS, Anti-tubucular and Marine natural products.

INTRODUCTION

Tuberculosis, a communicable respiratory malady, stems from *Mycobacterium tuberculosis*. (MTB), commonly targeting the pulmonary system, which can precipitate persistent coughing, elevated body temperature, and thoracic discomfort.[1] Scholars suggest *Mycobacterium's* origin over 150 million years ago During the Middle Ages, a novel manifestation of TB, termed scrofula, which impacts cervical lymph nodes, surfaced. TB has persisted for 70,000 years, now impacting nearly 2 billion people worldwide. Earliest records, found in India and China 3300 and 2300 years ago, underscore its historical importance.[2]

In 2022, globally, 7.5 million individuals were freshly diagnosed and officially recognized as TB cases. This surge exceeded pre-COVID levels (7.1 million in 2019) by 16%, and surpassed 2021 figures by 28%. It stands as the highest annual count since the WHO initiated global TB monitoring in the mid-1990s.[3] In India, there was a historic peak in notifications, with 2.42 million cases recorded, indicating a 13% rise from 2021.[4] TB is a significant contributor to global illness and death. It is estimated that around a quarter of the global population is harboring MTB infection, carrying a 5–10% chance of developing active TB disease during their lifetime.[6]

Mycobacterium tuberculosis, a Gram-positive bacillus, exhibits distinctive characteristics, being both alcohol and acid-fast, non-spore-forming, and non-motile. It thrives in obligate-aerobic conditions but showcases facultative behavior. Remarkably, it lacks catalase activity. For tuberculosis diagnosis, the Ziehl-Neelsen stain is commonly utilized, employing carbol fuchsin for initial staining, Subsequent to decolorization with acid-alcohol, the procedure involves counter-staining with methylene blue, yielding a pink and blue appearance, respectively.[11] This bacterium, with rod-shaped, nonmotile structures measuring range from 1 to 4 micrometers in length and 0.3 to 0.6 micrometers in diameter, possesses a unique cell wall composition rich in lipids, including mycolic acids and glycolipids. The specialized cellular membrane contributes to its diminished permeability and pathogenic nature.[5]

Infection transpires when individuals inhale droplet nuclei containing MTB. These minute particles traverse through the oral cavity, nasal passages, upper respiratory

tract, and bronchi before reaching the alveoli in the lungs. Active TB infection is more prevalent among individuals with HIV/AIDS and smokers. Diagnosis relies on chest X-rays, along with microscopic examination and fluid culture. The presence of drug-resistant strains such as multidrug-resistant TB (MDRTB) or extensively drug-resistant TB (XDR-TB) increases the risk of transmission due to their resilience and extended treatment periods, potentially necessitating extended exposure for transmission to occur.[6]

Current TB treatment involves a drug combination, with Rifampicin and isoniazid being primary. Rifampicin is particularly crucial for shortening treatment duration and ensuring positive results. Resistance to isoniazid, the predominant form of resistance is associated with treatment failure and the development of acquired resistance to rifampicin.[7] Due to the rapid resistance of cost-effective TB medications, there is a pressing demand to discover novel treatments. Nature present a promising reservoir for such indications, warranting thorough exploration for new therapeutic agents derived from natural sources.[8]

Natural reservoirs from various sources like plant, the marine and microbial sources offer a promising initial focus in the quest for more potent anti-tubercular drugs, given their abundant chemical diversity and potent antimicrobial characteristics. Traditional remedies like propolis have been historically employed for treating TB. Furthermore, compounds such as artemisinin, isolated from the *Artemisia annua* plant, an integral component of Chinese traditional medicine shows promise in both treating TB and augmenting the efficacy of conventional drugs.[9]

Marine algae, commonly known as seaweeds, have found diverse applications in medicine due to their rich bioactive compounds. Categorized into three primary types, Green algae (Chlorophyta), Brown algae (Phaeophyta), and Red algae (Rhodophyta). Each category possesses unique properties contributing to its medicinal uses. Seaweeds boast a plethora of secondary metabolites, encompassing alkaloids, glycosides, flavonoids, saponins, tannins, steroids, and related active compounds, renowned for their medicinal significance and widespread utilization in the drug and pharmaceutical sectors.[10]

Seaweeds are revered as the botanical marvels of the sea and heralded as the medicinal superfoods of the 21st century. Approximately 6,000 species of seaweeds have been documented. Algae sourced from the Indian coasts encompass a total of 844 species, including various forms and varieties, spanning across 217 genera. Seaweeds are rudimentary non-flowering organisms lacking genuine roots, stems, and leaves.

Seaweeds are recognized as a renewable natural resource due to their affordability, compatibility with animal test systems, and widespread availability. Extracts from algae yield various bioactive compounds with diverse physiological impacts on humans and other organisms, Seaweeds hold the potential to provide a broad range of biological activities targeting conditions like cancer, tuberculosis, inflammation, as well as diseases induced by fungi, bacteria, or viruses.[12]

Seaweeds are abundant in essential nutrients like polysaccharides, complete proteins, polyunsaturated fatty acids, vitamins, and minerals. However, they are garnering increasing attention for their bioactive components, notably antioxidants such as terpenes, acetogenins, alkaloids, phlorotannins, and various phenolic compounds like eckol, dieckol, and fucodiphloroethol. The marine ecosystem hosts a diverse array of seaweed species, also referred to as macrophytic or marine algae.[13]

Historically, the medicinal uses of seaweeds were confined to traditional and folk remedies. Dried or processed seaweeds have been traditionally consumed as folk remedies for ailments like tuberculosis, arthritis, and respiratory infections. It has been proposed that seaweeds, among other herbal products, possess therapeutic potential for treating tuberculosis, arthritis, colds, and influenza. However, in the late 1990s, the identification of bioactive compounds emerged through research involving marine bacteria, invertebrates, and algae. To date, Indian waters have been documented to host approximately 271 genera and 1153 species of marine algae, encompassing various forms and varieties.[12],[13]

Seaweed species against *Mycobacterium tuberculosis*

1. *Turbinaria conoides*

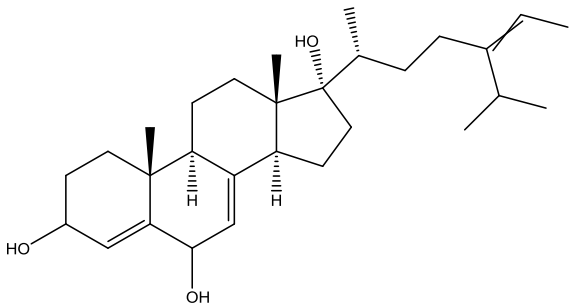
Turbinaria conoides, a species of Phaeophyta belonging to the Sargassaceae family, is renowned for its abundance in polysaccharides. It typically inhabits coral reef environments, *T. conoides* thrives particularly in tropical and subtropical regions across the globe. *T. conoides* is commonly found attached to rocky substrates or coral substrates in shallow, clear waters with moderate to strong water movement. Its habitat often includes reef flats and shallow reef slopes, where it forms extensive colonies. This species thrives in well-lit areas, making it prevalent in the upper portions of the reef where sunlight penetrates.

Figure 1: *Turbinaria conoides.*

The compounds identified, including 24xi-hydroperoxy-24-vinylcholesterol, fucosterol, and 29-hydroperoxystigmasta-5,24(28)-dien-3b-ol, were categorized as oxygenated fucosterols. Additionally, (8xi,9xi,14xi,17xi,24xi)-24-hydroperoxystigmasta-4,28-diene-3,6-dione, (6b,8xi,9xi,14xi,17xi,24E) 6-hydroxystigmasta-4,24(28)-dien-3-one, and (8xi,9xi,14xi,17xi,24xi) 24-hydroperoxy-6-hydroxystigmasta-4,28-dien-3-one are also classified as oxygenated fucosterols. 3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene and 14,15,18,20-diepoxyturbinarin were found in the cyclohexane extract.

The extracts exhibit various bioactivities, including anticoagulant and mosquitocidal effects, antipyretic properties, anti-adipogenic effects, protection against skin photo-damage, antibacterial activities, and cytotoxicity, underscoring the potential pharmacological significance of *T. conoides* and its extracts for therapeutic applications.[14]

The standard strain *M. tuberculosis* H37Rv was utilized in screening active seaweed against *M. tuberculosis* through the LRP assay. Ethanol extract of *T. conoides* demonstrated the highest antimycobacterial activity at 500 µg/mL, achieving 87.33% inhibition, followed by the hexane extract, which exhibited 74.68% inhibition against *Mycobacterium tuberculosis* H37Rv.[15]



3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene

Figure 2: structure of 3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene.

2. *Turbinaria ornata*

Turbinaria ornata, a Phaeophyta of the Sargassaceae family, is abundant in fucoids and sulphated polysaccharides. It is commonly found along the southeast coast of Tamil Nadu, India. *Turbinaria ornata* typically exhibits a perennial, macroscopic habit with a branched and bushy morphology. The thalli are flattened and often fan-shaped, with distinct branching patterns. This species can form extensive colonies on hard substrates such as rocks and coral reefs.[16]

Figure 3: *Turbinaria ornate.*

The stiff is a tall, erect plant, typically 2-20 cm high during reproduction. Its blades are conical, hard, and thick, with a double row of stiff spines along the triangular edge when viewed from above. The holdfast has one upright part and a basal portion that is conical or irregular, often with several root-like structures branching from the base.[17]

It is utilized as animal feed, food additive, and fertilizer. Phytochemical screening of T. ornata unveiled the existence of saponins, alkaloids, and amino acids, fixed oil and fat and phenolic compounds. This seaweed exhibits a diverse array of pharmacological activities, including antibacterial, anti-coagulant, anti-inflammatory, and antioxidant properties. Fucoidan extracted from Turbinaria spp. has demonstrated therapeutic potential in preventing myocardial injury, as well as exhibiting hepatoprotective, anticancer, and neuroprotective effects.[18]

Terpenoids, renowned for their therapeutic potential, play a pivotal role in the prevention and treatment of various diseases, including cancer. With a diverse range of pharmacological properties, terpenoids exhibit antimicrobial, antispasmodic, antifungal, anti-allergenic, antihyperglycemic, antiviral, anti-inflammatory, antiparasitic and immunomodulatory effects.

Additionally, tannins, another class of bioactive compounds, find application in medicine as mild antiseptics for treating diarrhea and controlling minor hemorrhages. They contribute to the management of these conditions effectively. Furthermore, cardiac glycosides, which are essentially steroids, possess a remarkable ability to exert specific and potent actions, particularly on the cardiac muscle. Their therapeutic significance lies in their capacity to regulate cardiac function, making them valuable in the treatment of various heart-related conditions.

Gas Chromatography-Mass Spectrometry (GC-MS) analysis of the seaweed extract revealed a rich array of compounds with potential therapeutic significance. These include ethyl [3-methyl-3-

(pentamethyldisilanyl)cyclohexylidene] acetate, neophytadiene, docosanoic acid derivatives, and various alcohols and hydrocarbons. Notably, squalene, hentriacontane, and turbinaric acid were identified alongside sterols such as saringosterol and (22E)-3b-hydroxycholesta-5,22-dien-24-one. Furthermore, the presence of allenicnor-terpenoid and apo-90-fucoxanthinone suggests the potential bioactivity of the seaweed extract in various health applications, including cancer prevention and treatment.[19]

T. ornata was subjected to processing to acquire $Mg(OH)_2$ nanomaterials. The antimycobacterial activity of the $Mg(OH)_2$ nanomaterials was evaluated through the LRP assay, revealing a 73% reduction in Relative Luminescence Units (RLU) at a concentration of 100 µg/mL. Comparatively, rifampicin, the standard drug, displayed a 90% reduction in RLU at a concentration of 2 µg/mL against M. tuberculosis H37Rv.[20]

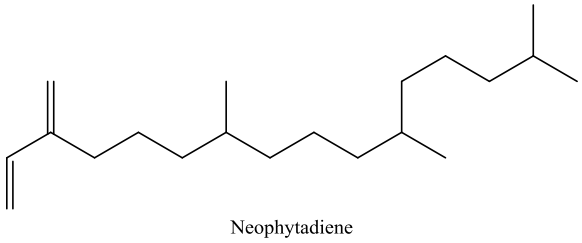


Figure 4: structure of Neophytadiene.

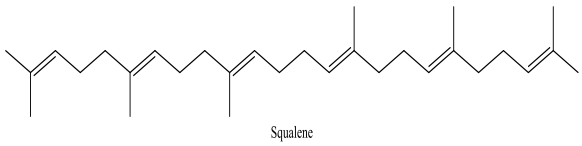


Figure 5: structure of Squalene.

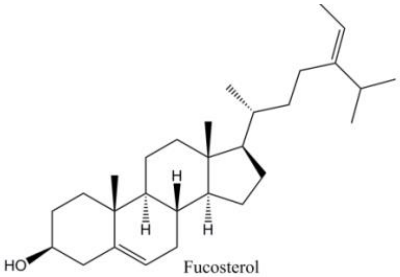
Figure 6: structure of 17-pentatriacontene.

3. *Bifurcaria bifurcate*

Bifurcaria bifurcata, a brown algae species belonging to the Bifurcariaceae family Bifurcaria bifurcate belongs to the family Bifurcariaceae. It exhibits a branched or dichotomously divided growth pattern, hence the species name "bifurcate." Its habitat typically includes rocky shores and coastal areas, where it can attach itself to rocks or other substrates via a holdfast.[57] Its distribution primarily encompasses southern areas, notably along the Atlantic coastline of France, Spain, and Portugal, extending to the southern and western coasts of England and the west coast of Ireland, with rare occurrences in Scotland.[58]

Figure 7: *Bifurcaria bifurcate.*

The dichloromethane extract of B. bifurcata was found to contain various diterpenes and other terpenoids upon analysis. Among these compounds were neophytadiene, phytol, trans-geranylgeraniol, 6,7,9,10,11,12,14,15-tetradehydrophytol, 6-hydroxy-13-oxo-7,7′,10,11-didehydrophytol, 1-acetyl-10,13-dioxo-6,7,11,11′,14,15-tridehydrophytol, and 6,10,14-trimethyl-2-pentadecanone.[21]



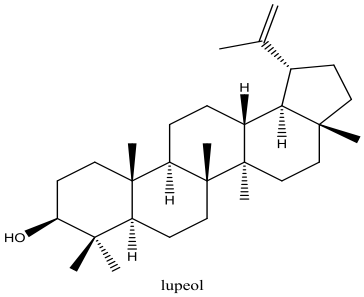


Figure 8 & 9: structure of Fucosterol and lupeol.

After being extracted overnight with CHCl3: MeOH mixtures, tested against MTB strain H37rv, the sole extract from B. bifurcate displayed limited antitubercular activity, with a minimum inhibitory concentration of 64.0 µg/mL.[22]

4. *Padina gymnospora*

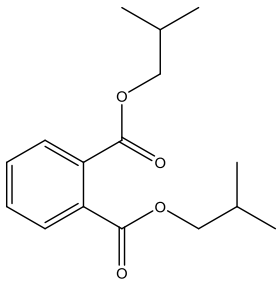
Padina gymnospora, a brown alga of the Dictyotaceae family, is notable along the Egyptian coast for its abundant biomass and broad distribution. Thriving primarily in tropical and subtropical marine settings, this alga predominantly resides in rocky reefs and coastal waters. Its calcareous nature, characterized by calcium carbonate deposits, further distinguishes it. Initially

identified in 1763, *Padina gymnospora* remains a prominent species in marine ecosystems, possessing anti-inflammatory, anti-oxidant, anti-bacterial and anti-noceptive effects.[55]

Figure 10: *Padina gymnospora.*

The ethyl acetate extract of P. gymnospora was found to contain several compounds, including Fucosterol (12.45%), L-(+)-ascorbic acid 2, 6-dihexadecanoate (8.13%), 1,2-benzene dicarboxylic acid bis(2-methyl propyl) ester, and acyclic diterpenoid phytol. Major constituents also included Dihydro-2-(10-(hydroxymethyl)-7,15-dimethyl-9-oxoundec-11-enyl)-2-methyl-2H-pyran-1(4H)-one and 1-(decahydro-1-hydroxy-7-methyl-8-vinyl naphthalene-2-yl) ethanone.

Chlorophyll a and chlorophyll b were detected in the nutritional profile. Additionally, numerous vitamins including B1, B2, B3, B6, B12, C, A, D, and E were identified in P. gymnospora. Amino acids such as aspartic acid, glutamic acid, asparagine, serine, glutamine, glycine, threonine, arginine, alanine, cysteine, tyrosine, histidine, valine, methionine, isoleucine, phenylalanine, leucine, lysine, proline, and tryptophan were present. Furthermore, fatty acids like palmitic acid were also detected.[23]



1, 2-benzene dicarboxylic acid bis(2-methyl propyl) ester

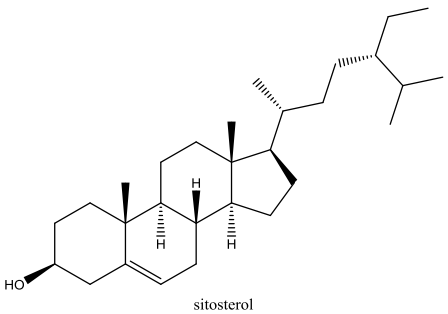
Figure 11: structure of 1,2-benzene dicarboxylic acid bis(2-methyl propyl) ester.

G.edulis, U.fasciata, and P.gymnospora extracts were tested, with *P.gymnospora* extracts showing anti-mycobacterial properties at both lower (250 g/ml) and higher (500 g/ml) concentrations. This investigation delved into *P.gymnospora's* potential in combating Tb bacteria and clinical pathogens, suggesting its utility in preventing bacterial infections.The presence of lupeol, n-hexadecanoic acid, and oleic acid in the extract may account for its antibacterial and anti-TB activities, as observed in the MABA Assay for Mycobacterium smegmatis bacteria.[24]

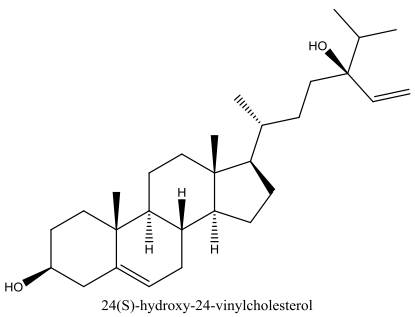
5. *Sargassum glaucescens*

Sargassum glaucescens, a member of the Sargassaceae family, is a large, multicellular seaweed characterized by a complex branching pattern. It forms dense mats or floating rafts of tangled fronds ranging in color from olive-green to brownish-yellow. Typically found in temperate to tropical coastal regions of the Pacific Ocean, particularly along the western coasts of North and South America, it thrives in shallow, nutrient-rich waters, attaching to rocky substrates or floating freely in the ocean.

The alcoholic extract of the marine seaweed *S. glaucescens* was utilized for the isolation of sterols, resulting in the identification of several key compounds. Fucosterol emerged as a primary component , alongside of 24(S)-hydroxy-24-vinylcholesterol and 24(R)-hydroxy-24-vinylcholesterol as a mixture. Additionally, cholesterol, β-sitosterol and stigmasterol were isolated from the extract.



sitosterol



24(S)-hydroxy-24-vinylcholesterol

Figure 12 & 13: Structure of Sitosterol and 24(s)-hydroxy-24-vinylcholestrol.

Among these compounds, β-sitosterol has garnered attention for its diverse biological activities, including hypocholesterolemic, analgesic, anti-inflammatory and immunomodulatory properties. Notably, it exhibits efficacy in the treatment of benign prostatic hyperplasia, prostatic cancer, diabetes, and possesses antioxidant properties. Similarly, stigmasterol has been recognized for its anti-inflammatory, hypocholesterolemic, and hypoglycemic effects, among others. It displays in vitro antitrypanosomal activity and inhibits the growth of Mycobacterium tuberculosis without significant toxicity to mammalian cells.[25]

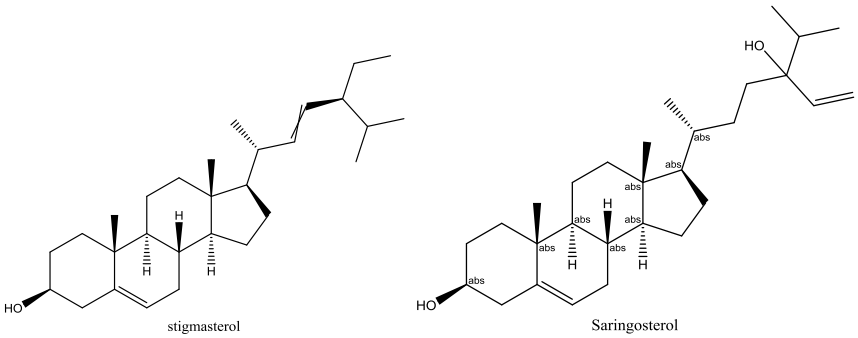


Figure 14 & 15: structure of stigmasterol and saringosterol.

6. *Lessonia nigrescens*

Lessonia nigrescens, also referred to as "black tree kelp" or "huiro negro," is a type of brown algae classified within the Lessoniaceae family and the Laminariales order. It thrives in the cold temperate waters of the southeastern Pacific Ocean,[59] primarily along the coastlines of Chile and Argentina. Indigenous communities, such as the Mapuche people, have historically utilized this seaweed for various purposes including food, fertilizer, and alginate extraction. Growing densely in kelp beds within subtidal zones, it features distinctive characteristics including long stipes that anchor it to rocky substrates and blade-like fronds extending several meters in length.[26]

Figure 16: *Lessonia nigrescens.*

Saringosterol, a fucosterol derivative present in Lessonia nigrescens and Sargassum ringgoldianum, has been recognized for its capacity to impede the proliferation of tubercle bacillus. The investigation into the antitubercular activity of saringosterol and its epimers extracted from L. nigrescens against MTB unveiled MIC values of 0.25, 1.0, and 0.125 µg/mL, respectively.[27]

7. *Laurencia johnstoni*

Laurencia johnstoni, a member of the red algae family, thrives in marine habitats, often found in intertidal and subtidal zones with rocky substrates along temperate and tropical coastlines worldwide. This fascinating species undergoes photosynthesis, serving as both habitat and food source for marine organisms, thus playing a crucial role in coastal ecosystems health and biodiversity. Used to treatment for anti-bacterial, anti-parasitic, anti tumor, insecticidal, and repellent properties.

Two brominated sesquiterpenes, Laurinterol and aplysin, derived from L. johnstonii, were assessed for their in vitro impact against six non-tuberculous mycobacteria (NTM) and nine M. tuberculosis strains. Laurinterol displayed significant antimycobacterial efficacy. M. tuberculosis H37Rv served as the susceptible-strain control, and the susceptibility of MTB to Laurinterol and aplysin was evaluated using Alamar Blue assay. Rifampicin served as the comparator. Laurinterol demonstrated superior activity against MTB with MIC of 25 µg/mL and exhibited inhibition against eight out of nine Mtb strains with MICs ≤ 100 µg/mL. Moreover, exhibited moderate activity against six *M. tuberculosis* strains with MIC 25–50 µg/mL and satisfactory activity against all NTM strains (MIC 6.25–25 µg/mL), including M. abscessus and M. intracellulare.[28]

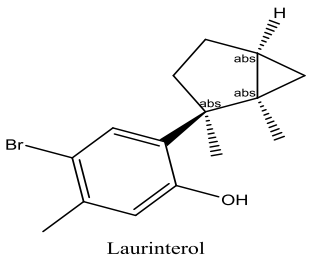


Figure 17: structure of Laurinterol.

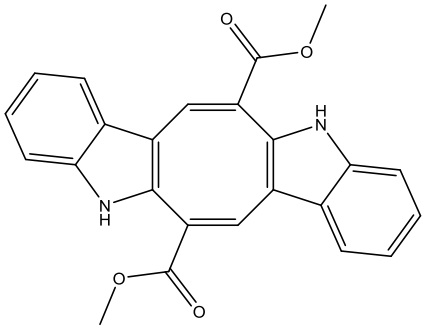
8. *Caulerpa racemosa*

Caulerpa racemosa, a member of the Caulerpaceae family in the Bryopsidales order, is green algae species found in warm temperate and tropical seas worldwide. It thrives in shallow coastal waters, forming extensive

meadows on sandy or rocky substrates. Adaptable to diverse marine environments, it tolerates varying levels of light, temperature, and salinity. Typically, it exhibits creeping growth with long, horizontally extending fronds that branch out, giving them a feathery appearance.

Figure 18: *Caulerpa racemosa.*

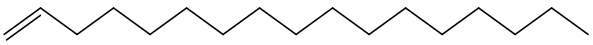
- The C. racemosa contains various phytoconstituents such as ceramides, sesquiterpenes, and other compounds. The extract contains amino acids including alanine, phenylalanine, glutamic acid, glycine, serine, isoleucine, lysine, aspartic acid, leucine, and valine and peptides. Polyunsaturated fatty acids (PUFA),
- Phthalic acid, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol), antinociceptive, antimutagenic , hypocholesterolemic, antiarthritic, anticoronary, antiandrogenic, anti-inflammatory and anticancer (3-hexadecene), phytochemical constituents such as glycosides, cardiac glycosides, terpenoids, saponins and phenols.



Caulerpin

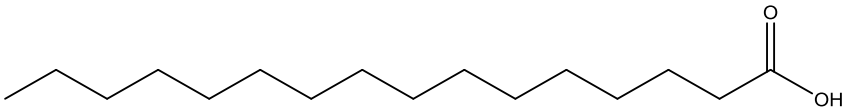
Figure 19: Structure of Caulerpin.

The GC-MS analysis unveiled the presence of tridecanoic acid, pentadecane, 1-heptadecene, n-Hexadecanoic acid, 1-Docosene, Hexadecane, 3-Octadecene, 9,12-Octadecadienoic acid, methyl ester, 2-aminophenol, Nonadecane and hexadecamethyl compounds in the extracts of *C. racemosa.*[29][30]



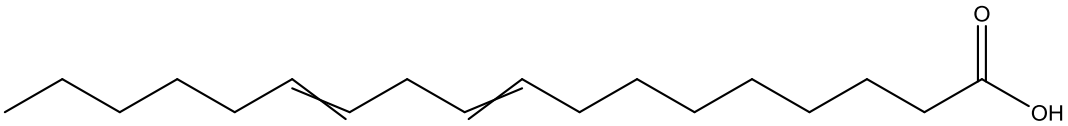
1-heptadecene

Figure 20: structure of Heptadecane.



, n-Hexadecanoic acid

Figure 21: structure of Hexadecanoic acid.



9,12-Octadecadienoic acid

Figure 22: structure of octadecadienoic acid.

Caulerpin, a distinct green algal pigment extracted from Caulerpa racemosa and C. serrulata, has demonstrated significant efficacy, with an IC50 value of 0.24 µM against MTB H37Rv strains.[31]

9. Ulva lactuca

Ulva lactuca, a species of flat green algae from the family Ulvaceae, boasts a global presence. Its thallus is characterized by its sheet-like structure, light green hue, delicate and translucent nature, reaching lengths of up to 250 mm. Persisting year-round, it thrives on rocks, in lower-shore rock pools, and in shallow subtidal regions.[60] Abundant and widely distributed in the Northeast Atlantic and North Pacific region, its status elsewhere necessitates further investigation. Increasingly, *Ulva lactuca* is under scrutiny for its potential applications in animal feed and bioenergy, although its greatest promise may lie in medicinal realms. Studies have revealed its potent anti-inflammatory, antiviral, antifungal, antiprotozoal, antibacterial and cytotoxic properties, hinting at a promising future in medicine.[32]

 [60]

Figure 23: *Caulerpa racemosa.*

Seaweed has been found to contain a diverse array of phytochemical constituents, including Alkaloids, Terpenoids, Saponins, Flavonoids, and Steroids. Through GC-MS analysis, several specific compounds have been identified, including

- Octadecenal,
- Erucic acid,
- 9-Octadecenoic acid,
- Tricosanol,
- Tramadol,
- Lucenin 2,
- Isopropyl myristate,
- Neophytadiene,
- Vincadifformine,
- Lactaropallidin,
- Phytol, and
- Digitoxigenin.

These findings underscore the rich phytochemical diversity of seaweed and its potential for various applications in pharmaceuticals, nutraceuticals, and other industries.[33]

The ethanolic extract of *Ulva lactuca* was prepared. Initially, the application of 25 mg/mL of algal extract resulted in the inhibition of mycobacterial growth on the M. smegmatis lawn. Subsequently, the minimum inhibitory concentration (MIC) of this extracts against *M. smegmatis* was determined using agar diffusion and serial dilution methods. The findings revealed that the MIC for the Ulva lactuca extract was determined to be 10 mg/mL, while the MIC for Ulva intestinalis was found to be 15 mg/mL.[34]

10. *Ulva intestinalis*

Ulva intestinalis, a striking grass-green seaweed, is distinguished by its inflated, irregularly constricted, tubular fronds emerging from a small discoid base. Typically unbranched, these fronds can extend from 10 to 30 cm or more, with diameters ranging between 6 and 18 mm, often terminating in rounded tips. Thriving in diverse shoreline habitats, *Ulva intestinalis* colonizes rocks, mud, sand, and rock pools, utilizing available substrates for support. Commonly found in brackish water regions with significant freshwater influx and moist areas of the splash zone, it frequently grows as an epiphyte on other algae and shells. Remarkably, *Ulva intestinalis* possesses the ability to detach from its substrate, buoyed by gas, and drift to the surface, where it forms floating masses and continues to proliferate.

Figure 24: *Ulva intestinalis.*

From the methanolic extract of Ulva intestinalis, a member of the Ulvaceae family, five major compounds have been identified in GCMS, were 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, Hexadecanoic acid, methyl ester, Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, n-hexadecanoic acid, Phenol and 3,5-bis(1,1-dimethylethyl).[54]

These compounds, identified within *Ulva intestinalis*, contribute to its chemical diversity and may hold significance for various applications in pharmaceutical and industrial sectors.

U. intestinalis extract, (25 mg/mL) was applied to the *M. smegmatis* lawn, resulting in inhibition of mycobacterial growth. Subsequently, the minimum inhibitory concentration MIC of these extracts against *M. smegmatis* was determined using agar diffusion and serial dilution methods.[35]

11. *Dictyota dichotoma*

Dictyota dichotoma is a brown algae belonging to the Dictyotaceae family are characterized by more than 400 diterpenes described from at least 35 species sampled worldwide. They are brown algae, characterized by their flattened, ribbon-like thalli and branching pattern. These algae typically exhibit a perennial, macroscopic habit, forming intricate and often densely packed colonies in marine environments.

Dictyota thrive in shallow coastal waters and intertidal zones, where they attach to hard substrates such as rocks, coral reefs, and mangrove roots.[36] They are typically encountered in tropical and subtropical regions across the globe, where they play significant ecological roles as primary producers and contributors to marine biodiversity. Additionally, Dictyota species are known for their production of bioactive compounds with various pharmacological and ecological importance, making them subjects of interest in marine natural product research.

The anti-tubercular diterpene, a rare compound, was extracted from Dictyota sp. It exhibited modest anti-tuberculosis activity against MTB, with a MIC value of 200 µg/mL.[37]

12. *Padina australis*

The study utilized *M. tuberculosis* strains H37Ra and H37Rv. The crude extract of *P.australis*, at a final concentration of 50 µg/ml, did not show inhibitory effects on 90% of growth. Negative control consisted of a 0.5% DMSO solution, while rifampicin, streptomycin, isoniazid, ofloxacin, and ethambutol served as positive controls, exhibiting MIC values ranging from 0.00312 to 0.0250 µg/ml, 0.156 to 0.625 µg/ml, 0.0234 to 0.0469 µg/ml, 0.391 to 0.781 µg/ml, and 0.234 to 0.469 µg/ml, respectively.[38]


[56]

Figure 25: *Padina australis.*

LCMS analysis revealed the presence of 11 compounds spanning various chemical classes, including carotenoids, sugar alcohols, polysaccharides, fatty acids, and terpenoids.

- Among the carotenoids detected, fucoxanthin stood out, being identified in both positive and negative ion modes. Other carotenoids identified include 3,6-epoxy-5,5′,6,6′-tetrahydro-b,b-carotene-3′,5,5′,6′-tetrol and (3S,4S,3′R)-4-hydroxyalloxanthin
- L-rhamnulose and Dulcitol demonstrated antioxidant activity.
- Fatty acid, including 2-hydroxyhexadecanoic acid, 9,16-dihydroxy palmitic acid, 9Z,12Z,15E-octadecatrienoic acid and 9-keto palmitic acid.[39]

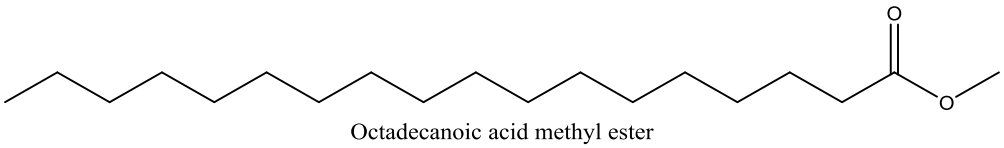
13. *Sargassum boveanum*

Sargassum boveanum, a brown macroalgae genus within the Sargassaceae family, typically thrives in warm, tropical, or subtropical waters, though it can also exist in temperate regions under suitable conditions. It flourishes in environments rich in nutrients and sunlight, such as coastal areas, reefs, and regions affected by nutrient-rich currents or upwelling zone. *S. boveanum* is confirmed to inhabit the coastal waters of the Persian Gulf.[40]


[61]

Figure 26: *Sargassum boveanum*.

Analysis via GC-MS identified several compounds present in S. boveanum, including 9-(Z)-Hexadecenoic acid methyl ester, Tetradecanoic acid methyl ester, 9-(Z)-octadecenoic acid methyl ester, Hexadecanoic acid methyl ester and Octadecanoic acid methyl ester.[41]



Octadecanoic acid methyl ester

Figure 27: Structure of octadecanoic acid methyl ester.

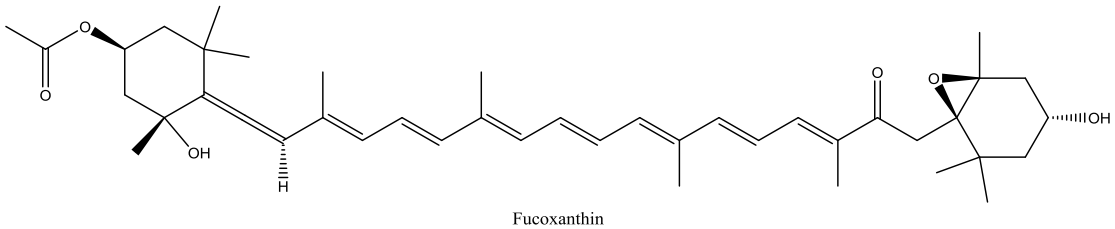
Benzoxazole diterpene alkaloids, specifically pseudopteroxazole and seco-pseudopteroxazole, were isolated from the gorgonian Pseudopterogorgia elisabethae, demonstrating inhibition rates of 97% and 66%, against MTB H37Rv at a concentration of 12.5 µg/mL, with no observed toxicity.[42] The CH3OH: CH3COOC2H5 (1:1) extract of *Sargassum boveanum* at a concentration of 50 µg/ml, exhibited no inhibitory effects on the growth of *M. tuberculosis*. This result was comparable to the standard drugs rifampicin, streptomycin, isoniazid, ofloxacin, and ethambutol.[43] Saringosterol, obtained through repeated column chromatography (CC), demonstrated significant activity against MTB H37Rv. At a concentration of 100 µg/mL, it inhibited 99% of growth in the BACTEC 460 assay system.[44]

MAJOR PHYTOCONSTITUENT AGAINST ANTITUBERCULAR ACTIVITY

1. FUCOIDAN

Fucoidan composed of fucose and sulphated sugar residues, has been utilized as a matrix for inhalable microparticles combining two primary antitubercular drugs. These microparticles efficiently associate with either isoniazid (95%) or rifabutin (81%), offering a promising approach for pulmonary tuberculosis therapy.[45]

Fucoxanthin, a naturally existing carotenoid abundant in consumable Phaeophyta and diatoms, falls under the category of xanthophylls and is a non-provitamin. Its antimycobacterial activity was evaluated alongside The standard drug isoniazid (INH) was evaluated using a microdilution assay against ten clinical isolates of Mtb, in addition to a reference strain. Notably, fucoxanthin demonstrated a significant bacteriostatic effect against All tested Mtb strains exhibited minimum inhibitory concentration (MIC) values ranging from 2.8 to 4.1 µM, whereas INH displayed MIC values ranging from 4.8 to 6.2 µM.[46]



Fucoxanthin

Figure 28: Structure of fucoxanthin.

2. CAULERPIN

Caulerpin, an uncommon orange-red pigment, was initially discovered by Santos from the green algae *Caulerpa serrulata*, C. *sertularioides*, and *C. racemosa* var. *clavifera*, classified as a Bis-indole alkaloid. Bis-indole alkaloids, prominent compounds in nature, demonstrate varied biological activities, including anti-tumor and antibacterial effects, particularly against Mycobacteria species.[47]

Caulerpin, extracted from Caulerpa racemosa and C. serrulata, was first isolated in 1970, was acquired with a yield ranging from 0.55% to 0.63% of the algal dry weight. Conversely, its synthesis from 3-formylindol-2-yl acetic ester yields a higher yield of 5%. Noted for low toxicity since 1984, caulerpin exhibits diverse biological activities.

In assessing compounds as inhibitors against MTB strain H37Rv, the evaluation was conducted at a specific concentration of 50 µM, showed a percentage of inhibition exceeding 70%. IC50 values ranged from 0.24 µM for caulerpin to 3.89µM. Rifampin (RIF), a standard treatment for Mycobacterium infections, including tuberculosis, was used as a reference. While RIF (IC50 = 0.55 µM) demonstrated higher potency than certain synthesized bis-indoles, caulerpin exhibited over twice the potency of RIF (IC50 = 0.24 µM).[48]

3. SARINGESTROL

The anti-TB activity of silver nanoparticles synthesized with the mediation of seaweed was evaluated using the Luciferase reporter phage (LRP) assay. Sargassum polycystum was investigated for its potential as an anti-mycobacterial agent. *S. polycystum* demonstrated significant activity against *Mycobacterium tuberculosis*. Specifically, S. polycystum displayed inhibition rates of 99.38%, 94.79%, and 82.44% against MTB H37Rv and MTB strains that are sensitive to all drugs, and MTD MTB strains, respectively. Meanwhile, S. wightii demonstrated inhibition rates of 42.17%, 98.75%, and 97.89% against the same strains, respectively. These findings suggest that S. polycystum holds promise as a potential candidate for combating MTB infections. Saringestrol is the compound which was present in all the species responsible for the anti-tubercular activity.[49]

CONCLUSION

Despite the array of synthetic drugs employed in tuberculosis treatment, they often lead to hepatotoxicity and contribute to the emergence of multidrug resistance in MTB. Therefore, there is an urgent need for the identification of novel compounds effective against *Mycobacterium tuberculosis*. The use of seaweeds and its products can supress the growth of mycobacterium and its inflammation in the lung caused due to its infection.[50]

The marine ecosystem hosts a diverse array of seaweed species, also refered to as macrophytic or marine algae. Traditionly seaweeds are used as food and medicine for treating various diseases and ailmennts such as, arthritis, respiratory infections, as its contains primary and secondary metabolites. Seaweeds are rich sources of essential nutrients, including polysaccharides, complete proteins, amino acids, polyunsaturated fatty acids, vitamins, and minerals. Also contain bioactive components, notably antioxidants such as terpenes, acetogenins, alkaloids, phlorotannins and various phenolic compounds.[51]

Aside from causing tuberculosis, MTB also associated with other diseases and metabolic syndrome. Hence, there seem to be emerging approaches, which include not only anti-tubercular activity but also the immune response and to supress other respiratory complications. A number of marine seaweeds have shown promising anti-tubercular activity. Many countries like China and Japan incorporate seaweeds into their food and treatment regimens.[52]

Invitro anti-tuberculae activity was performed in three methods. They are LPR assay method, MABA assay method and agar diffusion method. The activity was performed against H37Rv and H37Ra strains of mycobacterium species. Fucoidan, caulerpin, saringestrol and other alkaloid present in the reviewed seaweed species are responsible for anti-tubercular activity.

Individual constituents with their respective species responsible for the activity was tabulated.[53]

Table 1: Antitubercular activity of various seaweed species.

S.No.	Species	Active constituent	*Invitro* Method	Activity
1	*Turbinaria conoides*	Fucosterol	LRP assay, H37Rv strains	87.33% inhibition
2	*Turbinaria ornata*	Fucoidan	LRP assay, H37Rv strains	73% Reduction
3	*Bifurcaria bifurcate*	Lupeol, Fucosterol	H37Rv strains	MIC: 64.0 µg/mL
4	*Padina gymnospora*	Fucosterol, lupeol, n-hexadecanoic acid	H37Rv strains	Activity shown
5	*Sargassum glaucescens*	β-sitosterol, Saringosterol, stigmasterol	H37Rv strains	Activity shown
6	*Lessonia nigrescens*	saringosterol	H37Rv strains	MIC: 0.125 µg/mL
7	*Laurencia johnstoni*	Laurinterol	H37Rv strains	MIC: 25–50 µg/mL
8	*Caulerpa racemosa*	Caulerpin	H37Rv strains	IC50: 0.24 µM
9	*Ulva lactuca*	n-hexadecanoic acid, phytol.	*M. smegmatis*, Agar diffusion	MIC: 10 mg/mL
10	*Ulva intestinalis*	n-hexadecanoic acid	*M. smegmatis* Agar diffusion	MIC: 15 mg/mL
11	*Padina australis*	fucoxanthin	strains H37Ra	Not active
12.	Sargassum boveanum	1.Crude extract 2.pseudopteroxazole and seco-pseudopteroxazole	200 µg/mL	Not active MIC: 12.5 µg/mL
13.	Dictyota spp	-	200 µg/mL	MIC: 200 µg/mL

Invitro experiments have shown potential anti-tubercular activity. Thus, there is an evidence that seaweeds can have anti-tuercular property. More research on seaweed and seaweed derived constituents and its isolation may result in the discovery of potent anti-tubercular activity.

REFERENCE

1. Fogel, N. Tuberculosis: a disease without boundaries. Elsevier. Tuberculosis, 95(5): 527-531. DOI: 10.1016/j.tube.2015.05.017. Epub 2015 Jun 25.
2. Barberis, I., Bragazzi, N. L., Galluzzo, L., & Martini, M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. Elsevier, 2017; 58(1): E9-E12.
3. Global Tuberclosis Report 2023-WHO.
4. India TB report 2023 by Central TB Division.
5. Adigun, R., & Singh, R. (2023). Tuberculosis. Star Pearls.
6. Swalehe, H. M., & Obeagu, E. I. Tuberculosis: Current Diagnosis and Management. Elite Journal of Public Health, 2024; 2(1): 23-33.
7. Chan, E. D. Current medical treatment for tuberculosis. BMJ, November 30, 2002; 325(7375): 1282. doi: https://doi.org/10.1136/bmj.325.7375.1282.
8. Tabuti, J. R. S., Kukunda, C. B., & Waako, P. J. Medicinal plants used by traditional medicine practitioners in the treatment of tuberculosis and related ailments in Uganda. Journal of Ethnopharmacology, January 8, 2010; 127(1): 130-136. doi: 10.1016/j.jep.2009.09.035.
9. Kaur, T., Sharma, P., Gupta, G. K., & Ntie-Kang, F. Treatment of tuberculosis by natural drugs: A review. Plant Archives, January 2019; 19: 2168-2176.
10. Gómez-Cansino, R., Guzmán-Gutiérrez, S. L., Campos-Lara, M. G., Espitia-Pinzón, C. I., & Reyes-Chilpa, R. Natural compounds from Mexican medicinal plants as potential drug leads for anti-tuberculosis drugs. Annals of the Brazilian Academy of Science, Jan-Mar 2017. doi: 10.1590/0001-3765201720160298
11. Asif M. Biologically active compounds from natural and marine organisms with antituberculosis, antimalarial, leishmaniasis, trypanosomiasis, anthelmintic, antibacterial, antifungal, antiprotozoal, and antiviral activities. November 30, 2016; 6(4): e22. DOI: http://dx.doi.org/10.5667/tang.2014.0017
12. Mansour, H. A., Mahfouz, H., & Mahe, N. Anti-mutagenic potential of algal extracts on chromosomal aberrations in Allium cepa L. Acta Biologica Hungarica, (March 16, 2017). DOI: 10.1556/018.68.2017.2.2
13. Pandey, A.K., Chauhan, O.P., & Semwa, A.D.. Defense Life Science Journal, 2020; 5(4): 315-322.
14. Rushdia MI, Abdel-Rahman IAM, Saber H, Zekry AE, Abdelraheem WM, Madkour HA, Abdelmohsen UR. The genus Turbinaria: chemical and pharmacological diversity, 2020. DOI: 10.1080/14786419.2020.1731741.
15. Amudha, Prabuseenivasan, Naga Harika, Vanaja Kumar. Bioactivity of selected seaweeds from Gulf of Mannar, South-east coast of India. Journal of

Coastal Life Medicine, 2014, doi: 10.12980/JCLM.3.2015APJTB-2014-0302.
16. Marine Algae of Hawai'i (Turner) J. Agardh 1821, . Turbinaria ornate, University of Hawai'I, Botany Department. (https://www.hawaii.edu/reefalgae/invasive_algae/phaeo/turbinaria_ornata.htm)
17. Russell, D. J., & Balazs, G. H. Identification manual for dietary vegetation of the Hawaiian green turtle, Chelonia mydas. NOAA TM-NMFS-SWFSC-294, 2000; 49.
18. Deepak Paramasivam, Sowmiya Rajamani, Balasubramani Govindasamy, Perumal Pachiappan. Phytochemical profiling of Turbinaria ornata and its antioxidant and anti-proliferative effects, March 2017. http://dx.doi.org/10.1016/j.jtumed.2017.02.002
19. Rajkumar Gopalan, Bhavan Periyakali Saravana. Phytochemical characterization of the marine brown alga Turbinaria ornata. Research Journal of Chemistry and Environment, March 2017; 21(3).
20. Govindaraju K, Anand KV, Anbarasu S, Theerthagiri J, Revathy S, Krupakar P, Durai G, Kannan M, Subramanian KS. Seaweed (Turbinaria ornata)-assisted green synthesis of magnesium hydroxide [Mg(OH)2] nanomaterials and their anti-mycobacterial activity. Mater Chem Phys, 2020; 239: 122007. doi:10.1016/j.matchemphys.2019.122007
21. Sónia A. O. Santos, Stephanie S. Trindade, Catia S. D. Oliveira, Paula Parreira, Daniela Rosa, Maria F. Duarte, Isabel Ferreira, Maria T. Cruz, Andreia M. Rego, Maria H. Abreu, Silvia M. Rocha, Armando J. D. Silvestre. Lipophilic Fraction of Cultivated Bifurcaria bifurcata R. Ross: Detailed Composition and In Vitro Prospection of Current Challenging Bioactive Properties. Mar. Drugs, 2017; 15: 340. doi:10.3390/md15110340.
22. Spavieri Jasmine, Allmendinger Andrea, Kaiser Marcel, Casey Rosalyn, Hingley-Wilson Suzie, Lalvani Ajit, Guiry Michael D, Blunden Gerald, Tasdemir Deniz. Antimycobacterial, Antiprotozoal and Cytotoxic Potential of Twenty-one Brown Algae (Phaeophyceae) from British and Irish Waters. Phytotherapy Research Phytother. Res., 2010; 24: 1724–1729. DOI: 10.1002/ptr.3208
23. Rushdi, M. I., Abdel-Rahman, I. A. M., Saber, H., Attia, E. Z., Madkour, H. A., & Abdelmohsen, U. R. A review on the pharmacological potential of the genus Padina, September 2021; 141: 37-48.
24. ArokiaRajan MS, Thirunavukkarasu R, Mahesh F, Subaramaniyan K, Joseph J. Anti-Tuberculosis Evaluation of Bioactive Compounds from Marine Seaweeds. Journal of Survey in Fisheries Sciences, 2023; 10(4S): 817-827.
25. Payghami, N., Jamili, S., Rustaiyan, A., Saeidnia, S., Nikan, M., & Gohari, A. R. Alpha-amylase inhibitory activity and sterol composition of the marine algae, Sargassum glaucescens. Pharmacognosy Research, 2015; 7(4).
26. Percival EE, Venegas Jara MF, Weigel H. Carbohydrates of the Brown Seaweed Lessonia nigrescens. Phytochemistry, 1983; 22(6): 1429-1432.
27. Wa¨chter GA, Franzblau SG, Montenegro G, Hoffmann JJ, Maiese WM, Timmermann BN. Inhibition of Mycobacterium tuberculosis Growth by Saringosterol from Lessonia nigrescens. Journal of Natural Products, 2001; 64: 11.
28. García-Davis S, Leal-López K, Molina-Torres CA, Vera-Cabrera L, Díaz-Marrero AR, Fernández JJ, Carranza-Rosales P. Antimycobacterial Activity of Laurinterol and Aplysin from Laurencia johnstonii. Mar Drugs, 2020; 18(6): 287. doi:10.3390/md18060287.
29. Dhevika Sivakumar, Deivasigamani Balaraman. Phytochemical Profiling and GC-MS Analysis of Caulerpa racemosa. Life Science Informatics Publications, Sept–Oct, 2018; RJLBPCS 4(5): 155. DOI: 10.26479/2018.0405.12.
30. Palaniyappan Sivagaami, Sridhar Arun, Abdul Kari Zulhisyam, Téllez-Isaías Guillermo, Ramasamy Thirumurugan. Evaluation of Phytochemical Screening, Pigment Content, In Vitro Antioxidant, Antibacterial Potential and GC-MS Metabolite Profiling of Green Seaweed Caulerpa racemosa, Mar. Drugs 2023; 21: 278. https://doi.org/10.3390/md21050278.
31. Babu AS, Rao KVB. Anti-mycobacterial compounds derived from marine organisms: Mode of actions and potential in tuberculosis treatment. AsPac J. Mol. Biol. Biotechnol, 2021; 29(2): 26-34..
32. https://seaweedsolutions.com/sea-lettuce-ulva-lactuca
33. Anjali K P, Sangeetha BM, Devi Geetha, Raghunathan R, Dutta Susmita. Bioprospecting of seaweeds (Ulva lactuca and Stoechospermum marginatum): compound characterization and functional applications in medicine - a comparative study. Journal Pre-proof, 2019; S1011-1344(19): 30412-9. DOI: https://doi.org/10.1016/j.jphotobiol.2019.111622.
34. Mukherjee G, Mukhopadhyay B, Sil AK. Edible marine algae: a new source for anti-mycobacterial agents. Folia Microbiologica, 2021; 66: 99–105.
35. Freile-Pelegrín Y, Tasdemir D. Seaweeds to the rescue of forgotten diseases: a review. Botanica Marina, 2019; 62(3): 211–219. DOI: https://doi.org/10.1515/bot-2018-0071.
36. Othmani A, Bouzidi N, Viano Y, Alliche Z, Seridi H, Blache Y, El Hattab M, Briand J-F, Culioli G. Anti-microfouling properties of compounds isolated from several Mediterranean Dictyota spp. Journal of Applied Phycology, Oct 2013. DOI 10.1007/s10811-013-0185-2.
37. Jongaramruong J, Kongkam N. Novel diterpenes with cytotoxic, anti-malarial and anti-tuberculosis activities from a brown alga Dictyota sp. Journal of Asian Natural Products Research, 6 Oct 2011. http://dx.doi.org/10.1080/10286020701189203

38. Vaseghi G, Zakeri N, Mazloumfard F, Dana N, Yegdaneh A. Evaluation of the Anti-tuberculosis and Cytotoxic Potential of the Seaweed Padina australis. Iranian Journal of Pharmaceutical Sciences, 2019; 15(1): 29-38.
39. Vaseghi, G., Zakeri, N., Mazloumfard, F., Dana, N., & Yegdaneh, A. Evaluation of the Anti-tuberculosis and Cytotoxic Potential of the Seaweed Padina australis. Iranian Journal of Pharmaceutical Sciences, 2019; 15(1): 29-38.
40. Zahra R, Mehranian M, Vahabzadeh F, Sartavi K. Antioxidant activity of extract from a brown alga, Sargassum boveanum. African Journal of Biotechnology, 17 December, 6(24): 2740-2745.
41. Jassbi Amir Reza, Mohabati Maryam, Eslami Saba, Sohrabipour Jelveh, Miri Ramin. Biological Activity and Chemical Constituents of Red and Brown Algae from the Persian Gulf. Iranian Journal of Pharmaceutical Research, March 2013; 12(3): 339-48.
42. Akbari V, Zafari S, Yegdaneh A. Anti-tuberculosis and cytotoxic evaluation of the seaweed Sargassum boveanum. Research in Pharmaceutical Sciences, 2017, February 2018; 13(1): 30-37.
43. Al-Hashdy D, Raweh S, El-Shaibany A, Humaid A, El-Aasser M. A Review of Biological Activities of Genus Sargassum. Int J Res Dev Pharm Life Sci., 2022; 8(3): 1000130.
44. Wijesekara, I., & Kim, S.-K.. Application of Marine Algae Derived Nutraceuticals in the Food Industry, 2014. DOI: 10.1002/9783527679577.ch35.
45. Akremi N, Cappoen D, Anthonissen R, Verschaeve L, Bouraoui A. Phytochemical and in vitro antimicrobial and genotoxic activity in the brown algae Dictyopteris membranacea. South African Journal of Botany, 2016. http://dx.doi.org/10.1016/j.sajb.2016.08.009
46. Šudomová M, Shariati MA, Echeverría J, Berindan-Neagoe I, Nabavi SM, Hassan STS. A Microbiological, Toxicological, and Biochemical Study of the Effects of Fucoxanthin, a Marine Carotenoid, on Mycobacterium tuberculosis and the Enzymes Implicated in Its Cell Wall: A Link Between Mycobacterial Infection and Autoimmune Diseases. Mar Drugs, 2019; 17(11): 641. doi:10.3390/md17110641.
47. https://www.ingentaconnect.com/content/ben/mrmc/2019/00000019/00000009/art00007
48. Canché Chay, C. I., Gómez Cansino, R., Espitia Pinzón, C. I., Torres-Ochoa, R. O., & Martínez, R. Synthesis and Anti-Tuberculosis Activity of the Marine Natural Product Caulerpin and Its Analogues. Mar Drugs, 2014; 12(4): 1757–1772. doi: 10.3390/md12041757.
49. Thiurunavukkarau R, Shanmugam S, Subramanian K, Pandi P, Muralitharan G, Arokiarajan M, Kasinathan K, Sivaraj A, Kalyanasundaram R, AlOmar SY, Shanmugam V. Silver nanoparticles synthesized from the seaweed Sargassum polycystum and screening for their biological potential. Scientific Reports, 2022; 12: 14757. https://doi.org/10.1038/s41598-022-18379-2.
50. Rajan, M. S. A., Thirunavukkarasu, R., Joseph, J., Palliyath, G. K., Somarathinam, K., Kothandan, G., Subaramaniyan, K., Ullah, R., & Rajesh, R. P. Identification of the Seaweed Metabolites as Potential Anti-tubercular Agents Against Human Pantothenate synthetase: An In Silico Approach. Current Microbiology, 2023; 80(10): 318. doi: 10.1007/s00284-023-03422-w.
51. Ślusarczyk, J., Adamska, E., & Czerwik-Marcinkowska, J. Fungi and Algae as Sources of Medicinal and Other Biologically Active Compounds: A Review. Nutrients, 2021; 13(9): 3178. doi: 10.3390/nu13093178.
52. Shukla, S. D., Vanka, K. S., Chevalier, A., Shastri, M. D., Tambuwala, M. M., Bakshi, H. A., Pabreja, K., Mahmood, M. Q., & O'Toole, R. F. Chronic respiratory diseases: An introduction and need for novel drug delivery approaches. In Targeting Chronic Inflammatory Lung Diseases Using Advanced Drug Delivery Systems, 2020; 1–31. doi: 10.1016/B978-0-12-820658-4.00001-7.
53. Cho, S., Lee, H. S., & Franzblau, S. Microplate Alamar Blue Assay (MABA) and Low Oxygen Recovery Assay (LORA) for Mycobacterium tuberculosis. Methods in Molecular Biology, 2015; 1285: 281-292. doi: 10.1007/978-1-4939-2450-9_17.
54. Nazarudin, M. F., Isha, A., Mastuki, S. N., Mohd. Ain, N., Mohd Ikhsan, N. F., Abidin, A. Z., & Aliyu-Paiko, M. Chemical Composition and Evaluation of the α-Glucosidase Inhibitory and Cytotoxic Properties of Marine Algae Ulva intestinalis, Halimeda macroloba, and Sargassum ilicifolium. Evidence-Based Complementary and Alternative Medicine, 2020; 2020. https://doi.org/10.1155/2020/2753945.
55. Bhuyar, P., Sundararaju, S., Ab. Rahim, M. H., Unpaprom, Y., Maniam, G. P., & Govindan, N. Antioxidative study of polysaccharides extracted from red (Kappaphycus alvarezii), green (Kappaphycus striatus) and brown (Padina gymnospora) marine macroalgae/seaweed. SN Applied Sciences, 2021; 3: 485. https://doi.org/10.1007/s42452-021-04477-3
56. Raj, S. G., Ng, C. H., Mohd-Said, S., & Yu, K. X. Antibacterial Potential of Aqueous Extracts and Compounds from Selected Brown Seaweeds. INNOSC Theranostics and Pharmacological Sciences, 2019; 2(1): 29-33. DOI: 10.26689/itps.v2i1.804.
57. Santos, F., Monteiro, J. P., Duarte, D., Melo, T., Lopes, D., da Costa, E., & Domingues, M. R. Unraveling the Lipidome and Antioxidant Activity of Native Bifurcaria bifurcata and Invasive Sargassum muticum Seaweeds: A Lipid Perspective on How Systemic Intrusion May Present an Opportunity. Antioxidants, 2020; 9: 642. doi:10.3390/antiox9070642

58. https://www.seaweed.ie/descriptions/Bifurcaria_bifurcata.html
59. https://macapnea.wixsite.com/algae/lessonia-nigrescens-
60. Van Ginneken, V., & De Vries, E. Seaweeds as Biomonitoring System for Heavy Metal (HM) Accumulation and Contamination of Our Oceans. American Journal of Plant Sciences, 2018; 09(07): 1514-1530. DOI: 10.4236/ajps.2018.97111
61. Alkhalifa, A. H., Al-Homaidan, A. A., Shehata, A. I., Al-Khamis, H. H., Al-Ghanayem, A. A., & Ibrahim, A. S. S. Brown macroalgae as bio-indicators for heavy metals pollution of Al-Jubail coastal area of Saudi Arabia. African Journal of Biotechnology, 15 November, 2012; 11(92): 15888-15895. DOI: 10.5897/AJB12.2509