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A Review on Antibacterial and Antifungal Activity of Seaweed Extract Against Drug-Resistant Pathogens

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ABSTRACT

The global escalation of multidrug-resistant (MDR) pathogens has severely limited the efficacy of conventional antibiotics, creating an urgent need for novel antimicrobial agents. Marine seaweeds, or macroalgae, represent a prolific source of bioactive compounds with promising antibacterial and antifungal properties. These organisms produce a wide array of secondary metabolites, including polysaccharides, polyphenols, terpenes, alkaloids, and halogenated compounds, which exhibit potent activity against drug-resistant microbial strains. This review explores the antimicrobial potential of seaweed extracts with a focus on their activity against MDR bacteria and fungi. Special emphasis is placed on the evaluation of seaweed-derived antimicrobial compounds, detailing various solvent extraction techniques (aqueous, ethanol, methanol, and supercritical fluids) and screening methodologies such as agar diffusion, broth microdilution, and bioautography. The mechanism of microbial inhibition is discussed in relation to membrane disruption, inhibition of DNA/RNA synthesis, and oxidative stress induction. Additionally, the review highlights practical applications of seaweed extracts in medicine particularly in developing topical agents, wound dressings, and adjunct therapies and in food preservation, where they serve as natural preservatives enhancing shelf life and safety. The therapeutic and industrial potential of seaweed bioactive against drug-resistant pathogens underscores the need for continued research into their bioavailability, synergistic potential, and clinical viability. This review provides a consolidated understanding of the seaweed-based antimicrobial frontier and outlines strategic directions for future innovations in combating antimicrobial resistance.

Keywords: *Seaweed extract, Multidrug-resistant pathogens, Antibacterial, Antifungal, Bioactive compounds.*

INTRODUCTION

The global emergence and rapid spread of antimicrobial resistance (AMR) represent one of the most critical challenges to public health in the 21st century. The inappropriate and excessive use of antibiotics and antifungal agents in human medicine, agriculture, and aquaculture has led to the selection and proliferation of multidrug-resistant (MDR) pathogens. These resistant strains compromise the effectiveness of existing treatments, result in prolonged illness, increased mortality, and place a significant economic burden on healthcare systems worldwide [1]. The alarming rise of superbugs such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*, which have developed resistance to multiple classes of antibiotics and antifungals, necessitates the exploration of alternative and sustainable antimicrobial strategies. In this context, marine environments, particularly seaweeds (macroalgae), have gained attention as promising

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reservoirs of novel bioactive compounds. Seaweeds are the most primitive group of vegetation and they have gained great importance as a promising source of bioactive compounds that can be used for drug development. With a wide range of metabolites like polysaccharides, phlorotannins, glycoproteins, terpenoids, alkaloids, lectins, pigments, and ketones, seaweeds have contributed to numerous pharmaceutical applications on gall stones, renal disorders, cancer heart disease, asthma, psoriasis, and antibacterial, antifungal, and antiviral effects over the past three decades [2].

In many regions of Asia, seaweed is still a widely used culinary ingredient. It is also a significant source of high-value hydrocolloids including agar, alginates, and carrageenan. Seaweeds are also becoming more widely used in the nutraceutical, pharmaceutical, and cosmetic industries because to their growing recognition for their health-promoting properties. Additionally, prior research has demonstrated that chemicals and extracts derived from seaweed have a variety of intriguing bioactivities, including, anti-diabetic, anti-cancer anti-obesity, and anti-inflammatory characteristics. The variety of antioxidant chemicals present in seaweeds may play a role in the observed actions. Many environmental conditions that encourage the production of free radicals and potent oxidising agents in seaweeds. Seaweeds are extremely resistant to oxidative damage as a result of these challenging environmental factors, which may be facilitated by the antioxidant chemicals present in their cells. The presence of polyphenols or other antioxidant substances like carotenoids may be the cause of the health advantages seen in the ethanol extracts [3]. Seaweeds are used to make fertiliser and food all around the world. Additionally, seaweeds are employed in various industrial fields. Proteins, carbohydrates, fats, and fibres are all abundant in seaweeds. The global seaweed sector is growing quickly because to the significant economic benefits.

Historically used in Asian diets and folk medicine, seaweed extracts have demonstrated potential as natural antimicrobial agents capable of combating MDR bacteria and fungi. The antimicrobial action of seaweed-derived compounds is believed to be multifaceted. Mechanisms include disruption of microbial cell walls, interference with biofilm formation, inhibition of enzyme activity, and suppression of virulence factor expression *[4].* Unlike synthetic antibiotics that often target specific molecular pathways, seaweed compounds frequently exert broad-spectrum activity and are less likely to induce resistance. Furthermore, their biocompatibility, biodegradability, and environmental safety make them suitable candidates for use in pharmaceutical, food preservation, and agricultural applications. Recent studies have revealed that crude and solvent-extracted seaweed extracts exhibit significant inhibitory effects against both Gram-positive and Gram-negative bacterial pathogens, including drug-resistant strains such as Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus faecalis* (VRE), and carbapenem-resistant *Pseudomonas aeruginosa* [5,6]. Similarly, extracts have shown antifungal efficacy against clinically important fungi such as *Candida albicans*, *Aspergillus niger*, and *Cryptococcus neoformans* [7]. These findings highlight the potential role of seaweed-based formulations as adjuncts or alternatives to traditional antimicrobial therapies. The bioactivity of seaweed extracts can be influenced by various factors including the species of algae, season of collection, geographical location, extraction method, and the nature of solvents used [8]. For instance, methanol and ethanol extracts tend to yield higher antimicrobial activity than aqueous extracts due to better solubilization of non-polar bioactive compounds.

Therefore, a standardized approach in extraction and characterization is essential for comparing the efficacy across different studies. Despite the promising *in vitro* results, the

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translation of seaweed-derived antimicrobials into clinical or commercial applications remains limited. Challenges include variability in compound composition, difficulties in large-scale extraction, lack of comprehensive toxicological evaluations, and insufficient understanding of in vivo mechanisms of action. Nevertheless, advancements in biotechnology, metabolomics, and Nano formulation technologies are facilitating the identification and optimization of active principles from seaweeds for enhanced delivery and efficacy [9]. In addition to direct therapeutic applications, seaweed extracts are being explored as natural preservatives in the food industry due to their antimicrobial and antioxidant properties. Incorporation of seaweed compounds into food packaging materials, coatings, and edible films can help reduce spoilage and extend shelf life without relying on synthetic chemicals [10].

Similarly, in agriculture, seaweed-based biopesticides and antimicrobial agents are being developed to manage plant pathogens and reduce dependency on synthetic agrochemicals Moreover, the sustainability and renewability of seaweed biomass make it an attractive resource in the fight against AMR. Seaweeds can be cultivated without freshwater or arable land, and their farming contributes to carbon sequestration and nutrient cycling. These environmental advantages further support their integration into the global antimicrobial strategy. This review aims to critically examine the antibacterial and antifungal activities of seaweed extracts, particularly in the context of combating drug-resistant pathogens. It will explore the types of seaweeds and solvents used for extraction, highlight screening methods for antimicrobial efficacy, investigate mechanisms of microbial inhibition, and assess potential applications in medicine and food preservation. By consolidating current knowledge and identifying future directions, this review intends to contribute to the growing body of evidence supporting seaweed-derived compounds as viable solutions in addressing the global AMR crisis.

Seaweed Extract against Drug-Resistant Pathogens

Antimicrobial Potentials Against MDR Strains

The emergence of multidrug-resistant (MDR) strains poses a grave threat to global public health. MDR pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans*, have shown resistance to commonly used antibiotics and antifungal agents, making infections harder to treat and leading to increased mortality, healthcare costs, and prolonged hospital stays (11). In light of this crisis, there is an urgent need for alternative antimicrobial agents, and natural products especially those derived from marine sources like seaweeds are receiving increasing attention. This section evaluates the antimicrobial potentials of such agents against MDR strains through laboratory methods, bioassays, and phytochemical analysis. The rapid emergence and dissemination of multi-drug-resistant (MDR) pathogens those resistant to at least one agent in three or more antimicrobial categories represent a growing global health crisis. According to the World Health Organization, antimicrobial resistance (AMR) is one of the top 10 global public health threats facing humanity. The alarming increase in resistance among bacterial and fungal pathogens has prompted researchers to explore alternative strategies, including natural sources for novel antimicrobial compounds. Among these, marine macroalgae (seaweeds) have received considerable attention due to their abundant bioactive metabolites with potential antimicrobial properties.

Several *in vitro* and *in vivo* studies have established the efficacy of seaweed extracts against MDR bacterial strains. Aqueous and organic solvent extracts from species such as *Sargassum*

muticum, *Gracilaria edulis*, and *Caulerpa racemosa* have exhibited significant inhibitory effects against MRSA, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* notoriously drug-resistant nosocomial pathogens. A study by (12) demonstrated that methanolic extracts of *Ulva lactuca* and *Padina tetrastromatica* inhibited MRSA and *E. coli* with zones of inhibition comparable to ciprofloxacin. The minimum inhibitory concentrations (MICs) ranged from 62.5 to 250 µg/mL, suggesting strong antimicrobial potential. found that ethyl acetate extracts of *Sargassum latifolium* showed significant bactericidal effects against carbapenem-resistant *Klebsiella pneumoniae.* Moreover, seaweed nanoparticles synthesized from polysaccharide matrices have enhanced the antimicrobial potential. For instance, silver nanoparticles derived from *Gracilaria edulis* polysaccharides exhibited synergistic effects against MDR *Pseudomonas* spp. and *Acinetobacter* spp. when combined with traditional antibiotics [13].

Fungal infections caused by species such as *Candida albicans*, *Candida auris*, and *Aspergillus fumigatus* are becoming increasingly difficult to treat due to resistance to azoles, echinocandins, and polyenes. Seaweed extracts have shown potential antifungal activity by inhibiting spore germination, disrupting cell walls, and downregulating ergosterol synthesis. In one notable study, methanolic extracts of *Laurencia obtusa* and *Sargassum polycystum* demonstrated inhibitory activity against fluconazole-resistant *Candida albicans* strains with MIC values ranging from 125 to 500 µg/mL [14]. Likewise, aqueous extracts from *Gelidium amansii* inhibited the hyphal growth of azole-resistant *Aspergillus fumigatus*, suggesting promising antifungal properties that warrant further investigation [15].

Marine macroalgae such as *Ulva*, *Sargassum*, and *Gracilaria* are rich in bioactive compounds with notable antifungal properties. Rodrigo *et al.* [16] evaluated ethyl acetate and methanol extracts of these algae against plant pathogens (*Diaporthe eugeniae*, *Pseudopestalotiopsis theae*, and *Lasiodiplodia theobromae*) affecting *Silenus melongena*. While methanol yielded more extract, ethyl acetate extracts particularly from *Ulva* showed superior antifungal activity, inhibiting up to 79.29% of *D. eugeniae* at 2000 ppm. GC-MS analysis identified key compounds such as Dihydroactinidiolide, 4-Hydroxy-2-butanone, and 6,10,14-Trimethylpentadecan-2-one, known for antifungal activity. These findings align with earlier studies on *Ulva lactuca*, affirming consistent bioactivity across species. Solvent polarity and extraction methods significantly influenced outcomes. The study highlights the potential of macroalgae-derived biopesticides as eco-friendly alternatives in plant disease management and encourages further research into their mechanisms and field applications. The growing challenge of antibiotic resistance has prompted increased interest in marine seaweeds as alternative antibacterial agents. Rasyid *et al.* [17] conducted a comparative study to assess the antibacterial properties of *Ulva intestinalis*, *Galaxaura rugosa*, and *Halimeda opuntia* from West Nusa Tenggara, Indonesia. Using methanol, chloroform, ethanol, and diethyl ether as extraction solvents, the study revealed significant species- and solvent-dependent differences in antibacterial activity. Notably, chloroform and methanol extracts of *G. rugosa* exhibited strong inhibition against *Staphylococcus aureus*, *Bacillus subtilis*, and *Vibrio eltor*, with inhibition zones ranging from 8 to 10.5 mm. Methanol extracts of *U. intestinalis* also demonstrated notable efficacy, while *H. opuntia* showed limited activity, only against *V. eltor*.

These results are consistent with prior studies, such as those by Fayzi *et al.* [18], Kolanjinathan et al. [19], and Srikong *et al*. [20], which confirmed the antimicrobial activity of various seaweed species. The antibacterial effects are attributed to compounds like

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phenolics, flavonoids, terpenoids, and polysaccharides, which interfere with bacterial cell structures and functions. The observed differences in activity between Gram-positive and Gram-negative bacteria highlight the importance of compound specificity. Overall, seaweeds represent a valuable resource in the search for eco-friendly antibacterial agents.

The growing challenge of antimicrobial resistance and the ban on in-feed antibiotics have intensified the search for natural alternatives in livestock health management. Marine macroalgae, rich in bioactive compounds, offer promising potential. Hejna *et al.* [21] evaluated the antibacterial and antioxidant activities of extracts from *Ascophyllum nodosum* (AN), *Palmaria palmata* (PP), and *Ulva lactuca* (UL), including binary combinations. AN and UL exhibited significant antibacterial activity against *Escherichia coli* strains F4+ and F18+, particularly at higher doses (23 mg/mL), while PP showed only mild inhibition during early incubation. Interestingly, mixtures such as ANUL and PPUL failed to display synergistic effects, possibly due to antagonistic interactions. AN recorded the highest polyphenol content (4951.53 µg TAE/g), correlating with strong antioxidant capacity confirmed by DPPH and reducing power assays. AN also demonstrated the lowest EC_{50} value (55.86 mg/mL) in DPPH scavenging, highlighting its potent free radical-neutralizing ability. Mechanisms behind its antibacterial effects included membrane disruption and inhibition of oxidative phosphorylation. However, low digestibility (20.05%) of AN limits its direct dietary use. The study aligns with previous findings supporting AN's bioactivity and also confirms UL's antibacterial role. PP's limited efficacy may be due to extraction issues or complex biochemical factors.

Siddhnath and Kaur [22] evaluated the antimicrobial activity of five seaweeds from the Tuticorin coast using various solvent extracts. Petroleum ether extracts, particularly from *Caulerpa scalpelliformis*, showed strong antifungal activity against *Candida albicans*, surpassing fluconazole. *Ulva lactuca* and *Padina tetrastromatica* also exhibited notable antifungal effects. Methanol and chloroform extracts from *Padina tetrastromatica* and *Stoechospermum marginatum* showed moderate antibacterial activity against Gram-negative bacteria. No extracts were effective against *Staphylococcus aureus*. The antimicrobial properties were linked to lipophilic secondary metabolites like flavonoids and phenols. The study highlights seaweeds as promising natural sources of antimicrobial agents, especially via non-polar solvent extraction.

Patil and Nakade [23] explored the antimicrobial potential of *Ceramium diaphanum* extracts from the Kunkeshwar coast. Both ethanol (A1) and chloroform (A2) extracts showed antibacterial activity against *E. coli*, *P. aeruginosa*, *V. cholerae*, *S. aureus*, and MRSA, with chloroform extract demonstrating superior inhibition, especially against *S. aureus* (20 mm). Antifungal assays against *Aspergillus flavus* revealed moderate inhibition, with ethanol extract showing slightly better activity. The effectiveness was attributed to phytochemicals like flavonoids, halogenated compounds, and sulfated polysaccharides. The study highlights *C. diaphanum* as a promising source of antimicrobial agents, with solvent polarity influencing extraction efficiency and bioactivity.

Maray *et al.* [24] examined ulvan extracted from *Ulva lactuca*, revealing its broad pharmacological potential. The ulvan yield was 26.53% with high sugar and sulfate content. It showed strong cytotoxicity against lung (A-549) and prostate (PC-3) cancer cells, with greater potency against A-549. Antiviral assays showed moderate inhibition of Hepatitis A

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virus, but no activity against Adenovirus. Ulvan also displayed antibacterial activity against several pathogens but was ineffective against *S. aureus* and *E. coli*. Antioxidant activity was weak, likely due to low reducing groups. Despite limitations, ulvan demonstrates promise for anticancer and antimicrobial applications. Indraningrat *et al.* [25] investigated the antibacterial potential of *Pseudomonas aeruginosa* ISP1RL4, isolated from red seaweed *Eucheuma cottonii*. The crude ethyl acetate extract showed moderate activity against MDR strains like MRSA and ESBL-producing *E. coli* and *K. pneumoniae*, but was ineffective against *A. baumannii*. Bioassay-guided TLC revealed one active fraction (Rf = 0.06). LC-HRMS identified 11 antibacterial compounds, with 2-Amino-1,3,4-octadecanetriol being most abundant. Other compounds included ceramides, sorbitol derivatives, and short-chain alcohols. The study highlights marine bacteria as promising antibacterial sources and stresses the need for further compound isolation, structural confirmation, and toxicity evaluation.

Ali *et al.* [26] evaluated the antibacterial and antioxidant properties of four seaweeds from the Egyptian Red Sea. *Padina pavonica* showed the strongest antibacterial activity, with its DCM extract surpassing tetracycline against *E. coli*. *Turbinaria ornata* and *Ulva lactuca* also inhibited *S. aureus*. No extracts affected *Candida albicans*. DPPH assays revealed high antioxidant activity in DCM extracts of *T. ornata* and *P. pavonica*, with low IC50 values. Ethyl acetate extracts, especially from *A. fragilis*, were less effective. Brown algae demonstrated superior bioactivity due to higher polyphenol content, confirming their potential as sources of natural therapeutic agents.

Solvent Extraction Techniques and Screening Methods in Evaluating Antimicrobial Activity

Marine macroalgae, commonly known as seaweeds, have been recognized as rich reservoirs of bioactive secondary metabolites with antimicrobial properties. To identify and utilize these bioactive compounds, solvent extraction techniques are employed to isolate functional molecules from seaweed biomass. Following extraction, antimicrobial screening methods are used to assess the efficacy of these extracts against microbial strains. This article comprehensively discusses solvent extraction techniques and screening methods used to evaluate antimicrobial activity, especially targeting MDR pathogens. The exploration of natural products for antimicrobial activity has grown significantly due to the increasing threat posed by multidrug-resistant (MDR) pathogens. Marine macroalgae, commonly known as seaweeds, are among the most promising natural sources of bioactive compounds with antimicrobial potential. Before these bioactives can be evaluated or utilized, they must be carefully extracted from the algal matrix using appropriate solvent extraction techniques. This is followed by a series of antimicrobial screening assays to determine their efficacy against a range of microbial strains. Together, solvent extraction and screening methods form the foundational steps in the discovery and validation of natural antimicrobials, especially from marine organisms.

Solvent extraction is a method used to isolate bioactive compounds from dried seaweed biomass using various organic or aqueous solvents. The efficiency of the extraction largely depends on the choice of solvent, its polarity, the nature of the target compounds, and the extraction conditions such as temperature, duration, and particle size of the seaweed. The polarity of the solvent plays a key role in solubilizing different classes of compounds. For example, non-polar solvents such as hexane and chloroform are effective in extracting lipophilic substances like sterols and terpenoids, whereas polar solvents like methanol, ethanol, and water are suitable for extracting hydrophilic compounds such as polyphenols,

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flavonoids, and sulfated polysaccharides (27,28). Several techniques are available for solvent extraction, each with specific advantages and limitations. The simplest and most traditional method is maceration, where dried seaweed is soaked in a solvent for several hours or days at room temperature. This method is suitable for heat-sensitive compounds but often results in lower yields and is time-consuming. (28) and used methanol maceration to extract antibacterial compounds from *Gracilaria edulis*, demonstrating notable activity against *Staphylococcus aureus* and *Escherichia coli*. Another widely used method is Soxhlet extraction, which involves continuous solvent reflux and is effective in exhaustive extraction of compounds. (28) applied Soxhlet extraction using ethanol on *Sargassum wightii* and observed potent antibacterial effects against MDR *Pseudomonas aeruginosa*. Despite its efficiency, Soxhlet extraction involves prolonged heating, which may degrade thermolabile bioactives.

Ultrasonic-assisted extraction (UAE) has emerged as an effective modern alternative, using ultrasonic waves to generate cavitation bubbles that disrupt cell walls and enhance the release of intracellular compounds into the solvent. This technique significantly reduces extraction time and increases yield. (29) employed UAE to extract polyphenols from *Ulva lactuca*, resulting in strong antimicrobial activity against *Candida albicans* and Gram-negative bacteria. Similarly, microwave-assisted extraction (MAE) and pressurized liquid extraction (PLE) are also being explored for their efficiency and reduced solvent usage. One of the most advanced and eco-friendly techniques is supercritical fluid extraction (SFE), particularly using supercritical carbon dioxide (CO_2). This method allows selective extraction of non-polar compounds without the use of toxic solvents. (28) successfully used SFE to isolate bioactive compounds from various marine algae, revealing significant antibacterial properties with minimal environmental impact. However, the high cost and technical complexity limit its widespread use.

A common approach to maximize the range of extracted bioactives is sequential solvent extraction using solvents of increasing polarity. This allows selective fractionation of compounds, enabling targeted screening and characterization. (30) used this approach on *Padina pavonica*, extracting with hexane, chloroform, ethyl acetate, methanol, and water. They found the methanol and ethyl acetate fractions to be the most effective against both Gram-positive and Gram-negative bacteria. Once extracts are obtained, their antimicrobial properties must be validated through appropriate in vitro screening methods. These methods can be broadly categorized into qualitative and quantitative assays. The agar well diffusion method is one of the most common qualitative techniques, where wells are cut into agar plates inoculated with test organisms, and extracts are introduced into the wells. The diameter of the zone of inhibition (ZOI) around the well indicates antimicrobial potency (31) used this method to evaluate methanolic extracts of *Turbinaria conoides*, which demonstrated ZOIs up to 18 mm against *S. aureus*.

The disc diffusion method is similar but uses filter paper discs impregnated with extracts placed on the agar surface. While both methods are simple and cost-effective, they may not accurately reflect the activity of non-polar compounds due to limited diffusion in agar. Hence, they are primarily used for preliminary screening. For more accurate and quantitative evaluation, broth microdilution is preferred. This method involves preparing serial dilutions of the extract in microtiter plates and inoculating with standardized bacterial suspensions. After incubation, the minimum inhibitory concentration (MIC) is recorded as the lowest concentration that inhibits visible microbial growth (32). Following MIC determination, the

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minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFC) can be assessed by sub culturing the non-growth wells onto fresh agar. The absence of microbial colonies indicates bactericidal or fungicidal activity. These quantitative assays are essential for determining the therapeutic potential of the extract.

In addition to planktonic bacteria, biofilm-forming pathogens represent a major clinical challenge, as biofilms confer increased resistance to antibiotics. Hence, evaluating the antibiofilm activity of seaweed extracts is crucial. Methods such as the crystal violet assay, confocal laser scanning microscopy, and scanning electron microscopy (SEM) are used to assess biofilm formation and disruption. (33) demonstrated that sulfated polysaccharides from red algae could significantly inhibit biofilm formation in *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Time-kill assays provide further insight into the kinetics of microbial inhibition. These involve measuring colony-forming units (CFUs) at various time intervals after exposure to the extract. A ≥ 3 $\log_{10}$ reduction in CFUs compared to the initial count is considered bactericidal. Finally, synergistic activity testing, such as checkerboard assays, is used to evaluate the interaction between seaweed extracts and conventional antibiotics. The fractional inhibitory concentration (FIC) index is calculated, with values ≤ 0.5 indicating synergism, which can help enhance antibiotic efficacy against MDR strains.

Despite their effectiveness, these screening methods face certain challenges. Variability in microbial strain resistance profiles, extract composition, and solvent residues can influence results. Therefore, standardization of extraction protocols and assay conditions is essential to ensure reproducibility and comparability of findings across different studies in Table.1.

Table 1: Classification of Seaweed Studies Based on Type and Bioactivities

S. No.	Seaweed Type	Species Studied	Bioactivity Studied	Target Pathogens
1	Green Algae	*Caulerpa sertularioides*	Anti-inflammatory	General inflammation
2	Green Algae	*Caulerpa lentillifera*	Antioxidant	ROS scavenging
3	Brown Algae	*Sargassum polycystum*, *Padina* spp.	Antibacterial, Antioxidant	MDR bacteria, fish pathogens
4	Red Algae	*Eucheuma denticulatum*, *Laurencia obtusa*	Antibacterial, Antifungal	Drug-resistant fungi, bacteria
5	Red Algae	*Ceramium diaphanum*	Antibacterial	Pathogenic bacteria
6	Green Algae	*Ulva lactuca*, *Ulva intestinalis*	Antioxidant, Antimicrobial	Fungal & bacterial strains
7	Mixed Seaweeds	*Ulva*, *Gracilaria*, *Sargassum*	Antifungal	Fungal pathogens
8	Brown Algae	*Himanthalia elongata*	Antimicrobial, Antioxidant	General pathogens
9	Brown Algae	*Padina tetrastromatica*, *Padina pavonica*	Antibacterial	MDR strains
10	Green Algae	*Ulva* sp. (Ulvan	Antiviral,	Multiple including cancer

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		extract)	Antioxidant	cells
11	Various (Mixed)	Red, green, brown algae (multiple studies)	Antibacterial, Antifungal	MDR bacteria, fungi
12	Brown Algae	*Ecklonia cava*	Antibacterial	MRSA
13	Brown Algae	Fucoidan (extracted)	Therapeutic, Antibacterial	Hypertension, MDR pathogens
14	Brown Algae	Algal polysaccharides, phlorotannins	Antiviral, Antibacterial	Viral strains, *S. aureus*, etc.
15	Green Algae	*Ulva lactuca* (Ultrasound extract)	Biological activity	Various
16	Red Algae (via bacteria)	*Eucheuma cottonii* (host)	Indirect Antibacterial	MDR bacteria (via *Pseudomonas*)

Mechanism of Microbial Inhibition by Seaweed Bioactive Compounds

The mechanism of microbial inhibition refers to the ways in which antimicrobial agents act upon microorganisms to suppress their growth, reproduction, or survival. In the face of rising antimicrobial resistance, particularly among multidrug-resistant (MDR) bacterial and fungal strains, the identification of new agents and understanding their mechanisms of action have become central to the development of next-generation therapies.

Natural products, especially those derived from marine macroalgae (seaweeds), have shown considerable promise as sources of antimicrobial compounds with diverse mechanisms of inhibition. These compounds disrupt microbial viability through various pathways, including cell wall and membrane disruption, protein synthesis inhibition, enzyme inhibition, interference with nucleic acid replication, quorum sensing inhibition, and biofilm disruption. One of the most common and well-documented mechanisms of microbial inhibition by seaweed-derived compounds is the disruption of microbial cell walls and membranes.

Many bioactive molecules, such as terpenoids, fatty acids, and phlorotannins, are amphipathic and interact directly with the lipid bilayer of microbial membranes. This interaction compromises membrane integrity, causing leakage of intracellular components such as ions, ATP, and nucleic acids, eventually leading to cell lysis. For example, studies on methanolic extracts of brown seaweed *Padina tetrastromatica* revealed potent bactericidal activity attributed to terpenoid content, which disrupted the membrane of *Pseudomonas aeruginosa* (27).

Similar observations were reported by (29) on extracts of *Sargassum wightii*, which significantly altered the membrane permeability of MDR bacteria. Inhibition of protein synthesis is another critical mechanism through which seaweed compounds exert antimicrobial effects. Certain algal metabolites can interfere with ribosomal function, preventing the translation of mRNA into proteins. For example, alkaloids and some phlorotannins extracted from red and brown seaweeds have been shown to bind to bacterial ribosomal subunits, impeding polypeptide elongation. This leads to inhibition of essential protein formation required for microbial survival and proliferation. Although this mechanism is more commonly associated with antibiotics like tetracyclines and macrolides, some seaweed-derived compounds exhibit similar behavior in disrupting microbial biosynthetic machinery (4).

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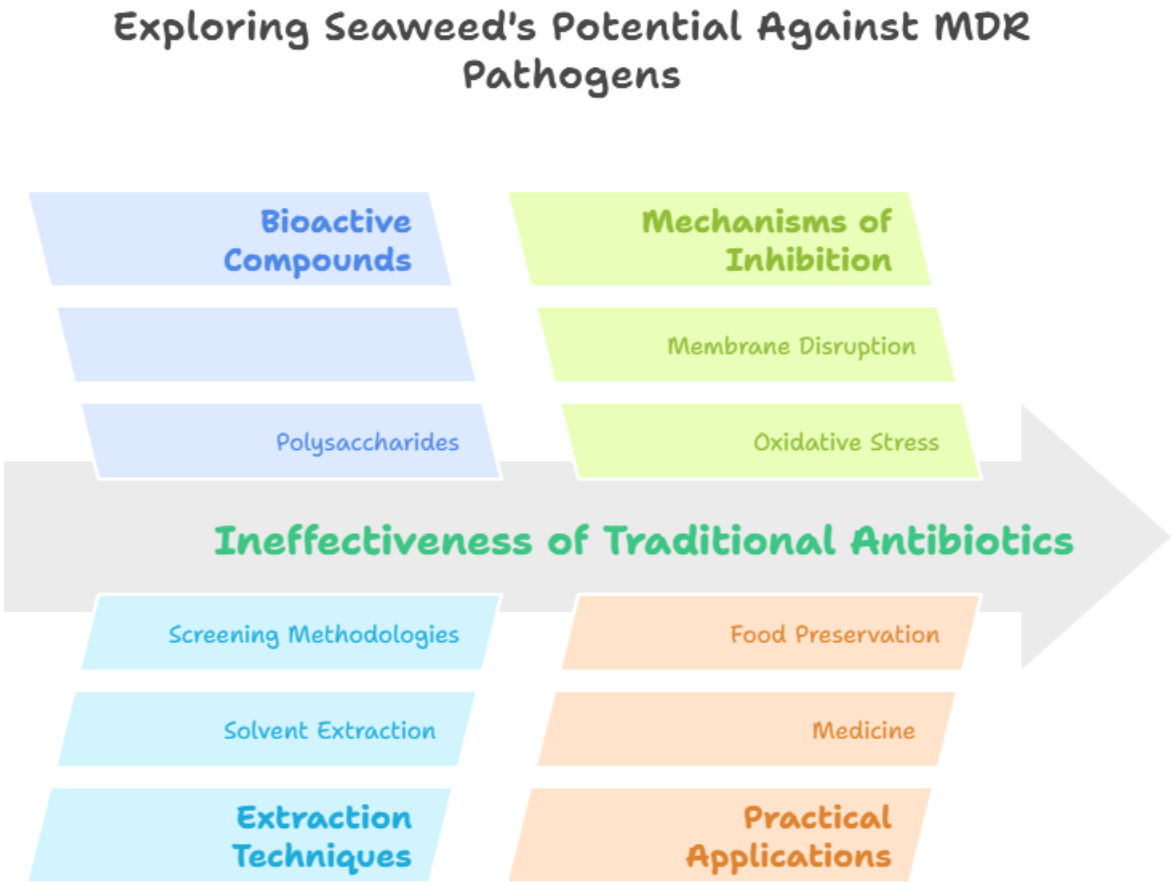

Moreover, nucleic acid synthesis interference plays a crucial role in microbial inhibition by certain seaweed extracts. Some secondary metabolites inhibit DNA replication or transcription by targeting DNA gyrase or RNA polymerase enzymes. Polyphenolic compounds, especially from brown algae like *Fucus vesiculosus* and *Sargassum muticum*, can bind to nucleic acids and block DNA synthesis pathways. Inhibition of DNA replication impairs microbial cell division, resulting in bacteriostatic or bactericidal outcomes. According to (34), extracts from *Gracilaria edulis* showed DNA-binding potential, resulting in decreased replication activity in *E. coli* and *S. aureus*. A growing body of evidence also supports the inhibition of microbial enzymes as a mechanism of action. Many microbial processes rely on key metabolic enzymes, such as β-lactamases, oxidoreductases, and proteases. Seaweed-derived polyphenols and sulfated polysaccharides have been shown to inhibit such enzymes by forming hydrogen bonds with the active sites, thereby reducing catalytic efficiency. For example, fucoidan from brown algae such as *Laminaria japonica* has been reported to inhibit bacterial urease and fungal glucosidases, limiting pathogen viability (35). Enzyme inhibition can particularly weaken MDR pathogens, which often overexpress certain enzymes as resistance mechanisms.

An additional target in microbial inhibition is quorum sensing (QS), which refers to cell-to-cell communication used by bacteria to regulate gene expression in response to population density. QS regulates the production of virulence factors and biofilm formation. Disruption of QS, known as quorum quenching, prevents coordinated microbial behaviors that are critical to pathogenicity. Algal compounds such as brominated furanones from red seaweed *Delisea pulchra* are known to interfere with the bacterial QS system by mimicking signal molecules and competitively inhibiting their binding to receptors. This results in reduced expression of

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virulence genes and inhibition of biofilm development (36). Such antivirulence strategies are increasingly attractive for targeting MDR strains without promoting resistance.

Biofilm inhibition is another major mechanism by which seaweed extracts combat microbial infections. Biofilms are complex microbial communities embedded in a protective extracellular matrix, rendering them highly resistant to antibiotics. Many seaweed-derived compounds, particularly sulfated polysaccharides like carrageenan and fucoidan, interfere with the initial stages of biofilm formation such as bacterial adhesion and surface colonization. reported that sulfated galactans from red algae disrupted biofilms of *P. aeruginosa* and *S. aureus*, effectively reducing microbial load. The compounds altered cell-surface hydrophobicity and interfered with extracellular polymeric substance (EPS) production, key elements in biofilm stability. Furthermore, oxidative stress induction has been identified as an indirect mechanism of microbial inhibition by seaweed extracts. Certain polyphenols, flavonoids, and carotenoids extracted from marine algae generate reactive oxygen species (ROS) inside microbial cells. These ROS can damage nucleic acids, proteins, and lipids, leading to cell death. Extracts from green seaweed *Ulva lactuca* have shown ROS-mediated antifungal activity against *Candida albicans* by inducing mitochondrial dysfunction and membrane depolarization (30). The pro-oxidant effect is especially valuable in targeting fungal pathogens, which often resist conventional antifungal drugs.

Another promising mechanism is the chelation of essential metal ions, which are required by microbes for enzymatic and metabolic functions. Seaweed polyphenols, particularly tannins, have strong metal-binding capacities and can sequester ions such as iron, zinc, and magnesium. The deprivation of these ions impairs microbial metabolism and inhibits growth. For example, chelation of iron limits the activity of catalase and peroxidase enzymes, leading to accumulation of toxic metabolites within microbial cells. This strategy offers a nutritional immunity-like approach, similar to how host organisms restrict metal access to pathogens. Additionally, some marine-derived antimicrobials operate via multi-target mechanisms, which is highly beneficial for combating MDR strains that often employ multiple resistance strategies. For example, the combination of membrane disruption, enzyme inhibition, and oxidative stress induction reduces the likelihood of microbial adaptation or resistance development. Multi-targeting is often observed in crude or semi-purified seaweed extracts containing a complex mixture of terpenes, phenols, and alkaloids acting synergistically. (31) emphasized this synergistic action in their evaluation of *Turbinaria conoides* extract, which effectively inhibited a wide range of Gram-negative and Gram-positive MDR strains.

In addition to these mechanisms, research is expanding into genomic and transcriptomic changes induced by algal compounds in microbial cells. Recent studies have shown that exposure to seaweed extracts can downregulate genes responsible for antibiotic resistance, virulence, and efflux pump expression. For instance, treatment with algal phlorotannins was found to suppress expression of mecA in MRSA strains, thereby restoring susceptibility to β-lactam antibiotics (37). This opens the door to using seaweed compounds as adjuvants or resistance modulators alongside conventional antibiotics. In conclusion, the mechanism of microbial inhibition by seaweed-derived bioactive compounds is multifaceted and involves diverse biochemical and molecular pathways. These include disruption of membranes, inhibition of protein and nucleic acid synthesis, enzymatic inactivation, interference with quorum sensing, inhibition of biofilms, and induction of oxidative stress. The complex and often synergistic nature of these mechanisms provides a strong advantage in tackling MDR pathogens, offering both direct antimicrobial action and modulation of resistance

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mechanisms. Continued research into the molecular basis of these effects, along with identification of specific active compounds, is critical for harnessing the full therapeutic potential of seaweeds in antimicrobial drug development.

Application of Seaweed Extracts in Medicine and Food Preservation

In the field of medicine, seaweed-derived compounds are of particular interest due to their multifaceted bioactivities and low toxicity to human cells. One of the most notable applications is in the development of antimicrobial agents against drug-resistant pathogens. For instance, phlorotannins extracted from brown seaweeds such as *Ecklonia cava* and *Fucus vesiculosus* have shown significant antimicrobial effects against multidrug-resistant (MDR) *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* by disrupting microbial cell membranes and inhibiting essential metabolic enzymes (26). Similarly, sulfated polysaccharides such as fucoidan and carrageenan have been reported to exhibit not only antibacterial but also antiviral activity, including inhibition of human immunodeficiency virus (HIV), herpes simplex virus (HSV), and influenza viruses by preventing viral attachment and entry into host cells (38). These findings underscore the potential of seaweed extracts as a foundation for next-generation antivirals and antibiotics, particularly given their low cytotoxicity and broad-spectrum efficacy.

Beyond direct antimicrobial use, seaweed-derived compounds are also being developed as adjuvants or resistance-modifying agents that can restore the activity of existing antibiotics. Certain phenolic compounds have been found to inhibit bacterial efflux pumps or downregulate resistance genes, thereby sensitizing bacteria to conventional antibiotion (39). For example, studies have shown that combining algal polyphenols with β-lactam antibiotics enhances bactericidal effects against methicillin-resistant *S. aureus* (MRSA), pointing to a valuable synergistic application in combating MDR infections. Moreover, the anti-inflammatory properties of seaweed compounds further complement their antimicrobial activity in treating chronic wounds and skin infections. Fucoidan, in particular, has demonstrated anti-inflammatory and pro-angiogenic effects in wound healing applications, making it a promising ingredient in bioactive wound dressings and tissue regeneration scaffolds (40).

In pharmaceutical formulations, seaweed polysaccharides such as alginate and carrageenan are widely used as drug carriers due to their gel-forming ability, biocompatibility, and controlled-release properties. Alginate-based hydrogels, derived from brown algae, are used in drug delivery systems for oral, topical, and injectable applications. They protect sensitive drugs from degradation in the gastrointestinal tract and enable sustained drug release. Carrageenan, obtained from red seaweeds, is used to form microcapsules and films that encapsulate probiotics, peptides, and other therapeutic molecules (30). The mucoadhesive properties of these polysaccharides also make them suitable for nasal and buccal drug delivery routes. In oncology, certain algal metabolites have demonstrated cytotoxicity against cancer cell lines through mechanisms including induction of apoptosis, inhibition of angiogenesis, and suppression of tumor-promoting pathways. For instance, fucoxanthin, a carotenoid pigment found in brown algae like *Undaria pinnatifida*, has been reported to induce cell cycle arrest and apoptosis in breast, prostate, and colon cancer cells (41). Though still in early stages, these findings suggest future clinical applications of seaweed compounds in anticancer therapies either as primary agents or adjuvants.

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In the domain of food preservation, seaweed extracts offer sustainable, natural alternatives to synthetic preservatives that are often associated with adverse health effects. Due to their antimicrobial and antioxidant properties, seaweed-derived compounds are now being incorporated into food packaging materials and directly into food products to extend shelf life and enhance safety. For example, phenolic-rich extracts from *Ascophyllum nodosum* and *Laminaria digitata* have been used as natural preservatives in meat and dairy products, significantly inhibiting the growth of *Listeria monocytogenes* and spoilage bacteria (32). Similarly, ethanol extracts of *Ulva lactuca* and *Gracilaria verrucosa* have demonstrated antifungal activity against foodborne fungi such as *Aspergillus* and *Penicillium* species, making them effective as biofungicides in baked goods and produce coatings (42). Another application in food preservation is the development of active edible films and coatings using seaweed polysaccharides such as alginate, agar, and carrageenan. These biopolymers not only form physical barriers to moisture and oxygen but also serve as carriers for embedded antimicrobial and antioxidant agents. Alginate-based films infused with essential oils or seaweed phenolics have shown enhanced activity against *Salmonella*, *E. coli*, and spoilage yeasts, particularly in seafood and fresh produce packaging (43). Such innovations contribute to food safety and shelf-life extension while reducing the need for synthetic preservatives.

Moreover, seaweed-derived antioxidants such as polyphenols and carotenoids help in preventing lipid oxidation in high-fat foods like meats and oils. Oxidative rancidity is a major cause of food spoilage and off-flavors, and natural antioxidants from seaweeds can delay or inhibit this process. Studies have shown that incorporation of *Fucus vesiculosus* and *Palmaria palmata* extracts into beef and poultry products significantly reduced peroxide values and thiobarbituric acid reactive substances (TBARS), indicating effective lipid stabilization (44). Additionally, fucoidan and laminarin not only act as antimicrobials but also enhance the functional and nutritional value of foods due to their prebiotic and immune-boosting properties. Beyond preservative functions, seaweed bioactives are also used as functional ingredients in food formulations due to their health-promoting effects. For instance, fucoidan and phlorotannins have been incorporated into functional beverages, dairy products, and dietary supplements to provide antioxidant, anti-inflammatory, and cholesterol-lowering benefits (45). These ingredients align with the global trend toward nutraceuticals and clean-label food products, promoting health and wellness through diet.

CONCLUSION

Evaluating the antimicrobial potentials of seaweed extracts and other natural products against MDR strains is a promising frontier in biomedical research. These evaluations not only identify alternative therapeutics but also contribute to the understanding of resistance mechanisms and drug development. Seaweed-derived compounds, due to their broad-spectrum activity, biodegradability, and eco-friendliness, represent a sustainable solution to the growing threat of antimicrobial resistance. Solvent extraction techniques and antimicrobial screening methods are essential tools in discovering novel antimicrobials from natural sources like seaweeds. The selection of extraction method and solvent greatly influences the range and activity of bioactive compounds. Similarly, precise and reproducible screening methods are vital to accurately evaluate antimicrobial potential. By integrating both traditional and advanced techniques, researchers can identify promising candidates to combat MDR pathogens. In conclusion, the bioactive compounds derived from seaweeds offer immense potential for application in both medicine and food preservation. In the medical field, they serve as antimicrobial agents, antivirals, anticancer agents, wound healing enhancers, and drug delivery vehicles. Their ability to combat MDR pathogens and modulate

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host immune responses makes them especially valuable in the era of antibiotic resistance. In the food industry, seaweed extracts are employed as natural preservatives, antioxidants, and components of edible packaging, aligning with consumer demand for sustainable, clean-label products. The continued integration of seaweed-derived compounds into pharmaceuticals and food systems represents a promising frontier for public health, food safety, and biotechnology. Further research and clinical validation will pave the way for their broader commercial adoption and therapeutic use.

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