CHAPTER 13

Antimicrobial Properties of Seaweeds

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Abstract: Antimicrobial activity is defined as the ability to destroy or inhibit the growth of microorganisms. Antimicrobial compounds are naturally occurring or synthetic organic compounds having antimicrobial activity. Recently, scientists have discovered many pharmaceutically active compounds that have antibacterial, antifungal, antiviral and antiprotozoal activities in seaweeds. To thrive in various environmental stresses, seaweed produces different metabolites such as polyphenols, polysaccharides, proteins, fatty acids, and pigments. These bioactive compounds are responsible for the antimicrobial activity exerted by seaweed. The antimicrobial activity of seaweed is influenced by various factors, such as the type of seaweed extract used, the target microorganisms, and the environmental conditions. The composition of the bioactive compounds from seaweed may depend on the extraction method and the solvent. It also depends on the seaweed sample, such as fresh or dried sample. Different mechanisms are followed by seaweed extract to acquire antimicrobial activities. Seaweed extracts exhibit various inhibition mechanisms, including disruption of the cell membrane, inhibition of target microorganism enzymes, and prevention of microorganism association with cellular receptors of the host cell. The location, salinity, temperature, *etc.* of the marine environment may affect the chemical composition of the bioactive compounds present in the seaweeds. The antimicrobial activity of seaweed can be evaluated in both *in vitro* and *in vivo* assays. Antimicrobial susceptibility tests and antimicrobial resistance tests are carried out by *in vitro* methods. The antimicrobial activity of seaweed can be a promising source in many applications, such as therapeutic applications, food industries, aquaculture, and biofouling.

Keywords: Antimicrobial, Antibacterial, Antifungal, Antiviral, Bioactive compound, Seaweed.

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INTRODUCTION

Antimicrobial refers to destroying (microbicidal) or inhibiting (microbistatic) the growth of a particular microorganism or group of microorganisms, especially if they are pathogenic to humans and animals. Basically, bacteria, viruses, fungi and parasites are the major pathogenic microorganisms. Antimicrobial compounds are naturally occurring or synthetic organic compounds, and they work at a cellular level to disrupt and prevent the growth of the respective microorganisms continuously (Fig. **1**). Some antimicrobial compounds are known for their ability to function at very low concentrations (*e.g.*, antibiotics in micrograms scale) [1]. Thousands of years ago, ancient Egyptian, Greek, and Asian cultures used antimicrobial agents to treat some infections. Later in the 19th century, Louis Pasteur and other microbiologists discovered the antagonism of bacteria, which led to the golden era of antimicrobial therapy [2].

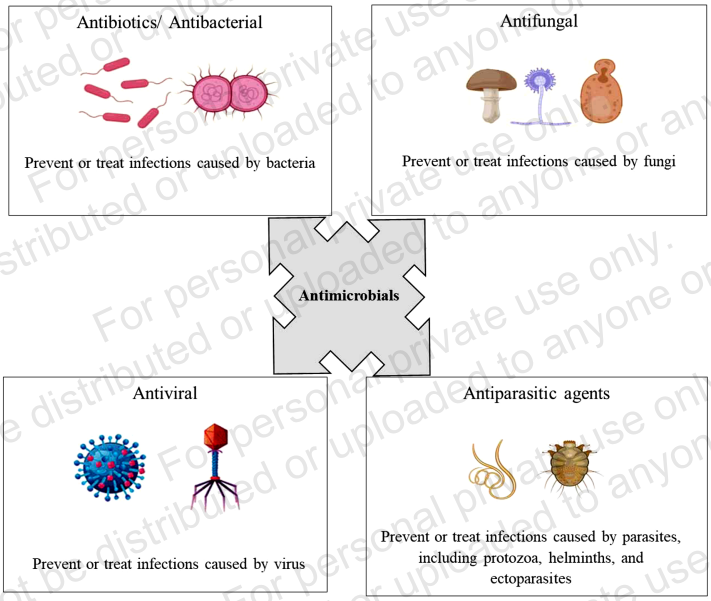

Fig. (1). Types of antimicrobial agents.

The ability of antimicrobials to inhibit or destroy microorganisms has applications in various sectors, including disease control in healthcare, food production, agriculture, aquaculture, cosmetics, animal feed production, and industries that use antifouling agents. The health sector utilizes antimicrobials to combat antibiotic-resistant pathogenic microorganisms [3]. In the food industry, antimicrobials are used as a food supplement for animals and to prevent food spoilage from microorganisms [4, 5]. Animal feed industry antimicrobial agents

are used for therapeutic purposes [6]. Antimicrobial peptides are used in plant disease control and the production of biopesticides in agricultural industries [7]. Antimicrobials are reported to be used in aquaculture to control diseases [8]. According to Nabavi *et al*. (2015), antimicrobials are also used in the cosmetics industry [9].

Food and cosmetics industries are demanding more naturally originated ingredients and preservatives. In the food industry, synthetic antimicrobial compounds such as ZnO nanoparticles are reported to have negative health effects [10]. Pathogenic microorganisms can cause significant economic losses due to their negative impact on the aquaculture and agriculture industries. However, conventional antimicrobial agents used to exterminate these harmful microbes can have negative effects on the product and the environment [11].

The chemical industry, in the production of bio-fouling preventive agents, is also reported to exploit harmful antimicrobial agents [11]. According to Banerjee *et al*. (2011), silver nanoparticles are used as antimicrobials to prevent befouling, which are found to be toxic to mammalian cells [12]. Biofoul preventive paints are reported to contain toxic compounds, such as As, Hg or TBT (tributyltin) [11].

Discerningly, these problems need to be necessarily addressed. Hence, it has led to the discovery of better environmentally friendly alternatives that are more potent with minimal toxicity, lesser side effects and good bioavailability [11].

Naturally derived compounds are reported to be a promising source for drug development due to the presence of a greater number of chiral centers [13]. According to Li *et al*. (2015), chiral centers are important for the recognition of biologically active molecules and their interaction with their target [14]. Therefore, different living organisms from terrestrial and marine systems, such as plants, animals, fungi, and micro and macroalgae (seaweed), are under the spotlight for discovering natural antimicrobial agents [15].

Seaweed as Candidates for the Development of Antimicrobials

The marine environment accounts for more than 70% of Earth's total surface and hosts a broad variety of genetically and biochemically unique marine plants and animals. Before 1950, the therapeutic properties of marine resources were only used in traditional and folk medicine [16]. Later, the concept of 'drugs from the sea' emerged, and many bioactive metabolites were discovered from sources such as macroalgae [17], sponges [18], fishes, prawns, shells, marine microorganisms, *etc* [19]. Many novel compounds from marine plants and animals were identified during the period between 1987-1997, out of which, 35% were from algae [20]. Among algae, seaweed has obtained interest among the scientific community in

the recent past. In general, they are collectively known as seaweeds. Seaweeds are photosynthetic, multicellular aquatic organisms found in almost every aquatic region, especially producing a large portion of marine biomass [15, 21]. Seaweed includes members of the phylum Rhodophyta (red algae), Chlorophyta (green algae), and Phaeophyta (brown algae). They are rich sources of different bioactive compounds such as polysaccharides, polyunsaturated fatty acids, phlorotannins and other phenolic compounds, carotenoids, minerals, and lipids [11]. Some of them are secondary metabolites that help the seaweed to thrive in their habitat, which can be a highly competitive and hostile marine environment with complex communities and environmental stresses [11]. Seaweed shows many important properties, including pharmacological properties such as antibacterial, antiviral, antiprotozoal, and antifungal activity due to the secondary metabolites. These properties may not be attributed to a single compound but can be related to a combination of metabolites [11]. As marine microalgae are found to be a repository of valuable antimicrobial compounds, seaweed extracts have been extensively studied, and the chemical structure of valuable compounds and their mechanisms of action have been well documented (Table **1**).

Table 1. Summary of the antimicrobial activity of different seaweeds.

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Acantophora nojadiformis (Red Seaweed)	*Candida sp.* *E. faecalis* *P. aeruginosa*	Diethyl ether, ethanol	NI	[22]
	E. coli	Diethyl ether, acetone	NI	
Acrosiphonia coalita (Green Seaweed)	HSV SINV	Methanol	NI	[23]
Alaria nana (Brown Seaweed)	SINV	Methanol	NI	[23]
Analipus japonicas (Brown Seaweed)	HNS	Methanol	NI	[23]
Calliblepharis jubata (Red Seaweed)	*M. tuberculosis*	Chloroform and methanol mixture	NI	[24]
Callithamnion pikeanum (Red Seaweed)	SINV	Methanol	NI	[23]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Caulerpa sp. (Brown Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]
Ceramium rubrum (Red Seaweed)	*E. coli*	Diethyl ether, ethanol	NI	[22]
Colpomenia sniosa (Brown Seaweed)	*E. coli*	Acetone	NI	[22]
Codium fragile (Green Seaweed)	SINV	Methanol	NI	[23]
Corallina vancouveriensis (Red Seaweed)	HSV SINV	Methanol	NI	[23]
Cystoseira mediterraa (Brown Seaweed)	*Candida sp.* *E. faecalis* *P. aeruginosa* *E. coli*	Diethyl ether, ethanol	NI	[22]
Dictyota carbea (Brown Seaweed)	*T. cruzi*	Dichloromethane:methanol (7:3)	NI	[26]
Dictyota linearis (Brown Seaweed)	*Candida sp.* *P. aeruginosa* *E. coli*	Ethanol	NI	[22]
Dictyopters membranacea (Brown Seaweed)	*Candida sp.* *E. faecalis*	Diethyl ether, ethanol	NI	[22]
Dilophys fasciola (Brown Seaweed)	*Bacillus subtilis* *E. coli*	Methanol: Chloroform (2:1 v/v)	Sulfolipids	[27]
Durvillaea antarctica (Brown Seaweed)	TMV	Ethanol	NI	[28]
Ecklonia arborea (Brown Seaweed)	Measles	Ethanol	NI	[29]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Ecklonia cava (Brown Seaweed)	*Trichophyton rubrum*	Methanol	Dieckol	[30]
Ecklonia kurome (Brown Seaweed)	*Compylobactor jejuni*	Methanol	Phlorotannins, dieckol and 8,8'-bieckol	[31]
	E. coli *P. aeruginosa* *Corynebacterium glutamicum* *Staphylococcus aureus* *Bacillus cereus*	Ethanol	NI	[32]
Ecklonia sp. (Brown Seaweed)	*Botrytis cinera*	Water extract	NI	[33]
Ecklonia stolonifera (Brown Seaweed)	*E. coli* *P. aeruginosa* *C. glutamicum* *S. aureus* *B. cereus*	Ethanol	NI	[32]
Ectocarpus siliculosus (Brown Seaweed)	*Candida sp.*	Diethyl ether, ethanol	NI	[22]
	E. faecalis *P. aeruginosa*	Diethyl ether, ethanol, acetone	NI	
	E. coli	Diethyl ether, ethanol	NI	
Egregia menziesii (Brown Seaweed)	SINC HSV	Methanol	NI	[23]
Eisenia bicyclis (Brown alga)	*Propionibacterium acnes*	Methanol	NI	[34]
	murine norovirus	Ethyl acetate	NI	[35]
Enteromorpha intestinalis (Green alage)	SINV	Methanol	NI	[23]
Enteromorpha linza (Green Seaweed)	*Candida sp.* *E. faecalis*	Diethyl ether, ethanol Diethyl ether, ethanol	NI	[22]
	P. aeruginosa	Diethyl ether	NI	
	E. coli	Diethyl ether, ethanol	NI	
	Aspergillus niger	Ethanol	NI	[36]
	P. intermedia *P. gingivalis*	Methanol	NI	[37]
	SINV HSV	Methanol	NI	[23]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Eucheuma denticulatum (Red Seaweed)	*Botrylis cinerea* *Monilinia laxa* *P. digitatum*	n-Hexane, methanol, water	NI	[38]
Fucus evanescens (Brown Seaweed)	*Hemophilus influenza* *Legionella pneumophila* *P. acnes* *Streptococcus pyogenes* *Clostridium difficile* *S. aureus*	Ethyl acetate	NI	[39]
Fucus spirali (Brown Seaweed)	*C. albicans*	Hexane, Acetone:water	Pholotannins	[40]
Galaxoura cylindriea (Red Seaweed)	*B. subtilis* *E. coli*	Methanol: Chloroform (2:1 v/v)	Sulfolipids	[27]
Gelidium pusillum (Red Seaweed)	*B.cinerea* *M. laxa* *P. digitatum*	n-Hexane, methanol, water	NI	[38]
Gelidium sp. (Red Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]
Gracilaria gracilis (Red Seaweed)	*Candida sp.*	Diethyl ether, ethanol, methanol, acetone	NI	[22]
	E. faecalis	Diethyl ether, ethanol, acetone	NI	
	P. aeruginosa	Diethyl ether, ethanol	NI	
	E. coli	Diethyl ether, acetone	NI	
Gracilaria pacifica (Red Seaweed)	SINV HSV	Methanol	NI	[23]
Hedophyllum sessile (Brown Seaweed)	SINV	Methanol	NI	[23]
Himanthalia elongate (Brown Seaweed)	*Listeria monocytogenes*	Methanol	NI	[41]
-	-	-	Fucoxanthin	[42]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
-	-	ethanol/water (70:30 v/v) acidified with 1% formic acid (CH_2O_2)	NI	[43]
-	*Salmonella abony* *E. faecalis* *P. aeruginosa.*	Methanol	NI	[44]
-	*Salmonella* spp. *E. coli* *S. aureus*	ethanol/water (70:30 v/v) acidified with 1% formic acid (CH_2O_2)	NI	[43]
Hydroclathrus clathratus (Brown Seaweed)	HSV-1 HSV-2	Water	NI	[45]
Hypnea musciformis (Red Seaweed)	*C. albicans* *C. guilliermondii*	phosphate buffered saline	NI	[46]
Hypnea sp. (Red Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]
Jania sp. (Red Seaweed)	*B. cinera*	Water	NI	[33]
Kappaphycus alvarezii (Red Seaweed)	*P. gingivalis*		Bromophenol	[47]
Laminaria digitata (Brown Seaweed)	*B. cinerea* *M. laxa* *P. digitatum*	n-Hexane, methanol, water	NI	[38]
Laminaria japonica (Brown Seaweed)	*Fusobacterium nucleatum* *Actinomyces naeslundii* *Actinomyces odontolyticus* *P. gingivalis*	Ethanol	NI	[48]
Laminaria saccharina (Brown Seaweed)	*P. aeruginosa*	Methanol	NI	[41]
Laurencia dendroidea (Red Seaweed)	*M. tuberculosis*	Dicloromethane:methanol (1:1)	Halogenated sequiterpenes	[49]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Laurencia majuscula (Red Seaweed)	*Staphylococcus epidermidis*	Methanol	Elatol,	[50]
			Allolaurinterol (10-bromo-7-hydroxylaurene), Cupalaurenol, Elatol, Iso-obtusol	[51]
	S. aureus	Methanol	Elatol,	[50]
			Allolaurinterol (10-bromo-7-hydroxylaurene), Cupalaurenol, Elatol, Iso-obtusol	[51]
	S. aureus[a] *Staphylococcus haemolyticus* *Streptococcus mitis* *P. aeruginosa* *Streptococcus pneumonia* *S. pneumoniae*[b] *S. pyogenes* *E. faecalis* *E. faecalis*[c] *E. faecalis*[d] *E. faecium*[d] *Morganella morganii* *Enterobacter cloacae* *Serratia marcescens* *Moraxella catarrhalis*[a]		Allolaurinterol (10-bromo-7-hydroxylaurene), Cupalaurenol, Elatol, Iso-obtusol	[51]
	Pseudomonas sp. *Streptococcus sp.*	Methanol	Elatol,	[50]
	Klebsiella pneumonia	Methanol	Elatol, Iso-obtusol	[50]
			Allolaurinterol (10-bromo-7-hydroxylaurene), Cupalaurenol, Elatol, Iso-obtusol	[51]
	Salmonella sp.	Methanol	Elatol, Iso-obtusol	[50]
	E. coli	Methanol	Iso-obtusol	[50]
			Allolaurinterol (10-bromo-7-hydroxylaurene), Cupalaurenol, Elatol, Iso-obtusol	[51]
	C. freundii	Methanol	Iso-obtusol	[50]
	Acinetobacter baumannii *Bacillus substilis*	Ethanol	NI	[52]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Laurencia sp. (Red Seaweed)	*Salmonella sp.*	Methanol	NI	[50]
Laurencia okamurae (Red Seaweed)	*S. aureus* *S. aureus*[a] *Staphylococcus epidemidis* *S. haemolyticus* *S. pyogenes* *S. pneumoniae*		Laurinterol Isolaurinterol	[51]
-	*S. pneumoniae*[b] *S. mitis* *Enterococcus faecalis* *Enterococcus faecalis*[c] *Enterococcus faecalis*[d] *Enterococcus faecium*[d] *E. coli* *Klebsiella pneumoniae* *M. morganii* *E. cloacae* *S. marcescens* *P. aeruginosa* *M. catarrhalis*[a]		-	-
Laurencia popillose (Red Seaweed)	*B. subtilis* *E. coli*	Methanol: Chloroform (2:1 v/v)	Sulfolipids	[27]
Laurencia similes (Red Seaweed)	*S. aureus* *S. aureus*[a] *S. epidemidis* *S. haemolyticus* *S. pyogenes* *S. pneumoniae* *S. pneumoniae*[b] *S. mitis* *Enterococcus faecalis*	-	2,3,5,6-tetrabromoindole 1-methyl-2,3,5,6-tetrabromoindole	[51]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
-	*Enterococcus faecalis*[c] *Enterococcus faecalis*[d] *Enterococcus faecium*[d] *E. coli* *K. pneumoniae* *M. morganii* *E. cloacae* *S. marcescens* *P. aeruginosa* *M. catarrhalis*[a]	-	-	-
Lobophora variegata (Brown Seaweed)	HSV-1 HSV-2	Water	NI	[45]
	T. cruzi	Dichloromethane:methanol (7:3)	NI	[26]
Mastocarpus stellatus (Red Seaweed)	*P. falsiparum.* *Leishmania donovani* *T. cruzi*	hydroalcoholc extract	NI	[53]
Nereocystis luetkeana (Brown Seaweed)	HSV	Methanol	NI	[23]
Odonthaa corymbia (Red Seaweed)	*C. albicans,* *Aspergillus fumigatus,* *T. rubrum,* *T. mentagrophytes*		NI	[54]
Odonthaa floccose (Red Seaweed)	SINV	Methanol	NI	[23]
Osmundaria sp. (Red Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]
Padina pavonia (Brown Seaweed)	*Candida sp.* *E. faecalis* *P. aeruginosa* *E. coli*	Ethanol	NI	[22]
	A. niger	Ethanol	NI	[36]
Polysiphonia hendryi (Red Seaweed)	SINV	Methanol	NI	[23]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Polysiphonia virgata (Red Seaweed)	*Mycobacterium smegmatis*	Methanol	Lauric acid, Linoleic acid, Oleic acid	[55]
	M. tuberculosis	Methanol	Lauric acid, Linoleic acid, Myristic acid Oleic acid	
	M. tuberculosis (MDR)	Methanol	Lauric acid, Linoleic acid, Myristic acid	
Porphyra umbilicalis (Red alage)	*B. cinerea* *M. laxa* *P. digitatum*	n-Hexane, methanol, water	NI	[38]
Postelsia palmaeformis (Brown Seaweed)	HSV	Methanol	NI	[23]
Pterocladia capillacia (Red Seaweed)	*C. albicans* *T. hamatum* *A. flavipes* *F. solani* *F. oxyporum*	Ethyl acetate, methanol	NI	[56]
Rissoella verruculosa (Red Seaweed)	*T. brucei.*	Ethyl acetate	NI	[57]
Sargassum vulgare (Brown Seaweed)	*T. brucei.*	Ethyl acetate	NI	[57]
Sargassum sagamianum (Brown Seaweed)	*P. intermedia* *P. gingivalis*	Methanol	NI	[37]
Sargassum thunbeergii (Brown Seaweed)	*Vibrio parahaemolyticus*	Ethanol	Pholorannin	[58]
Solieria filiformi (Red Seaweed)	Measles	Ethanol		[29]

(Table 1) cont.....

Seaweed Species	Inhibited Microorganism	Extract Type	Active Compound	Reference
Taonia atomaria (Brown Seaweed)	*B. subtilis* *E. coli*	Methanol: Chloroform (2:1 v/v)	Sulfolipids	[27]
Ulva fasciata (Green Seaweed)	*C. albicans* *T. hamatum* *A. flavipes* *F. solani* *F. oxyporum*	Ethyl acetate, methanol	NI	[56]
	B. subtilis *E. coli*	Methanol: Chloroform (2:1 v/v)	Sulfolipids	[27]
Ulva lactuca (Green Seaweed)	*C. albicans* *T. hamatum* *A. flavipes* *F. solani* *F. oxyporum*	Ethyl acetate, methanol	NI	[56]
Ulva pertusa (Green Seaweed)	*P. intermedia* *P. gingivalis*	Methanol	NI	[37]
Ulva rigida (Green Seaweed)	*Candida sp.* *E. faecalis*	Diethyl ether, ethanol	NI	[22]
-	*P. aeruginosa*	Diethyl ether, methanol	NI	
-	*E. coli*	Diethyl ether	NI	
Ulva sp. (Green Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]
	SINV HSV	Methanol	NI	[23]
Undaria pinnatifida (Brown Seaweed)	*B. cinerea* *M. laxa* *P. digitatum*	n-Hexane, methanol, water	NI	[38]
Zonaria sp. (Brown Seaweed)	*R. solani* *Verticillium sp.*	Ethanol	NI	[25]

[a]Methicillin-resistant S. aureus; [b] Penicillin-resistant S. pneumoniae; [c,d] Vancomycin-resistant strain; NI – Not Identified Yet

Antibacterial Effects

Antimicrobial compounds that are effective against several clinically important bacterial pathogens, including antibiotic-resistant bacteria, acne-causing bacteria, oral pathogens, and food poisoning bacteria, have been identified from seaweeds

(Table **1**). These antibacterial activities can occur due to the presence of one or a few biochemical compounds, such as polyphenols, polysaccharides, proteins/ peptides, fatty acids, and pigments [59].

Tuney *et al*. (2006) described the antimicrobial activity of some selected seaweeds (*Cystoseira mediterranea, Enteromorpha linza, Ulva rigida, Gracilaria gracilis, Dictyota linearis* and *Ectocarpus siliculosus*) collected from the coast of Urla, Turkey [22]. The extracts from solvents, methanol, acetone, diethyl ether, and ethanol were tested for antimicrobial activity against 3 gram-positive (*Enterococcus faecalis*, *Staphylococcus aureus,* and *Streptococcus epidermidis)* and 2 gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacterial species. According to the study, diethyl ether extract showed the most significant antibacterial effect, with the exception of *D. linearis*. The ethanolic extract of *D. linearis* showed antimicrobial effects against gram-negative bacteria (*P. aeruginosa* and *E. coli*) and *Candida sp.,* while its diethyl ether extract was ineffective. This could be related to the bioactive metabolites' solubility in different solvents. This study also showed the difference in antimicrobial activity of dried extracts and fresh extracts. Dried extracts are almost ineffective towards the pathogen, maybe due to the loss of active volatile compounds during the drying process.

According to the study by Vairappan (2003), Malaysian red seaweed, *Laurencia majuscule,* has halogenated compounds in its phytochemical profile, which shows antimicrobial effects against six pathogenic bacteria [50]. The compound 'elatol' from *L. majuscule* showed an antimicrobial effect against *Streptococcus sp.* (hemolyticus), *Pseudomonas sp*., and *S. aureus,* with remarkable inhibition of *Staphylococcus epidermidis, Klebsiella pneumonia,* and *Salmonella sp*. Another halogenated compound, iso-obtusol, showed significant inhibition of *K. pneumonia* and *Salmonella sp*., along with minor inhibition in *Citrobacter freundii* and *E. coli*. The same study comparatively analyzed the activity of several commercially available antibiotics and antimicrobials from *L. majuscule, which* showed comparatively higher levels of inhibition against some of the tested pathogens, surpassing the commercial antibiotics.

Another recent research regarding the antibacterial activity of red seaweed, *Laurencia majuscule,* shows fairly similar results for the inhibition of *Streptococcus sp.* (*S. pyogenes*), *Pseudomonas sp.* (*P. aeruginosa*), *S. aureus, S. epidermidis, E. coli* and *K. pneumonia* with some deviation in the extent of inhibition [52]. Al-Enazi *et al*. (2018) determined the inhibition using the crude ethanolic extract of *L. majuscule* with a higher concentration (100 mg/mL) using the well diffusion method, while Vairappan (2003) reported the inhibition related to the selected chemical compounds isolated from the methanolic extract of *L.*

majuscule using disc diffusion method with lower concentrations from each compound (30 µg per disc) [50]. Moreover, Al-Enazi *et al*. (2018) discovered *Proteous mirablilis* (gram-negative) and *Streptococcus sanguis's* (gram-positive) resistance and susceptibility of *Acinetobacter baumannii* (gram-negative) and *Bacillus substilis* (gram-positive) to the ethanolic extract of *L. majuscule* [52]. Moreover, Vairappan *et al*. (2004) reported the antibacterial effects of the red seaweed genus *Laurencia* against 22 human pathogenic bacterial species, interestingly, 7 of which were antibiotic-resistant [51].

Fucoxanthin, a macroalgal pigment, was reported to inhibit *Streptococcus agalactiae*, *S. epidermidis*, and *S. aureus* [60]. Several green (*Ulva fasciata*), brown (*Dilophys fasciola, Taonia atomaria*) and red (*Laurencia popillose, Galaxoura cylindriea*) seaweeds were reported to have antibiotic effects against *Bacillus subtilis* and *E. coli* due to the presence of sulpholipids [27]

Past studies reveal the antibacterial activity of seaweed extracts against several food-borne pathogens. According to Gupta *et al*. (2010), the extracts of Irish edible brown seaweeds *Himanthalia elongata* and *Laminaria saccharina* showed inhibition against food pathogenic and food spoilage bacteria, *Listeria monocytogenes* and *P. aeruginosa,* respectively [41]. Recent research has reported that the extract of *H. elongata* using ethanol/water (70:30 v/v) acidified with 1% formic acid (CH_2O_2) showed antimicrobial activity against several food-borne pathogens, including *L. monocytogenes, Salmonella* spp., *E. coli*, and *S. aureus* [43]. Rajauria *et al*. (2013) reported the antimicrobial activity of the methanolic extract of *H. elongata* against 2 foodborne pathogens, *L. monocytogenes* and *Salmonella abony,* along with 2 non-foodborne pathogens, *E. faecalis* and *P. aeruginosa* [42]. The presence of a strong bactericidal effect against the food poisoning bacterium *Compylobactor jejuni* from the brown seaweed *Ecklonia kurome* extracts was stated by Nagayama *et al*. 2002. Later, Kuda *et al*. (2007) showed the antimicrobial activity of *E. kurome,* along with another edible brown seaweed *Ecklonia stolonifera,* against *E. coli, P. aeruginosa, Corynebacterium glutamicum, S. aureus*, and *Bacillus cereus* [32]. Dried or wet (raw/boiled) products of the above seaweed species have been tested separately, revealing interesting results. The ethanolic extract of dried *E. stolonifera* (with few exceptions) inhibited almost all the tested bacterial strains, while the wet (boiled) product did the opposite. They reported that *E. stolonifera* extracts with a low concentration of phenolic acids (few dried and all boiled samples) were not effective in the growth of tested bacterial species.

The inhibition of oral pathogens from seaweed extracts was also reported. According to the study by Choi *et al*. (2012) [37], the extract of green seaweeds, *Enteromorpha linza, Sargassum sagamianum*, and *Ulva pertusais,* are capable of

strongly inhibiting the oral pathogens, *Prevotella intermedia,* and *Porphyromonas gingivalis*. The inhibition of oral pathogens, *Fusobacterium nucleatum*, *Actinomyces naeslundii*, *Actinomyces odontolyticus,* and *P. gingivalis,* by the brown seaweed extract *Laminaria japonica* was observed [48].To control the oral pathogens, the potential of exploiting fucoidan, a sulfated polysaccharide primarily extracted from brown seaweeds, in combinations or alone with available antibiotics, has been documented by Lee *et al*. (2013) [61].

Several marine seaweeds reveal the possibility of developing acne treatments. According to Lee *et al*. (2014), the methanolic and ethyl acetate extracts of marine brown seaweed *Eisenia bicyclis* can inhibit the high-level erythromycin and lincomycin resistance of *Propionibacterium acnes*, an acne-related bacterium [34]. Glycolipid-rich extracts of the brown seaweed, *Fucus evanescens,* showed strong antibacterial activity against *Hemophilus influenzae, Legionella pneumophila,* and *Propionibacterium. acnes,* along with several other pathogenic bacteria, *Streptococcus pyogenes*, *Clostridium difficile* and methicillin-resistant *S. aureus* [39].

Seaweed is enriched with a diverse range of natural bioactive compounds. Therefore, all these studies suggested seaweed as a potent natural antimicrobial agent that could replace synthetic chemical products.

Antifungal Effects

Many studies reveal the antifungal properties of seaweed extracts on several fungal species that are harmful to humans, animals, and plants. Among many potent antifungal agents, seaweed is reported to be a rich source of phenolic compounds, terpenoids, and polyunsaturated fatty acids.

The extract consisting of dieckol of brown seaweed, *Ecklonia cava,* can inhibit the dermatophytic fungus *Trichophyton rubrum,* which is known to be a causative agent of human nail infection [30]. Bromophenols isolated from the extracts of the red seaweed *Odonthalia corymbifera* have shown inhibitory activity against several fungal species: *Candida albicans*, *Aspergillus fumigatus*, *T. rubrum*, and *Trichophyton mentagrophytes* [54]. The extracts of red seaweed, *Hypnea musciformis* with protein fractions rich in lectins, have exhibited fungicidal effects of human pathogenic fungi, *C. albicans* and *Candida guilliermondii* [62]. Generally, lectin is considered the only macro algal protein that shows antimicrobial properties [46]. ERTÜRK and TAŞ (2009), reported the antifungal activity of *Enteromorpha linza* and *Padina pavonica* against *Aspergillus niger*, which is comparatively higher than the inhibition of Nystatin, which is a commercially available antifungal medicine [36]. According to Shobier *et al*. (2016) , ethyl acetate and methanolic extracts of green seaweed, *Ulva lactuca*

(from two different locations-Abu Qir Bay and Al Selsela, Egypt) *and U. fasciata* and red seaweed, *Pterocladia capillacia,* showed inhibitory activity against fungal pathogens, *C. albicans, Trichoderma hamatum, Aspergillus flavipes, Fusarium solani* and *Fusarium oxyporum* [56]. The highest antifungal activity has been observed in the extracts of *U. lactuca* (from Al Selsela). The GC/MS analysis of the extracts showed the presence of different chemical profiles, which can be a causative factor for the observed difference in the antifungal activity of two seaweeds collected from two different locations. The methanolic extract of *U. fasciata* showed bioactive compounds, including palmitic acid, methylester, trichloromethyloxirane, linolenic acid, ethylester, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, 11-octadecenoic acid, and 12,15-octadecadienoic acid. The methanolic extract of *P. capillacea* showed comparatively high percentages of palmitic acid, n-heptacosane, 2-methylhexadecan-1-ol, methoxy acetic acid, 2-tridecylester and myristic acid.

An interesting revelation for the food industry is the antifungal properties of several red seaweed (*Porphyra umbilicalis*, *Eucheuma denticulatum,* and *Gelidium pusillum*) and brown seaweed species (*Laminaria digitata* and *Undaria pinnatifida*) towards postharvest fungal pathogens, *Botrylis cinerea*, *Monilinia laxa*, and *Penicillium digitatum* identified by de Corato *et al*. (2017). According to this study, brown rot in peaches and grey mold in strawberries are mostly inhibited [38]. Furthermore, the compound characterization results showed that the presence of polysaccharides, phenolic compounds, and fatty acids has a major contribution to the inhibition of the latter. A study on red seaweed species *Jania sp.* and brown seaweed *Ecklonia sp.* shows that their water extract consisting of polysaccharides can inhibit the fungal pathogen *Botrytis cinera,* which is a necrotrophic fungus that affects many plant species [33]. *In vitro* assays of polysaccharide extracts from the above red and brown seaweeds address different target sites. *Ecklonia sp.* extract reduces the colony growth of the pathogen, while the extract of *Jania sp.* inhibits the fungal spore germination. The antifungal activity of *Caulerpa sp., Ulva sp., Zonaria sp., Hypnea sp., Gelidium sp.,* and *Osmundaria sp.* extracts showed more than 50% inhibition of the fungal pathogens *Rhizoctonia solani* and *Verticillium sp* [25].

According to current studies, seaweeds exhibit great antifungal activity against many pathogenic fungi. Generally, brown seaweeds show higher antifungal activity than red seaweeds due to their biologically active compounds [38].

Antiviral Effects

Seaweed is reported to have inhibitory activity against several harmful animal and plant viruses. These antiviral compounds from marine seaweed species are potent

sources of antiviral drugs for the pharmaceutical industry. According to many studies, the presence of diverse polysaccharides and their derivatives in seaweeds is responsible for antiviral properties against human viruses. For instance, sulfated polysaccharides such as agar, ulvan, fucoidan, and laminarian from the cell wall of marine seaweed, have shown antiviral activity against a wide range of viruses [63]. According to Wang *et al*. (2008), Herpes Simplex Virus 1 and 2 (HSV-1 and HSV-2) can be inhibited by seaweeds attained from Hong Kong, *Hydroclathrus clathratus* and *Lobophora variegate* [45]. Queiroz *et al*. (2008) reported the antiviral effects of several brown seaweed extracts, such as *Dictyota mertensil, Lobophora wariegata, Fucus vesiculosus,* and *Spatoglossum schroederi* against Human Immunodeficiency Virus (HIV). Furthermore, sulfated fucans act as active compounds [64]. Marine seaweeds have been evaluated for their antiviral activity against dengue virus (DENV). According to Pujol *et al*. (2012), several seaweed extracts consisting of polysulfated are evaluated for their antiviral activity against several serotypes of DENV, showing the highest susceptibility in serotype DENV-2 [65]. The red seaweed *Ceramium rubrum* showed antiviral activity against several influenza viruses [66]. Seaweeds with phlorotannins have been reported to inhibit the Murine norovirus (MNV) as well as the Newcastle disease virus [35]. Several red and brown seaweed extracts with polyphenols showed antiviral effects against the Measles virus [29]. Hudson *et al*. (1999) studied a total of 16 red, brown, and green seaweed species: *Acrosiphonia coalita, Codium fragile, Enteromorpha intestinalis, Enteromorpha linza, Ulva sp., Alaria nana, Analipus japonicus, Egregia menziesii, Hedophyllum sessile, Nereocystis luetkeana, Postelsia palmaeformis, Callithamnion pikeanum, Corallina vancouveriensis, Gracilaria pacifica, Odonthalia floccose*, and *Polysiphonia hendryi* from British Columbia for their antiviral activity against Herpes simplex type-1 (HSV), Poliovirus type-1 and Sindbis virus (SINV) [23]. According to this study, all the extracts except one seaweed extract (*Analipus japonicus*) were predominantly virucidal for these well-known viruses.

Seaweed extracts exert antiviral activity towards plant viruses. The ethanolic extract of *Durvillaea antarctica* was effective in the reduction of leaf damage which is caused by the Tobacco Mosaic Virus (TMV) [28].

Taken together, seaweed's bioactive compounds have been shown to effectively combat many harmful viruses that affect humans and plants.

Antimycobacterial, Antitrypanosomal, Antiplasmodial, and Antinematodal Effects

Beyond antibacterial, antifungal, and antiviral activities, seaweed is reported to have antimycobacterial, antitrypanosomal, antiplasmodial, and antinematodal

effects. The growth of *Mycobacterium smegmatis*, *Mycobacterium tuberculosis* and a clinical multi-drug resistant (MDR) strain of *M. tuberculosis* can be inhibited by the methanolic extract of red seaweed *Polysiphonia virgate* [55]. This study identified the presence of fatty acids, including Lauric acid, Linoleic acid, Myristic acid, and Oleic acid, using the GC/MS analysis. Oleic acid reported the highest inhibition of *M. smegmatis* and 100% growth inhibition towards *M. tuberculosis*. Furthermore, *M. tuberculosis* was reported to be weakly inhibited by the marine red seaweed *Calliblepharis jubata* found in Ireland and England [24]. *M. tuberculosis* inhibitory red seaweed, *Laurencia dendroidea,* detected from the Brazilian sea, showed halogenated sesquiterpenes as the bioactive compounds responsible for the antimycobacterial activity [49].

The antimicrobial activity of seaweed extracts against several species of Trypanosome, parasitic flagellate protozoa, has been revealed in several studies. León-Deniz *et al*. (2009) reported the importance of the extracts of *Dictyota carbea* and *Lobophora variegata* in controlling *Trypanosoma cruzi* [26]. The ethyl acetate extracts of the brown seaweed *Sargassum vulgare* and red seaweed *Rissoella verruculosa* showed a significant inhibition toward *Tryponosoma brucei* [57]. The above study investigated the antiplasmodial activity against *Plasmodium falsiparum* and reported a minor inhibitory activity in the ethyl acetate fraction of the above algal extracts. The results of the study conducted by Vonthron-Sénécheau *et al*. (2011) on 20 species of French marine seaweed revealed that more than half of the seaweed species, such as *Mastocarpus stellatus* (hydroalcoholic extract), were inhibitory to *P. falsiparum* [53]. The same study showed the inhibition of *Leishmania donovani* and *T. cruzi* by a few seaweed species.

Bioactive Compounds and their Mechanisms of Action in Antimicrobial Activity

As previously mentioned, the antimicrobial activity of seaweed can be an effect of individual bioactive compounds or a consequence of the synergic effect of multiple compounds. In general, these compounds are known to inhibit bacteria and fungi through the inhibition of the electron transport chain, combined with cell membrane glycoproteins, alteration of DNA, and inhibition of enzymes (Fig. **2**). Furthermore, the disruption of the cell membrane eventually leads to the leakage of cell cytoplasm. In the context of viruses, the obstruction occurs through the inhibition of viral enzymes, preventing their propagation and inhibiting the virus particle by preventing its association with cellular receptors (Fig. **3**). Depending on the causative bioactive compound, it/they may trigger one/few of the above mechanisms.

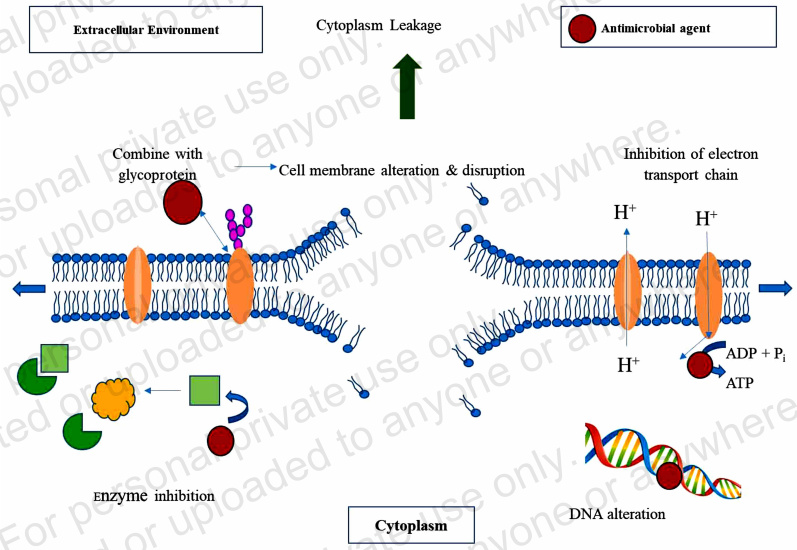

Fig. (2). General mechanism of bacterial and fungal inhibition by seaweed antimicrobials.

Previous studies showed a wide variety of biochemical compounds with antimicrobial activity, which can be categorized under polyphenols, polysaccharides, proteins/ peptides, fatty acids, and pigments.

In the context of polyphenols, compounds such as phlorotannins, phlorofucofuroeckol, bromophenols, and dieckol are reported in the literature to show antimicrobial activity. Phlorotannins are reported to exert antimicrobial activity mainly *via* the alteration of cell membrane/wall (Fig. **2**). However, it depends on the degree of polymerization and the number of hydroxyl groups. Condensed phlorotannins with a high degree of polymerization can alter the cell membrane by the oxidative potential of hydroxyl groups and inhibit the growth of bacteria [67]. According to Wei *et al*. (2016), low molecular weight phlorotannins fractionated from *Sargassum thunbeergii* are tested against the pathogenic gram-negative bacteria *Vibrio parahaemolyticus* [58]. The observations of the morphology of colonies/cells and the extracellular environment showed evidence of critical damage. According to the electron microscopic observations, cells are reported to undergo shrinking, adhesion, swelling, and disintegration. The presence of intracellular enzymes such as alkaline phosphatase, β-galactosidase, ions, and proteins in the culture media showed the increased membrane permeability induced by phlorotannin treatment. The alteration of the cell membrane can cause leakage of the cytoplasm with electrolytes like potassium ions, which leads to the hindrance of many metabolic pathways, enzyme activity,

and membrane stability (Fig. **2**). Changes in membrane fluidity can obstruct cell imbibition and lead to cell death. Phlorotannins from seaweed inhibit the dermatophyte *C. albicans* in an interesting way. According to Lopes *et al*. (2013), purified phlorotannins of brown seaweed *Fucus spirali* exert an inhibitory effect on *C. albicans* virulence factors, dimorphic transition, and adherence to epithelial cells [40]. Phlorotannins inhibit the dimorphic transition, which defines a morphologic phase transition in the lifecycle of *C. albicans* and the formation of the germ tube, which functions in adhesion to the mucosa. Furthermore, phlorotannins can reduce the amount of *Candida* cell membrane component, ergosterol, a sterol to maintain cell membrane integrity. The same study reports the deformation of mitochondrial function by phlorotannins, increasing mitochondrial respiration. According to Ryu *et al*. (2011), hydrogen bonds and steric hindrance between hydroxyl and aryl groups of phlorotannins with amino acids of the enzyme neuraminidase (a glycoprotein found on the surface of influenza virus particle) deform the activity of neuraminidase, which leads to the formation of the aggregates of virus particles limiting the spread of infection [68].

Bromophenol, which is categorized under polyphenols, is reported to induce antimicrobial activity by the inhibition of virulence proteins [47]. Bromophenols from marine red seaweed *Kappaphycus alvarezii* are found to inhibit the gingipain and hemagglutination activities induced by the virulence proteins, gingipain R and hemagglutinin A, of oral pathogen *P. gingivalis*. The study further suggests that a down-regulation function is induced by the bromophenols, which results in low mRNA levels of the virulent genes in *P. gingivalis* in exposure to bromophenols.

The antimicrobial content of polysaccharides depends on the molecular weight, charge density, structural characteristics, and sulfated content (in the context of sulfated polysaccharides). Polysaccharides such as depolymerized fucoidans, fucoidans, and carrageenans are reported to have antimicrobial activity in several studies. Referring to the bactericidal activity of depolymerized fucoidans (a sulfated polysaccharide), it is suggested that the pathway should be through the impairment of the cytomembranes. Depolymerized fucoidans, which are polyanionic, attack the membrane proteins that are positively charged, altering the membrane composition, which can result in the change of membrane fluidity, further activating the autophagocytosis. The same study discovered that depolymerized fucoidan induces damage to the phospholipid bilayers of cell membranes. The electron microscopic evidence showed nucleic acid release with morphological changes (deformed, pitted, shriveled, and adhered nature of cells) in the test bacteria (*S. aureus* and *E. coli*). Membrane structure assays also proved that depolymerized fucoidans might have severe effects on the cell membrane. Researchers have discovered that dextran sulfate (20% of sulfate content) does not show obvious inhibition towards bacterial cells (*S. aureus*). Therefore, the

antimicrobial activity of sulfated polysaccharides may also be triggered by the monosaccharide component and/or conformational characteristics.

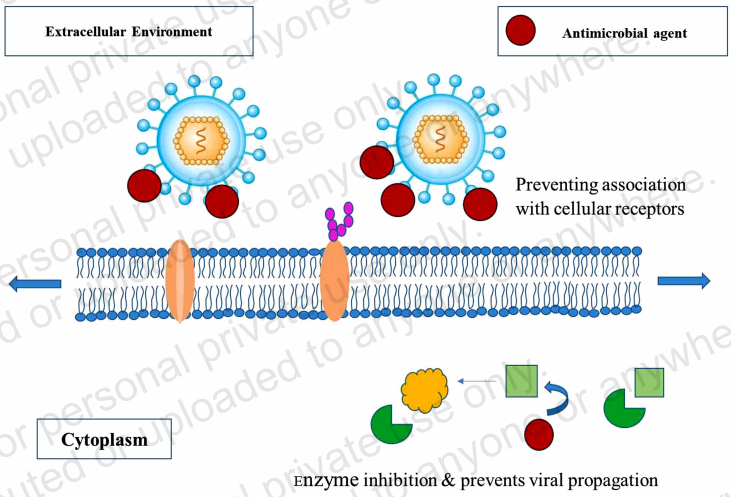

Fig. (3). General mechanism of viral inhibition by seaweed antimicrobials.

Sulfated polysaccharides induce their antiviral activity mainly by intervening in the initial attachment of virus particles to the target cell, consequently blocking the entry of the virus (Fig. **3**). In enveloped viruses (*e.g.*, HIV, influenza), the initial attachment to the host cell occurs *via* ionic interaction between negatively charged cell membrane components and positively charged viral external glycoprotein domains [69]. Sulfated polysaccharides, which are negatively charged due to the presence of sulfate anions, interact with the virus particle, replacing the host cell membrane components. The inactivation of the virions can consequently lead to the loss of the virion's ability to infect the cell in a similar way to antibody-mediated virus neutralization. This phenomenon is induced by the additional negative potential of sulfated polysaccharides disrupting the viral-host cell contact. Sulfated polysaccharides isolated from red seaweed *Gigartina skottsbergii* are reported to inhibit HIV, as explained above [59]. Non-enveloped viruses (*e.g.*, norovirus, rhinovirus) are reported not to be inhibited by sulfated polysaccharides. According to Greco and Cinquegrani (2018) [70], fucoidans (a sulfated polysaccharide) from brown seaweed *Cladosiphon okamuranus* inhibit the dengue virus potently by exclusive binding to the virus envelop glycoproteins. Furthermore, some sulfated polysaccharides trigger additional inhibitory steps by the obstruction of the virus replication pathway. According to Greco and Cinquegrani (2018), a sulfated polysaccharide, carrageenan, extracted from red seaweed, could co-internalize into the host cell along with HSV particles,

inhibiting their activity [70]. In HIV-infected cells, it ceased the formation of the syncytium and inhibited the activity of reverse transcriptase, a specific retroviral enzyme, used by retroviruses to replicate their genome.

The information regarding the antimicrobial activity of seaweed proteins is lesser as compared to other active compounds. However, the antimicrobial activity of lectins has been investigated in several studies. Being proteins, lectin molecules have an advantageous physical structure that has an amphiphilic nature, leading to interactions with polar and nonpolar sites on the bacterial cell membrane or viral envelope. According to Pina-Pérez *et al*. (2017), red seaweed *Eucheuma serra* and *Galaxaura marginata* extracts inhibit the growth of *Vibrio vulnificus*, a pathogenic bacterium, due to the presence of lectins [71]. This inhibition of the growth of bacteria is mediated *via* the interaction between lectins and bacterial cell wall constituents such as teichoic acids, peptidoglycans, and lipopolysaccharides. Lectins are known as carbohydrates recognizing proteins, which have carbohydrate binding sites in their structure. Therefore, they bind to carbohydrate components on bacterial cell walls, inducing the formation of bacterial clumps. Ensuring extensive contact between the sugar and lectin binding sites, all the binding sites have an aspartic acid that forms hydrogen bonding with sugars.

Lectins are reported to block the cell-to-cell fusion and entry of viruses, such as HIV-1, Hepatitis C, and SARS-CoV-2, to target cells. According to Singh and Walia (2018), Griffithsin (GRFT), a lectin derived from red seaweed *Griffithsia sp.,* has a high affinity to mannose-rich N-linked glycans, a type of glycoprotein [72]. GRFT has a dimeric structure, and each monomer has three specific carbohydrate binding sites. HIV envelop glycoproteins (gp120), which have high mannose oligosaccharides, tend to bind with GRFT. This prevents the interaction of gp120 with HIV co-receptors, obstructing the initiation of signaling cascades that are important to the entry process to the host cell.

Bioactive fractions, consisting of fatty acids extracted from seaweeds, have been shown to inhibit bacteria by altering the cell membrane, causing cell rupture, and resulting in cytoplasmic leakage and cell death. According to El Shafay *et al*. (2016), diethyl ether extract of *Sargassum fusiforme* and ethanol extract of *S. vulgare* perforate the *K. pneumonia* and *S. aureus* cell wall, causing cytoplasmic leakage, which leads to cytoplasmic vacuolation, a decrease in cytoplasmic density and deformation of cell structure [73]. Silva *et al*. (2020) reported that fatty acid, Sulfoquinovosyldiacylglycerol, from green seaweed, *Caulerpa racemosa,* inhibits HSV type 2, disrupting the initial stage of the virus life cycle [59].

Several research findings exhibit the antimicrobial activity of seaweed pigments. Karpiński and Adamczak (2019) reported that a properly proven direct antibacterial mechanism mediated by fucoxanthin is not known yet [60]. However, the possible mechanism is suggested to be similar to the mechanisms of other active compounds extracted from seaweed following the basic steps: alteration of outer membrane permeability, cytoplasm leakage, and inhibition of nucleic acid formation.

Factors Affecting the Antimicrobial Activity of Seaweed

The antimicrobial activity of seaweed depends on a number of factors, mainly from three aspects.

- The antimicrobial seaweed extract itself
- Target microorganism
- Environmental factors

In the context of seaweed extract, the active compound/compounds, concentration of active compound, mode of action (mechanism), solvent used for extract and method of extraction affect antimicrobial activity. Therefore, the extent of antimicrobial activity can vary depending on the seaweed extract.

As antimicrobial activity is a property triggered by one or a group of bioactive compounds, the chemical composition of the seaweed extract directly affects the antimicrobial activity of a particular seaweed. The chemical composition varies with species and physiological status [11]. In the context of the chemical structure of bioactive compounds, molecular weight, degree of halogenation/sulfation, constituent sugars, conformation, and dynamic stereochemistry affect antimicrobial activity. According to Damonte *et al*. (2012), sulfated phenolic polysaccharides with a low degree of sulfation are inactive toward viruses when compared with highly sulfated polysaccharides [65]. Antimicrobial activity depends on the region of the seaweed thallus acquired for the extract. The inhibition of *B. subtilis* by the ethanolic extract from the stolon of green seaweed *Caulerpa paspaloides* was higher than the extracts from basal or apical regions of the thallus [74].

The method of extraction and conditioning procedure prior to extraction can affect the bioactivity yield. Most of the bioactive compounds, such as fatty acids and pigments, are highly volatile and can be damaged or denatured at high temperatures when drying. Kuda *et al*. (2007) reported the comparison of extracts from dried and wet/boiled samples of *E*. *kurome* and *E. stolonifera*, indicating that

the antimicrobial activity could vary [32]. The wet sample extract from *E. kurome* could inhibit *E. coli,* while the dried sample was not inhibitory. The same study revealed that the extract of the boiled sample of *E. stolonifera* could not exert antimicrobial activity towards any tested microbe, which was inhibited by the extract of the dried sample. Hydrothermal processing could reduce the total phenolic content and antioxidants, which is causative to the inhibition of microorganisms. Some researchers have revealed that the high-temperature drying processes can increase the permeability of algal cell membranes and increase bioactive compound yield, leading to higher inhibitory activity [11]. The inhibitory potential was also reported to be enhanced by drying followed by boiling, which increases the phytochemical yield.

Some bioactive compounds can be microbistatic to a particular microbe, while other compounds can be microbicidal. Nagayama *et al*. (2002) reported that phlorotannins and catechins from *E. kurome* act differently toward *C. jejuni.* Phlorotannins and catechin exert their antimicrobial activity *via* the interaction with proteins and damaging cell membranes, respectively [31]. The difference in the mode of action also influences the antimicrobial activity of a particular active compound. The concentration of antimicrobial compounds also directly affects antimicrobial activity. The minimum inhibitory concentration (MIC) of antimicrobial compounds shows the lowest concentration needed to inhibit the growth of a particular microorganism. The high concentrations of the antimicrobial compound can also be microbicidal.

The antimicrobial activity can depend on the solvent that is used for the extraction of antimicrobial compounds. According to Tuney *et al*. (2006), marine seaweed extracts of 4 different solvents gave varying results of inhibitory activity [22]. According to the chemical properties of each solvent, such as polarity and functional groups, the solubility of bioactive compounds can vary, which directly affects the antimicrobial activity. According to the literature, an exact solvent with the highest efficiency cannot be suggested. The solvent's efficiency differs depending on the seaweed species and target microorganisms.

The presence of epiphytic microorganisms also can affect the antimicrobial activity of seaweeds [11]. Some bacterial inhabitants, epiphytes on the seaweed thallus, produce bioactive compounds that can be highly antimicrobial and protective towards the host against pathogens. These bioactive compounds also can trigger the antimicrobial activity of seaweeds. Among the factors affecting antimicrobial activity, targeting microorganisms is an indispensable aspect. The structural status of a microorganism decides its susceptibility or resistance to a particular antimicrobial. Many researchers have revealed that the antimicrobial activity of bioactive compounds is different towards gram-negative and gram-

positive microorganisms due to the structural difference of their cell membranes. Gram-positive bacteria are more susceptible to seaweed extract than gram-negative, which may be due to the complex structure of gram-negative bacterial cell walls [73]. As already discussed in the mechanisms section, bioactive compounds have to get inside the cell or a media by themselves. The gram-negative cell membrane is composed of two layers and holds 90-95% of lipids which is the majority, compared with the gram-positive bacteria with 5-10% of lipids. The high amount of lipid in the gram-negative cell membrane does not support the antimicrobial's entrance into the cell, preventing cell membrane alteration and cytoplasm leakage, leading to the resistivity of gram-negative microorganisms to the antimicrobials [73].

In the context of environmental factors affecting antimicrobial activity, a number of environmental aspects can be considered, such as climate, location, salinity, temperature, *etc.* Studies have reported that even seasonal changes can affect antimicrobial activity due to changes in chemical composition [11]. The study by Xu *et al*. (2018) discovered that the antimicrobial activity of seaweed colonizing in the low-tide zone is higher than those in middle- and high-tide zones [75]. They reported that this difference may be due to the different stress levels of sun exposure, nutrition, desiccation, temperature, dissolved oxygen (DO), and salinity fluctuations in each tidal region. The antibacterial activity of *U. fasciata, Sargassum vachellianum,* and *Pachydictyon coriaceum* significantly changed due to dissolved oxygen and nutrition in several bacteria. Further, the chemical composition of seaweed and the total phenolic content of *U. fasciata* are positively affected by nutrition and negatively affected by the DO or salinity of the water. Compared with that, only the ammonium-nitrogen content of water positively affected the total phenolic content of *S. vachellianum*.

Evaluation of Antimicrobial Activity

Antimicrobial activity can be evaluated using several methods related to *in vitro* or *in vivo* assays; however, *in vitro* methods are widely used. Sometimes, an initial *in vitro* assay is followed by an *in vivo* assay [11].

In vitro Assay

Antimicrobial Susceptibility Tests (AST) are *in vitro* methods based on phenotypic observations and used to determine the potential of antimicrobials in each concentration against a given microorganism. AST methods can be used for both qualitative and quantitative assessment of antimicrobial activity as they are based on the growth of tested microorganisms and the concentration of antimicrobials. In quantitative assessment, the MIC is the lowest antimicrobial

concentration, which prevents the visible growth of microorganisms. Several AST methods are widely used.

Disc Diffusion Method

In this method, plates with culture media are seeded with tested microbial isolates and antimicrobial-impregnated wells, discs or strips of known concentration. The diffusion of antimicrobials through culture media brings out inhibition zones. Zone size and the corresponding concentration of the antimicrobials determine the MIC value.

Dilution Method

This method is useful for testing where growth is limited or not visible. The broth dilution method is widely used when there is a large number of samples, providing robust results. Antimicrobial compounds are dissolved in different concentrations in a liquid growth medium with the inoculates of microorganisms of interest. The broth medium with the lowest concentration of visible growth of tested microbial is considered the MIC. Using a microtiter plate and measuring optical density lead to accuracy in this test results.

The methods for detecting antimicrobial resistance (AMR) can predict or identify resistance to antimicrobials. These methods use genomics, transcriptomics, and proteomics tools to detect changes or expressions of specific resistance genes rather than directly measuring cell viability. For the rapid detection of AMR genes, several genotypic methods can be used, including nucleic acid amplification methods, mainly real-time quantitative PCR (qPCR), DNA hybridization-based methods, DNA microarrays, Luminex xMAP technology, and next-generation sequencing methods. These methods are highly sophisticated and rapid results can be obtained in sizeable applications. However, these methods only target well-studied microorganisms or resistance genes, and the scarce availability of user-friendly bioinformatics programs impedes their use in routine applications [76].

In vivo Assay

In vitro studies are carried out in controlled environments, which are different from the conditions of *in vivo* models. Therefore, the safety, efficiency, and toxicity of an antimicrobial compound can be better evaluated by *in vitro* assays followed by *in vivo* assays in a relevant complex model. *In vivo* assays are more expensive and time-consuming as compared to *in vitro* AST assays and are controversial subjects in ethics [76]. Among many *in vivo* models used by scientists, rats, zebrafish, and mice are widely used in this type of analysis. Most

of the *in vivo* testing of seaweed extracts is carried out using non-vertebrates or cold-blooded vertebrates. According to Vatsos and Rebours (2015). in aquaculture, seaweed compounds are incorporated directly into animal feed or growth media, which is water [15].

Red seaweed extract of *Asparagopsis sp*. measured *in vivo* antimicrobial activity against vibrio pathogens of shrimps by the oral administration of commercial shrimp feed treated with seaweed extract [76]. After feeding the shrimps with seaweed extract rationalized feed, the shrimps were exposed to vibrions as an artificial bacterial challenge. The study reported a high therapeutic effect towards controlling vibrion infection in shrimps.

Thanigaivel *et al*. (2015) [77] reported the antimicrobial effect of seaweeds *via* an *in vivo* assay by direct administration to water. In this study, seaweed extracts of *Gracilaria folifera* and *Sargassum longifolium* were directly administered to the water where *Oreochromis mossambicus* (Tilapia) fishes were grown and challenged by pathogenic *Aeromonas salmonicida*. The results showed a significant decrease in bacterial load in the water with seaweed extract.

Applications of Seaweed Antimicrobial Activity

Therapeutic Applications

Many studies have revealed the antimicrobial activity of seaweed that can be used for therapeutic purposes [11]. The findings of the study by Vairappan (2003) and Al-Enazi *et al*. (2018) showed that antimicrobial compounds from *L. majuscule* could inhibit human pathogenic bacteria, *S. pyogenes*, *P. aeruginosa, S. epidermidis, E. coli* and *K. pneumonia* [52, 50]. Therefore, seaweed can be used as a solution for the current antibiotic-resistant bacterial infections. Antimicrobials from *Laurencia sp.* could inhibit the growth of antibiotic-resistant pathogenic bacteria, Methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and Vancomycin-resistant *Enterococcus* (VRE). The antimicrobial activity of *E. linza* towards *P. intermedia* and *P. gingivalis* can be used to treat periodontitis, which is a chronic inflammatory disease caused by pathogens such as *P. intermedia* and *P. gingivalis* [37]. The same study showed therapeutic effects against gingivitis, a form of gum disease [37]. Antimicrobials from seaweed can be therapeutic agents for chronic gastritis and peptic ulceration. Lee *et al*. (2013) showed that ethanol extracts from *Ishige okamurae* exhibited strong inhibitory activity towards *Helicobacter pylori* [78]. An antimicrobial wound dressing developed by Tan *et al*. (2013) was effective against nine wound-associated clinical pathogens, including MRSA [79]. This wound dressing is reported to be efficient, similar to the commonly used silver-based antimicrobial barrier dressing, Acticoat. The study reported that 70-

90% of the bacterial population can be inhibited within 1st 30 minutes by using cost-effective seaweed wound dressing. Antimicrobials derived from seaweed can be used to treat acne vulgaris, which is a common chronic skin disease. Ethyl acetate extracts of *F. evanescens,* which contain β-D-galactosyl O-linked glycolipid as an active compound, strongly inhibit the clinical isolates of acne-forming *P. acnes* [39].

Seaweed can be used for antiprotozoal treatment towards *L. donovani* and *T. cruzi* [53].

Seaweed antimicrobial compounds can also be used to treat a number of viral diseases, such as Herpes, togaviruses, paramyxoviruses, rhabdoviruses, HIV, dengue virus, and metapneumovirus [11].

Food Industry

Food spoilage by microorganisms leads to a harmful impact on human health and the economy. Bacterial enzymatic reactions produce undesirable biochemical properties in texture, odor, color, and toxic compounds [80]. Seaweed extracts can be incorporated as a natural food preservative by replacing synthetic additives. This will increase food quality and safety [11]. According to Gupta *et al*. (2012), the extracts from brown seaweed, *H. elongata,* inhibited the growth of food spoilage microorganisms, *P. aeruginosa* and *E. faecalis,* and food pathogens, *L. monocytogenes* and *S. abony* [81].

Mainly, seaweeds can be used in nutraceutical production due to their therapeutic value [82]. Seaweed polysaccharides can be used as prebiotics, which are non-digestible growth stimulators of beneficial gut microbiota. Seaweed polysaccharides can modify the population of *Lactobacillus spp*., *Bifidobacterium,* and *Enterobacterium* in feces and colon [83].

According to Siahaan *et al*. (2014), food-borne bacteria can be inhibited by *S. japonica,* which contains an inhibitory bioactive compound, allyl isothiocyanate [84]. In this study, *S. japonica* is incorporated as a powder for the desorption release of allyl isothiocyanate and inhibition was detected against foodborne pathogens, *E. coli*, *S. typhimurium,* and *B. cereus*.

Aquaculture

In the context of aquaculture, harmful microbial activities can cause serious damage to the industry by high mortality rates or chronic lesions on fish skin [11]. Vatsos and Rebours (2015) showed that seaweed can be a promising source of antimicrobials for prophylaxis in fishes and shrimps [15].

The disease vibriosis is commonly seen in fish and seafood species in aquaculture, which is caused by *Vibrio sp*., such as *V. parahaemolyticus, Vibrio anguillarum Vibrio ordalii, Vibrio salmonicida, Vibrio alginolyticus* and *Vibrio vulnificus*. According to Cavallo *et al*. (2013), six seaweed species, including *Chaetomorpha linum, Cladophora rupestris*, *Gracilaria dura*, *Gracilaria gracilis*, *Gracilariopsis longissima,* and *Ulva prolifera,* were tested for antibacterial activities against six fish pathogenic *Vibrio* species [85]. All six of the seaweed extracts inhibited *V. ordalii*. Only *G. longissima* showed activity against *V. ordalii, V. salmonicida, V. alginolyticus,* and *V. vulnificus.*

In vivo test of *Asparagopsis sp*. crude extract showed antibacterial activity against shrimp Vibrio pathogens [86]. Cortés *et al*. (2014) showed the antimicrobial activity of *C. rubrum* against the oomycete *Saprolegnia parasitica*, causing saprolegniasis, which is a common fungal disease in aquaculture [87]. As stated earlier, seaweed extracts of *Gracilaria folifera* and *Sargassum longifolium are* directly applied to fresh water to control furunculosis in Thilapia fish [77].

Biofouling

Biofouling is undesirable for many applications in medical, marine, and industrial fields [88]. In the context of marine environment, biofouling of the ship surfaces is a well-recognized issue [11]. The epibiont content of seaweed thalli is lower compared with other marine substrates. Therefore, seaweed can be a source of metabolites that can be used as biofoul preventives [11]. The antifouling activity showed a number of seaweeds with bioactive compound 3-bromo-5-(diphenylene)-2(5H)-furanone extracted from green seaweed *U. rigida* and floridosid from *Galdieria sulphuraria* [89].

As mentioned earlier, seaweeds are promising sources of antimicrobials that can be used to prevent biofoul causative bacteria. Aqueous, ethanolic, and dichloromethane extracts of seaweed showed antifouling activity [90].

CONCLUDING REMARKS

Seaweed is a massive field for researchers in biomining of chemicals. Novel compounds are continuously discovered with various antimicrobial potentials due to the variety of biomass [76]. There are various studies on the antimicrobial activity of seaweed, which are *in vitro* or *in vivo* assays of non-purified/characterized seaweed antimicrobials. These studies discovered that seaweed antimicrobials have antibacterial, antifungal, antiviral, and antiprotozoal activity. Well-characterized antimicrobial compounds can be promising sources for several applications, including disease control and drug development, the food industry, aquaculture, and biofouling. According to existing literature,

antimicrobial compounds are mostly examined by *in vitro* assays, therefore, information on *in vivo* assays is scarce [11]. By conducting *in vivo* assays, antimicrobial efficiency, toxicity, and other influences on the antimicrobial activity of seaweed can be effectively measured [11].

In most of the studies, antimicrobial properties are tested using crude extract. Therefore, the exact antimicrobial mechanisms of seaweed are still unknown [76]. So, by isolation and chemical characterization of seaweed extracts with antimicrobial properties, the structure and functional relationship and mechanisms of action are well-deserving fields to explore. In spite of the numerous favorable properties of seaweed, they can be harmful due to the presence of chemical hazards, such as metals and/or biological hazards like biomass (*e.g.*, *Salmonella*) or biotoxin contamination [91]. Therefore, examination for hazardous compounds can be very important prior to their application in the industries.

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