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Comprehensive reviews on phenolic compounds from Phaeophyceae as potential therapeutic agent

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ABSTRACT

Seaweeds are an excellent source of natural bioactive compounds. The exploration of novel natural compounds from marine resources has gained interest lately which possesses greater pharmaceutical and nutritional values. Seaweed phenolic compounds, particularly phlorotannin, have been discovered to have a variety of biological implications. Phlorotannin is a polyphenol that is found majorly in brown seaweed and is made up of polymeric units of phloroglucinol. The structural configuration and degree of polymerization were shown to influence biological activity. Several *in vitro* studies demonstrated that the phlorotannin derivatives had substantial bioactivity and were moderately appraised *in vivo*. Antioxidant, anticancer, anti-inflammatory, anti-allergic, anti-diabetic, and anti-microbial effects have been discovered in phlorotannin compounds. Recently, they have been evaluated for exhibiting anti-viral capacity against various harmful viruses. The findings suggested that phlorotannin could be an effective anti-viral molecule that requires intense research. This review focuses on the advanced techniques and research based on the experiments on phlorotannin for their extraction and purification. The phlorotannin as a potential drug molecule has been described from extraction to application. With the advent of technology, it is now possible to isolate the target molecule efficiently in less time. To make phlorotannin a novel nutraceutical and pharmaceutical molecule with wide industrial uses, preclinical and clinical research is required to assess its efficacy, toxicity, bioavailability, and drug delivery mechanism.

1. INTRODUCTION

Humans are constantly threatened by a variety of microorganisms that cause a wide range of diseases. Microorganisms such as bacteria, fungus, and viruses cause infections. Viruses are among the most dangerous pathogens because they induce a variety of severe illnesses and weaken immunity. At present, breakouts of novel viral variants are becoming more common where adequate treatment and prevention are lacking. Viruses influence all kinds of life, with humans being the most affected [1]. The drugs and medicines being used so far could not be an accurate remedy to the evolving infections and disorders and may have negative effects. There are natural compounds enormously present in seaweeds that may hold the key to treating diseases and ailments that affect humans.

This article focuses on the naturally existing polyphenols from marine brown algae especially phlorotannin on their various biological properties. Based on the reports, marine algae have been recognized as a proficient source of natural bioactive compounds as they are found to exhibit various biological properties. In many countries, seaweeds are being added to the diet as they possess nutritional properties as well as several health benefits [2]. Phlorotannin derivatives are one of the important bioactive metabolites of brown seaweeds belonging to the family *Phaeophyceae* that could be a promising pharmaceutical component [3]. The commercial source of the major polysaccharides and phenolic compounds depends on the marine algal resource [4], predominantly from the brown algae [5]. The macro algae are found to carry larger polyphenolic content and their various biological activities were explored and recorded. Major polyphenol present in brown algae is phlorotannin which is found in smaller amounts in red and green algae [6]. The present review deals with the data provided on works of the literature about the phlorotannin structure, sources, extraction, characterization, and biological significance.

2. AVAILABILITY OF PHLOROTANNIN

Larger amount of phlorotannins was identified and reported in marine brown algal species. More than 1800 species are known for the availability of polyphenols from brown seaweed [7,8]. The species of brown algae belonging to *Sargassaceae*, *Alariaceae,* and *Fucaceae* have been used to isolate phlorotannin to evaluate various biological activities. *Ecklonia cava*, a brown seaweed, has been widely recorded for possessing several biological activities The type of phlorotannin and its content in *E. cava* and *Ecklonia kurome* was mentioned by Shibata *et al*. [9,10]. The phlorotannin content from *Ecklonia stolonifera*, *Fucus serratus*, *Cystoseira nodicaulis*, *and Fucus vesiculosus* was mentioned by Chowdhury *et al*. [11]. The phlorotannin content from *E. cava* was also reported by Kim *et al*. [12]. These are the species majorly reported for the presence phlorotannin and its derivatives.

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3. PHLOROTANNIN DERIVATIVES

The structures of phlorotannin compounds were classified according to the arrangement of its phloroglucinol polymers. The classification of phlorotannin is of six subgroups which include fucols, phlorethols, fucophlorethols, fuhalols, eckols, and isofuhalols, respectively [13]. Different structures of phlorotannin derivatives such as dieckol, fucodiphlorethol G, phlorofucofuroeckol A, 7-phloroeckol, 6,6'-bieckol, triphlorethol-A, and 2,7'-phloroglucinol-6,6'-bieckol were present and reported by Venkatesan *et al*. [14]. Some of the basic structures of different phlorotannin compounds are shown in Figures 1 and 2. Either the addition of OH-groups in the compound or the addition of some bonds within the monomers may lead to the structural variation of phlorotannin. These distinctive structures make phlorotannin very unique among the other classes of phenolic compounds. The structural divergence and categorization reveal the function and biological property of phlorotannin. The phlorotannin was widely studied due to the presence of various bioactive compounds [15]. The structural configuration possesses hydroxylated aromatic rings which prevent the species from UV radiation and withstand the surrounding environment [16].

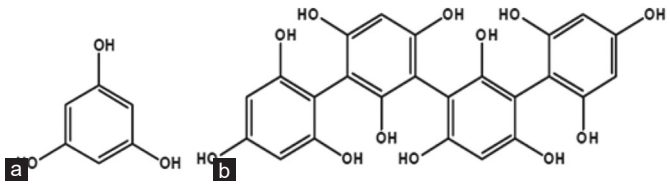

Figure 1: Phloroglucinol. (a) The phloroglucinol units are bonded to one another by C-C or C-O-C bonds forming the oligomer called the tetrameric phlorotannin (b).

4. DIFFERENT TYPES OF EXTRACTION OF PHLOROTANNIN

The isolation of phlorotannin compounds from the brown seaweed is a vital step to analyze their biological activities. The extraction was carried out after undergoing some pretreatments such as washing, drying, and grinding [17]. Solid-liquid extraction and Soxhlet extraction are two conservative extraction procedures that use solvents based on the requirements. Solvent extraction with ethanol is one of the most often utilized solvents because of their cost-efficiency on a commercial scale [18]. In Soxhlet extraction, the solvent is continuously recirculated until the complete extraction takes place. The aqueous solvents were predominantly used for their efficient extraction [19]. Some of the phlorotannin compounds were extracted using enzymes at varying concentrations. The enzymes such as termamyl enzyme, cellulose enzyme, and viscozyme were used by Boi *et al*. [13] to extract phlorotannin from *Sargassum duplicatum*.

The advanced procedures of ultrasound and microwaves are being exploited for the commercial large scale of production of phenolic compounds. They facilitate the efficient disruption of the cell wall thereby releasing the bound target molecule on larger exposer to the solvent [20,21]. Microwave extraction of several phlorotannin compounds is deemed more competent because it takes less time and yields more [2]. The microwave-assisted extraction of phlorotannin produces a yield of 5.59 ± 0.11 mg PhE/g with optimum conditions, according to Toan *et al*. [22]. The ultrasonic-assisted extraction of phlorotannin from some brown algae also gave a similar effect compared to microwave-assisted extraction, especially in an eco-friendly manner [23]. Ultrasound-assisted extraction can also be used to extract phenolic compounds with a high molecular weight [24]. The supercritical fluid extraction was also found to be the efficient method of extraction in which organic solvents and their combinations were

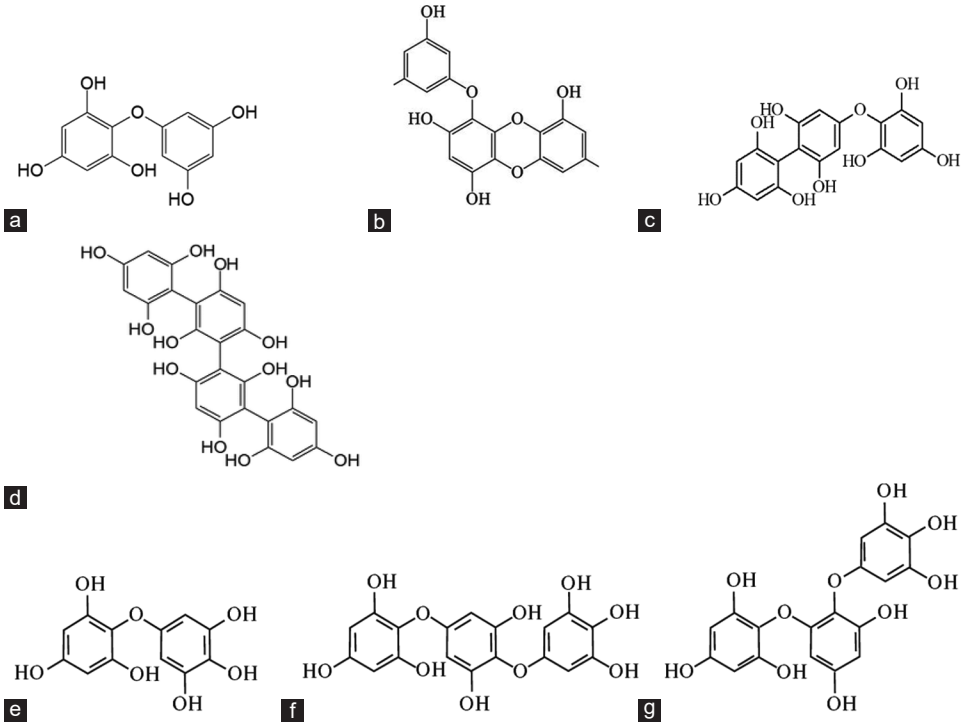

Figure 2: Chemical structures of five different types of phlorotannins: (a) Diphlorethol, (b) Eckol, (c) Fucophlorethol-A, (d) Tetrafucol-A, (e) Bifuhalol, (f) Trifuhalol A, and (g) Trifuhalol B.

used to extract phlorotannin. This method is widely accepted due to its efficacy and low extraction time. Phlorotannins were extracted from brown seaweeds *Sargassum vulgare, Sargassum muticum, Porphyra/Pyropia* spp., *Undaria pinnatifida, and Halopithys incurva* using ecofriendly carbondioxide providing greater yield [25]. The advancement of technologies together will deliver the potential molecule more efficiently.

5. ISOLATION OF PHLOROTANNIN COMPOUNDS

Calorimetric methods, such as Folin-Ciocalteu (F-C), Folin-Denis, or Prussian blue tests, were used to measure phenolic chemicals, particularly phlorotannins [16]. F-C is the most widely used for the quantification of phenolic compounds in some brown seaweed such as *Fucus spiralis, Macrocystis pyrifera, Fucus spiralis, Laminaria digitata,* and *Sargassum fusiforme* [26]. The Fourier transfer infrared (FTIR) spectrum, which exposes the typical functional groups such as C=C, O-H, and C-H, was studied to determine the existence of phlorotannin. Several brown algal species such as *Durvillaea antarctica* and *Hormosira banksii* were examined using the FTIR spectrum [27].

Nuclear magnetic resonance spectroscopy was used to detect the presence of phlorotannin compounds possessing lower molecular weight. The high-resolution magic angle spinning displayed the phlorotannin content from *Cystoseira tamariscifolia* [28]. The high-pressure liquid chromatography (HPLC) system was widely used to isolate the desired compound in less time and provide more yield. It is an automated approach that was employed in conjunction with high-resolution mass spectrometer for the proper recognition of phlorotannins [29]. Many phlorotannin compounds were isolated using HPLC such as catechin, gallic acid, epicatechin, epigallocatechin, and pyrocatechol from *S. fusiforme, Laminaria japonica, Eisenia arborea, Undaria pinnatifida,* according to the report by Machu *et al*. [30]. The desired phenolic compounds were also isolated using reverse-phase-HPLC.

The phlorotannin from brown algae was identified utilizing the modified advanced technique of UHPLC-electrospray ionization-mass spectroscopy which allowed for rapid profiling [7]. The matrix-assisted laser desorption/ionization-time-of-flight and UHPLC revealed phlorotannin profiles that varied depending on the degree of polymerization [31,32]. This approach was used to investigate phloroglucinol from *Sargassum wightii* and 22 different phlorotannins from *Fucus* species [33,34]. Using HPLC-MS-TOF and a modified UHPLC-QQQ-MS technique, several phlorotannin derivatives, Eckol, Fuhalol, and phloroglucinol from *Silvetia compressa* and *Sargassum fusiforme* were discovered [35,36]. UHPLC-HRMS2 was used to analyze phlorotannin derivatives from brown seaweeds such as *F. spiralis, Ascophyllum nodosum*, and *Saccharina latissima*, which yielded phlorotannin-rich extracts [37,38]. These approaches could be used to characterize and discover biologically important phlorotannin molecules.

6. BIOLOGICAL ACTIVITIES OF PHLOROTANNIN

Phlorotannin from brown algal species was studied and reported for possessing numerous biological activities and is still under exploration. They have been studied to exhibit nutraceutical and health supplements for livestock. The biological activities reported include antioxidant, anticancer, anti-inflammatory, anti-diabetic, anti-viral, neuroprotective, radioprotective, anti-allergic, anti-microbial, and immune-modulating potential. The biological significance of various phlorotannin compounds was described by Chitikela *et al*. [39]. In this review article, various biological activities and recent finding of phlorotannin from brown algae are analyzed. The biological activities of phlorotannin compounds studies latterly are mentioned in Table 1.

6.1. Antiviral activity

Since viruses have the capacity of evolving and recurring nature and the discovery of new effective antiviral drugs becomes a continual process. Several polyphenolic compounds have been studied against harmful viruses and their replication through performing antiviral assays [40]. Recently, phlorotannin, a polyphenolic compound from marine brown algae, has been studied for its antiviral effect against several viruses [41,42]. The antiviral activities from phlorotannin extracted using ethyl acetate from brown algae *Eisenia bicylis* were found to have inhibitory effect on the human papillomavirus (HPV), which was performed in 293T cell lines with the help of bioluminescence. They were found to have an inhibitory effect against HPV 16PVs (Type16-pseudovirions) and HPV 18PVs at the concentration range of 50 µg/ml thereby eliminating the viruses [43].

The ethyl acetate fraction containing phlorotannins such as dieckol and phlorofucofuroeckol-A extracted from the brown seaweed *E. bicylis* was found to exhibit a powerful antiviral effect against murine norovirus (MNV). Among the phlorotannins extracted, phlorofucofuroeckol-A was found to possess increased anti-MNV potential than dieckol with 50% effective concentration (EC_{50}) of 0.9µM [44,45]. The phenolic compounds obtained from the aqueous extraction of marine brown algal species, *Cystoseira myrica, and Ulva lactuca* were tested on different viruses to evaluate their antiviral potential. The cytotoxicity assay and neutralization assay for anti-viral activity have been performed on hepatitis A virus-H10, Coxsackie B4 virus, herpes simplex virus Type 1 (HSV-1), and Type 2 (HSV-2). They were found to exhibit anti-viral potential and brought pathological changes in Vero cell lines [46].

The phlorotannin derivative 8, 4'-dieckol from *E. cava* was evaluated for the suppression of human immunodeficiency virus Type 1 (HIV-1) activity. They were found to possess 91% inhibition ratio of HIV-1 reverse transcriptase enzyme at 50 µM [47]. The extraction of phenolic compounds from *Ecklonia arborea* and *Solieria filiformi* was subjected to anti-viral assays against the Measles virus. The extracts exhibited better antiviral and low cytotoxicity comparing the standard, ribavirin, and were established through qPCR [48]. The antiviral and cytotoxicity activity of extracts from *S. muticum* showed inhibition against HSV-1 on African green monkey kidney cells (Vero cells) [49]. The methanol extract from *Ecklonia species* containing 13 different phlorotannins was investigated for antiviral activity against two strains of influenza A virus (H1N1 and H9N2). Among them, phlorofucofuroeckol A was found to exhibit more efficiency as an antiviral agent with the inhibitory concentration (IC_{50}) value of 13.48 ± 1.93 µM [50]. Severe acute respiratory syndrome coronavirus virus was found to be inhibited by phlorotannin compounds from *E. cava* depending on the dosage. Dieckol showed the IC_{50} value of 2.7 ± 0.6 µM and triphlorethol A with 164.7 ± 10.8 µM [51]. According to the data analyzed, phlorotannin could be an effective anti-viral compound.

6.2. Anti-inflammatory Activity

Immunomodulators play a key role in modifying the immune system by provoking innate and adaptive immune responses thereby preventing various disease conditions. Immunomodulation is established by the enhancement of immune regulatory mechanisms as well as inhibition of uncontrolled immune responses by fighting infections and cancer.

Table 1: Recent researches in health benefits of phlorotannins from brown seaweed.

Brown seaweed	Compound	Analysis	References
		Antiviral activity	
Ecklonia arborea, Solieria filiformis	Polyphenols	Syncytia reduction assay against Measles virus and MTT assay for cytotoxicity	[48]
Sargassum tenerrimum	Enzymatic extract	Against antiviral and cytotoxicity activity Herpes simplex virus type 1 using African green monkey kidney cells	[49]
E. cava	Phlorotannin (triphlorethol A)	inhibit SARS-CoV 3CLpro in a dose dependent manner with the IC_{50} values ranging from 2.7±0.6 (dieckol) to 164.7±10.8 µM	[51]
		IMMUNO MODULATING ACTIVITY	
F. vesiculosus	Polyphenol	Enhancement of phagocytosis, neutrophils, lymphocytes *in vivo* in outbred white mice at concentration of 5pg/ml	[53]
E. cava	Eckol	Activate phagocytosis, dentritic cells and T lymphocytes	[56]
F. vesiculosus	Phlorotannin	At100 µg/mL reduced the NO production and iNOS expression	[54]
E. cava	Dieckol	Reduction in NO and iNOS at the concentration between 5–20µM	[58]
E. cava, Sargassum horneri	Ethanol extract	Inhibition of pro-inflammatory responses	[55]
		ANTICANCER ACTIVITY	
Cystoseira sedoides	Phlorotannins	Apoptotic cell death with IC_{50} value of 78 µg/mL	[60]
Ecklonia maxima	Phlorotannin derivatives	Growth inhibitory activity of cancer cells (*HeLa* cells, H157 and MCF7)	[61]
F. vesiculosus	Polyphenols	Cytotoxic potential with IC_{50} value of 72 on µg/mL and 77 µg/mL on Pancreatic cell lines	[62]
E. cava	Dieckol	Down regulated the expression of inflammatory factors and induces apoptosis of cancer cells	[59]
		Antioxidant activity	
Cystoseira compressa	Fuhalol	DPPH and ABTS assay showed remarkable antioxidant activity	[66]
Sargassum dupplicatum	Phlorotannin	Total antioxidant assay showed 11.17±0.28 mg ascorbic acid equivalent/g DW, reducing power activity showed 11.09±0.24 mg $FeSO_4$ equivalent/g DW	[65]
Fucus serratus	Phlorotannin	DPPH assay (29.1±0.25 mg trolox equivalent/g) and FRAP assay (63.9±0.74 mg trolox equivalent/g) showed potential antioxidant activity	[67]
Carpophyllum flexuosum, Carpophyllum plumosum and Ecklonia radiata	Fuhalol	DPPH activity showed 62.1 mg gallic acid equivalents/g dw of seaweed better than standards	[2]
Species of Agarum, Thalassiophyllum, Fucus and Cystoseira	Ethanol extract	*Agarum turneri* showed antioxidant activity of 38.8 mg ascorbic acid/g and 2506.8 µmol Trolox equiv/g dry algae	[68]
		Antimicrobial activity	
Sargassum thunbergii, Laminaria digitata, Padina tetrastromatica	Phlorotannins	Revealed antimicrobial activity against gram-negative and gram-positive bacteria	[69]
Eisenia bicyclis	Fucofuro-eckolA	Antibacterial activity against *Listeria monocytogenes* showed MIC ranging from16 to 32 µg/ml	[55]
Padina tetrastromatica	Solvent fraction	Antibacterial activity towards *Staphylococcus*	[64]

E. cava: Ecklonia cava, F. vesiculosus: Fucus vesiculosus

Diphlorethohydroxycarmalol (DPHC), a phlorotannin derivative from *Ishige okamuarae,* was found to suppress interleukin (IL)-6. The suppression of the activity of the NF-kB pathway was also displayed on murine macrophage RAW 264.7 cell lines [52]. According to the report by Catarino *et al*. [53], phlorotannin from *F. vesiculosus* limited the production of nitric oxide (NO) by 85% at 100 µg/mL. It was also found to suppress the expression of induced NO synthase (iNOS) and cyclooxygenase2 (COX-2) and IL-1β. Immunomodulatory activity of phlorofucofuroeckol A exhibited improved potential comparing epigallocatechin gallate. They possess no cytotoxicity and reduced the production of NO at low concentrations [54]. The cytokine production and immune-related gene expression were boosted with the combined ethanol extracts of *E. cava* and *Sargassum horneri* on LPS-stimulated RAW 264.7 cell lines [55].

Eckol from *Ecklonia* species was reported to stimulate cytokines, phagocytosis, dendritic cells, and T-lymphocytes thereby increasing the activity of immune responses [56]. According to the data given by Bogolitsyn *et al*. [57], polyphenols extracted from *F. vesiculosus* on tested in outbred white mice showed a potential immune modulation effect. They stimulated phagocytosis by evaluating the act of erythrocytes, neutrophils, and lymphocytes without damaging the cell membrane. The movement of myeloid and lymphoid components to the peritoneal region was confirmed the immune-modulating activity of polyphenols. Eckol, dieckol, and 8,8'-bieckol from *E. cava* were found to inhibit the formation of tumor necrosis factor (TNF-α) and IL-1β at the protein level. The expression of iNOS and COX-2 was found to be down-regulated. In another study, the anti-inflammatory effects of phlorotannin derivatives extracted from marine brown algae and *E. cava* such as eckol, dieckol,

and 8,8'-bieckol were tested in PC12 cells against damage caused by $A\beta_{25-35}$ peptide which causes neurogenerative disease. They were found to suppress the production of PGE_2, TNF-α, and IL-1β at the protein level. The results indicated that the phlorotannins suppressed the regulation of proinflammatory responses such as iNOS and COX-2 and downregulated the NF-κB pathway. Based on the reports, phlorotannin can act as an effective immune-modulating agent [58].

6.3. Anticancer Activity

The abnormal growth of cancer cells has always been a threatful condition, which suppresses immunity and is capable of invading other tissues thereby damaging various organs. Many synthetic drugs have failed in curing cancer which destroys normal body cells and exhibits remarkable side effects. A natural source of anticancer drug with low concentration and no side effect is being explored from marine algal species. The phloroglucinol derivatives extracted from marine brown algae and *E. cava* were investigated for anti-proliferative activity in human breast cancer cell lines. The proliferation of cancer cells were inhibited through the apoptosis mechanism with the extract dose-dependently. The compound upregulated the expression of the pro-apoptotic gene, caspase-3 and-9, and downregulated the expression of anti-apoptotic gene and genes involved in NF-kB pathway. Hence, phloroglucinol could be a potential chemotherapeutic agent [59].

Phlorotannin was obtained from *Cystoseira sedoides*, brown seaweed with the help of microwave-assisted extraction. The anticancer activity was evaluated against breast cancer cell lines (MCF-7) which indicated the apoptotic cell death with IC_{50} value of 78 µg/mL and could be an anticancer molecule [60]. Phlorotannin derivatives such as phloroglucinol, eckol, 7-phloeckol, 2-phloeckol, and fucosterol extracted from brown seaweed *Ecklonia maxima* were examined for its cytotoxic potential. MTT assay was performed on various available cancer cell lines such as *HeLa* cells, H157, and MCF7. The phlorotannins exhibited efficient inhibitory activity on the growth of these cancer cells and could be a prominent anti-cancer agent [61].

Polyphenols from *F. vesiculosus* were investigated for anticancer activity in human pancreatic cell lines (Panc89 cells and PancTU1 cells). The extract exhibited cytotoxic potential with IC_{50} value of 72 on µg/mL and 77 µg/mL on Panc89 cells and PancTU1 cells. The result revealed that the polyphenols from marine algae could be a good candidate against cancer [62]. Dieckol from *E. cava* reduces cancer cell proliferation and activates apoptosis, which could be a potential chemotherapeutic molecule against cancer [63].

6.4. Antioxidant Activity

Reactive oxygen species are capable of damaging cellular functions such as DNA and protein damage, deactivation of enzymes, gene alteration, and lipid peroxidation which, in turn, creates many disorders and pathological conditions. A powerful antioxidant is required to scavenge the free radicals that cause oxidative damage to maintain healthy bodily cells. Several studies have been conducted on the high antioxidant potential of phlorotannin from marine brown algae. Free radicals and reactive oxygen species are formed as a result of oxidative stress, which contribute to the course of many viral infections [64].

Phlorotannin from Carpophyllum flexuosum, Carpophyllum plumosum, and *Ecklonia* radiata was evaluated for antioxidant potential. The antioxidant activity of *C. flexuosum* extract was 62.1 mg gallic acid equivalents/g dry weight (DW) of seaweed. FRAP experiment revealed that phlorotannin from *F. serratus* has a considerable antioxidant activity of 63.9 0.74 mg trolox equivalent/g [2].The antioxidant activities of isolated and purified phlorotannin from *Sargassum dupplicatum* were studied. The enzyme-assisted extraction of phlorotannin was subjected to antioxidant assays for evaluating their antioxidant potential. The activity of total antioxidant assay was found to be 11.17 ± 0.28 mg ascorbic acid equivalent/g DW and the reducing power activity was found to be 11.09 ± 0.24 mg $FeSO_4$ equivalent/g DW. Lipoxygenase enzyme inhibition activity was performed and showed the antioxidant activity as 66.19–87.09 µM linoleic acid equivalent/100 µl of the sample, respectively [65].

The crude extract and dichloromethane (DCM) fraction from a marine brown algae *Cystoseira trinodis* were evaluated for antioxidant capacity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity. The DCM fraction was the solvent extracted sample using methanol which showed 69.62% activity was found to have the prominent anti-oxidant capacity [66]. The antioxidant activity of the solvent extracted fraction of phlorotannin from five distinct seaweeds including *S. latissima, Alaria esculenta, Laminaria digitata, F. vesiculosus,* and *A. nodosum* was tested. When compared to typical antioxidants butylated hydroxytoluene and ascorbic acid, phlorotannin showed outstanding antioxidant potential in the DPPH assay [67]. DPPH radical scavenging assay was performed in which ethanol fraction of *Agarum turneri* exhibited the highest antioxidant capacity evaluated as 38.8 mg ascorbic acid/g and 2506.8 µmol Trolox equiv/g dry algae [68].

6.5. Antimicrobial Activity

Microorganisms evolved over time and became drug-resistant in a variety of ways. When used for a long time, synthetic preservatives like food additives can cause tumors in various parts of tissues and organs. Antifungal activities have been discovered in various phlorotannin classifications. Disc diffusion and microdilution methods were used to test Fucofuroeckol-A, a phlorotannin from *Eisenia bicyclis*, against *Listeria monocytogenes*. The inhibitory concentration of (MIC) of phlorotannin was reported to be between 16 and 32 g/ml [55], indicating that it has a high antibacterial activity. Phlorotannin from marine seaweed was studied as an antibacterial agent by Besednova *et al*. [69], who found it to be a promising candidate against both Gram-negative and Gram-positive bacteria.

Antibacterial activity of phlorotannin from marine brown algae, *Padina tetrastromatica,* and *Padina gymnosporia* was studied against *Staphylococcus aureus*. The zone of inhibition of bacterial reproduction ranged from 7.1 to 26.5 mm using methicillin as standard [64]. According to the findings, brown seaweed phlorotannin could be a powerful antibacterial agent against drug-resistant infections. Phlorotannin from marine brown algae has been investigated for various other biological activities including anti-diabetes, anti-allergic, and radioprotective activity.

6.6. Anti-diabetic Activity

Phlorotannin compounds found in brown seaweed were examined for their ability to inhibit diabetic enzymes such as -amylase, -glucosidase, aldose reductase, dipeptidyl peptidase-4, and protein tyrosine phosphatase [70]. The phlorotannin derivatives such as eckol, dieckol, 6,6'-bieckol, phlorofucofuroeckol-A, phloroglucinol, and 7-phloroeckol isolated from E. stolonifera were found to inhibit α-glucosidase at the concentration of IC_{50} -10.7 µM [71]. At an inhibitory dose of 300 mg/kg, phenolic compounds from *Sargassum hystrix* were found to lower blood glucose levels [72]. Phlorotannin has also been demonstrated to reduce diabetes-related complications, implying that it could be

a promising anti-diabetic compound. *Ishige okamurae*, a brown seaweed, contains numerous phlorotannin derivatives, one of which, DPHC, inhibited-amylase and -glucosidase with IC_{50} = 0.53 0.08 mM and IC_{50} = 0.16 0.01 mM, respectively [73]. According to Sugiura *et al*., phlorofucofuroeckol-A, eckol, phloroglucinol, fucofuroeckol A, dieckol, and 8,8'-bieckol from *E. cava* demonstrated anti-diabetic activity. The maximum effect was reported by fucofuroeckol A and dieckol at an IC_{50} value of 7.4 × 10^2 μM [74]. According to these studies, phlorotannin could be employed as an anti-diabetic agent.

6.7. Anti-allergic Activity

Allergy is a reaction to the invasion of foreign particles, which mandates the use of anti-allergic drugs to suppress them. Certain immunological factors responsible for allergic reactions include lymphocytes, cytokines, and chemokines. Eckol, dieckol, 6,6'-bieckol, 8,8'-bieckol, phlorofucofuroeckol-A, and other phlorotannin derivatives from brown seaweed have been shown to have anti-allergic properties in recent investigations [75]. They were discovered to inhibit IgE and receptors on the cell membrane, as well as suppress the release of histamine, which is responsible for allergic reactions. Sugiura *et al*. [76] highlighted the activity of five distinct phlorotannin compounds against Type 1 and Type 4 allergens. On mice strains, *in vivo* experiments on seven different phlorotannin derivatives resulted in the decrease of mouse ear enlargement induced by an allergic response. According to these findings, phlorotannin may be a viable anti-allergic compound.

7. CONCLUSION

According to the scientific sources, phlorotannin contains bioactive compounds that have a higher potential than synthetic substances while having less adverse effects. Phlorotannin was abundant in brown seaweed, which could be used either naturally or by cultivating them in their native habitat. The utility and production of brown algal species besides providing nutraceutical and health benefits also contribute to ecosystem equilibrium. The extraction processes discussed in this review might be used to isolate the desired component so that specific functionalities could be investigated. With advancements in technology, phlorotannin could become a promising medication candidate for a variety of diseases and ailments. *In vivo* investigations for numerous activities are currently absent, which are required for the application of phlorotannin study findings.

8. HIGHLIGHTS

- Availability of phlorotannin from various sources of brown algal species.
- Structure and function of different phlorotannins having unique structure depending on its polymerization.
- Types of extraction methods of phlorotannin from brown algae.
- Quantification, purification, and characterization of phlorotannin using different techniques.
- Various antiviral potential of phlorotannin derivatives.
- Recent researches on various biological application of phlorotannin as anticancer, antioxidant, antioxidant, antiviral, and immunomodulating agent.

9. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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Essentially this study does not require any ethical approval.

13. DATA AVAILABILITY

The data will be provided and made available as per the genuine interest and as per the journal policy.

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