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REVIEW ARTICLE **OPEN ACCESS**

A Review on Pharmacological Aspects of Phlorotannins derived from Brown Algae

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ABSTRACT

Brown algae are a rich source of various specialized secondary metabolites which play a very important role in defense mechanism against pathogens and also play a vital role in various biological activities. Phlorotannin is one of the prominent secondary metabolites which is found in brown algae and is formed by the polymerization of phloroglucinol. Their molecular weight ranges from 126 kDa – 650 kDa. The Phlorotannins exhibit different biological activities like anti – diabetic, anti-proliferative, antioxidant, anti –HIV, antimicrobial and skin protection. These activities of the Phlorotannins are used in the field of pharmacology and medicine to cure serious ailments/diseases. The main objective of this review is to highlight the importance of the various biological activities of Phlorotannins in the field of medicine and pharmacology. The study also includes structure, biosynthesis, isolation and extraction of Phlorotannins from brown algae.
Keywords: *Brown algae, seaweeds, Phlorotannins, medicinal uses, pharmacological activity*

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INTRODUCTION

Seaweeds or benthic marine algae are the group of plants that are present either in marine or brackish water ecosystem. Like the terrestrial plants, seaweeds also have photosynthetic pigments and with help of sunlight and available nutrients of seawater they are able to perform photosynthesis and produce their own food. Seaweeds are located in the coastal region between high tide to low tide and also in sub-tidal region up to a depth where 0.01% light for photosynthesis is available. Seaweeds do not have true roots, stem and leaf and their whole plant body is called thallus which consists of holdfast (for attachment and nutrient absorption), stipe (for support of blade for photosynthesis) and blade (for photosynthesis and absorption of nutrients). The different algal groups are categorized on the basis of photosynthetic pigments, stored food material, cell wall composition, fine structure of cell and flagella. Based on this, algae are classified into three major groups [2]:

1. Chlorophyta (green algae)- possess photosynthetic pigments chlorophyll a and b, found in fresh and marine habitats. Eg: *Ulva, Chlorodesmis*
2. Phaeophyta (brown algae)- exclusively marine, their color varies from olive – yellow to deep brown and is due to accessory carotenoid pigment and fucoxanthin. The other photosynthetic pigments include chlorophyll a and c, β- carotene and xanthophylls. Eg : *Ectocarpus, Fucus, Laminaria.*
3. Rhodophyta (Red Algae)- exclusively marine, presence of water-soluble pigments the red phycoerythrin and the blue phycocyanin gives them their characteristic red color. Other pigments present are chlorophyll a ,b , carotene etc. Eg: *Porphyra, Champia, Gelidium* [2]

Seaweeds are very important plants and are used for various purposes like in chemical and textile industries, agriculture, pharmaceuticals and medicines [2]. Nowadays major attention is being given to the seaweeds because of their potential health benefits and they are also considered to be rich source of various bioactive substances which can be used in pharmaceutical industries. A brief account of the various biologically active compounds found in seaweed extracts are listed below in the following table:

Name of the compound	Biological Activity	Examples	References
Polysaccharides	Prebiotics, antimicrobial, antiviral, anti -tumor, anti – inflammatory, antioxidant, antithrombotic, anticoagulant activity	Fucoidan, Alginates and Laminarin obtained from brown seaweeds	[3], [49-57]
Proteins	Antiviral, antimicrobial, anti-inflammatory and antioxidant activity, mediate intercellular communication, source of essential and important amino acids	Lectins – an important bioactive protein extracted from macroalgae	[3], [58-59]
Polyunsaturated fatty acids (PUFAs)	Antibiotic, health improving and antifungal activity	The major classes of lipids found in seaweed are phospholipid and glycolipids. At low temperature PUFA gets accumulated in seaweeds.	[3], [60-61]
Pigments	Antioxidant, anti –inflammatory, antiviral, neuroprotective, anti – obesity, anti – angiogenic, anticancer activity	Chlorophylls, carotenoids (β-carotene, fucoxanthin, tocopherol), phycobiliproteins	[3], [55], [69-73]
Polyphenols	Host defense activity, antioxidant, antimicrobial, antiviral, anti – photoaging, anti-obesity, antiallergic, anticancer activity	Phenolic acids, flavonoids, isoflavones, cinnamic acid, benzoic acid, quercetin, lignans and Phlorotannins.	[3], [53], [62], [64], [74-82]
Minerals	Health improving activity and promotes growth	Metal ions (K^+, Mg^{2+}, Ca^{2+}, Na^+) from marine water get accumulated by seaweeds and they concentrate them as carbonate salts in their fronds.	[3], [62]
Plant growth hormones	Growth stimulators, regulate cell division, host defense and protective activity, stimulates root formation, source of nitrogen for plants	Cytokinins, Auxin, Gibberellins	[3], [63-68]

Among all the different groups of algae, brown algae are abundant in the bioactive compounds mainly Phlorotannins. Phlorotannins are the polyphenols of brown algae that possess different biological and pharmacological activities like anti- diabetic, anti- cancer, anti- hypertension, antioxidant, anti-HIV, anti-allergy, antimicrobial, anti – photoaging etc. These biological activities of Phlorotannins help in the treatment of various ailments thus becoming promising candidates in the pharmacological industry [4-5].

Structure and biosynthesis of Phlorotannins

The monomeric unit of Phlorotannins is phloroglucinol (1,3,5- trihydroxybenzene) and is biosynthesized by acetate – malonate pathway and its polymerization through C-C and/or C-O-C oxidative coupling which leads to more than 150 highly hydrophilic Phlorotannins. Two molecules of acetyl co- enzyme A are converted to malonyl co- enzyme A by the addition of carbon dioxide. A polyketide structure is created by the formation of a polykeyomethylene chain which is in turn formed by three malonyl CoA units. This structure undergoes a Claisen type cyclization reaction to generate a hexacyclic ring system. This ring undergoes tautomerization to form phloroglucinol which is thermodynamically more stable. An enzyme complex carries out all these reactions that converts acetyl CoA to malonyl CoA into final product without formation of any intermediates. This enzyme complex is known to combine both polyketide synthase and polyketide cyclase activities. Phlorotannins are categorized into six major groups based on the type of linkages between the phloroglucinol units and their content of hydroxyl groups. The six major groups are fucols with aryl-aryl linkages, phlorethols with aryl-ether linkages, fucophlorethols with aryl-aryl and aryl-ether linkage, fuhalols with aryl-ether linkage and additional –OH group in every third ring, carmalols with a dibenzodioxin moiety and is a derivative of phlorethols and lastly eckols with one three ring moiety with a dibenzodioxin element substituted by a phenoxyl group at carbon -(C) 4 **(Fig 1.)** [6-8], [82-84].

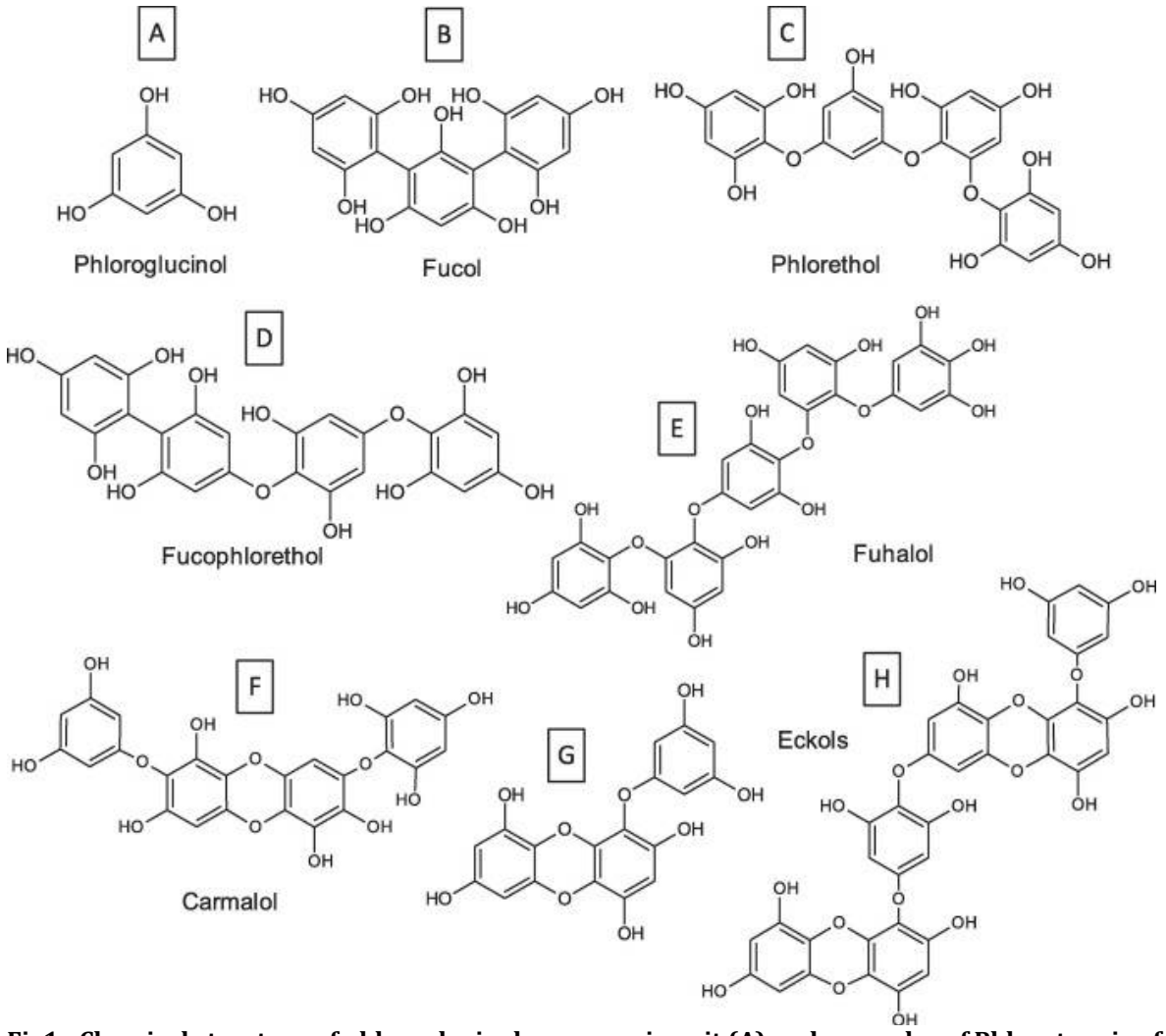

Fig1: Chemical structure of phloroglucinol monomeric unit (A) and examples of Phlorotannins for each of the six major categories: B- Trifucol, C- tetraphlorethol, D- Fucodiphlorethol, E- Pentafuhalol, F- Diphlorethohydroxycarmalol, G- Eckols, H- Dieckol.

Isolation and Extraction of Phlorotannins

Natural deep eutectic solvents (NADES) are environment friendly and clean green solvents (made by combining substances with high melting points to create a eutectic combination that has a lower melting point than its individual constituents) which were used to extract Phlorotannins from brown algae *Fucus vesiculosus* L. and *Ascophyllum nodosum* L. Algae were extracted by maceration for 120 min at 50ºC with a 1:5 raw material: extractant ratio and quantification of Phlorotannins was done by spectrophotometry using the Folin-Ciocalteu method. The maximum extraction was achieved through aqueous NADES solution based on choline chloride with added lactic or malic acid and also on betaine and malic acid [9]. The traditional method of extraction is the solid liquid extraction (SLE) by maceration. In SLE technique the yield and composition of extracts depends on the type of solvent, the solid- liquid ratio, extraction time and temperature. In this method the matrix is in contact with high volumes of solvents for long periods at room or high temperature [7], [85-87]. High polyphenol content and antioxidant activities were achieved with *S muticum* extracts by using the pressurized hot liquid extraction (PHLE) with a 75:25 ethanol-water mixture [7]. Microwave –assisted extraction (MAE) and ultrasound- assisted extraction (UAE) are some eco-friendly processes used for extraction. Phlorotannins yield and purity of extracts was enhanced using optimized aqueous MAE procedure (solid to solid ratio 1:30, 160ºC, 3min) thereby reducing the extraction time when compared to SLE with organic solvent. This is due to the ability of MAE to decompose the cellular structures according to the images generated through scanning electron microscopy. UAE with ethanol/water mixtures enhances the phenolic content and the antioxidant activity and also reduces the maceration time [7], [13], [88-90]. Enzyme assisted extraction (EAE) is another method which is based on the hydrolytic activity of proteases and carbohydrases to unbound the cell wall Phlorotannins [7], [91-92]. During

extraction along with Phlorotannins other algal compounds are also extracted thus it is necessary to employ some additional steps like liquid-liquid extraction, solid phase extraction and molecular weight cut-off (MWCO) dialysis to separate the Phlorotannins. Further separations are achieved by using size exclusion chromatography with Sephadex LH-20, reverse phase chromatography and thin layer chromatography. They are either used alone or all at once to achieve a better fractionation [7].

PHARMACOLOGICAL PROPERTIES

Anti-oxidant activity

A free radical is an atom or a molecule that has one or more unpaired electrons in its atomic orbital and is capable of independent existence. Free radicals are formed when oxygen reacts with certain molecules. High concentration of free radicals in body can cause severe oxidative damage and can lead to serious diseases. These generated free radicals are eliminated by antioxidants as they have the ability to neutralize ROS and free radicals. Phlorotannins were extracted from five marine brown algal species (*Saccharina latissima, Alaria esculenta, Laminaria digitata, Fucus vesiculosus and Ascophyllum nodosum)*. Three Phlorotannins groups including soluble Phlorotannins SP, membrane bound Phlorotannins MP and extracted membrane bound Phlorotannins eMP were obtained by two solvent extraction methods (method 1 – methanol, chloroform, deionized water and ethyl acetate applied in sequence and method 2 - methanol, dichloromethane, ethyl acetate and n-butanol used) and were tested for their antioxidant properties by DPPH radical scavenging activity. The DPPH (1,1-diphenyl1-2-picrylhydrazyl) scavenging activity of SP extracts expressed as IC_{50} value was strongest for Ascophyllum nodosum (0.0072±0.0010 mg/ml) and Fucus vesiculosus (0.0038±0.0002 mg/ml) among all the five species by method 1. Method 1 was better for *Fucus vesiculosus* and method 2 was better for *Ascophyllum nodosum* for demonstrating the antioxidant activity of the SP extract. The antioxidant potential which includes Phlorotannins yield and antioxidant activity was higher in MP extracts of Fucus vesiculosus and *Ascophyllum nodosum*, 5890ml/g and 52278ml/g algae respectively when compared to the SP and eMP extracts. The extraction method also had an impact on the antioxidant potential of the different extracts and method 1 was less time and solvent consuming and was much simpler than method 2 [10]. Oligomers of phloroglucinol, eckols, Phlorofucofuroeckol A, dieckol and 8,8' dieckol were isolated from the Laminarian brown algal species *Eisenia bicyclis, Ecklonia cava* and *Ecklonia kurome* which displayed potential phospholipid peroxidation inhibition at 1μM in the liposome system. These Phlorotannins compounds also showed radical scavenging activities against superoxide anion and DPPH at 50% effective concentrations values: 6.5-8.4μM and 12-26μM respectively and were found to be more effective when compared to standard ascorbic acid and α-tocopherol [11]. Extracts obtained from *Fucus serratus* through ultrasound assisted extraction UAE method also showed the strongest DPPH scavenging activity (29.1±0.25 mg trolox equivalent/g) and ferric reducing antioxidant power FRAP values (63.9±0.74 mg trolox equivalent/g) [12]. Extraction of Phlorotannins from *Carpophyllum flexuosum* through microwave assisted extraction showed significant antioxidant activity (62.1 mg gallic acid equivalent/g dw of seaweed) and more than 5.5 times greater DPPH scavenging activity than ascorbic acid thus becoming a promising natural antioxidant [13]. Phlorotannins isolated from *Sargassum vulgare* also displayed potential antioxidant activity which was tested using DPPH, ABTS, superoxide and galvinoxyl and cupric reducing antioxidant capacity (CUPRAC), reducing power (FRAP) and phenanthroline assays [128].

Anti –inflammatory activity

Inflammation is an important defense mechanism of the body. Phlorotannins from brown algae like *Eisenia bicyclis* showed potential anti-inflammatory activities by inhibiting various activities like lipopolysaccharide (LPS) induced nitric oxide (NO) production, t-BHP (tert-butyl hydroperoxide) induced ROS (reactive oxygen species) formation and also reduced the expression of iNOS (inducible nitric oxide synthase) and COX-2(cyclooxygenase-2) in RAW 264.7 murine macrophage cells which eventually lead to the suppression of NF-kB pathway [14]. Phlorofucofuroeckol A isolated from *Ecklonia stolonifera* also inhibited the LPS induced NO and PGE_2 (prostaglandin E_2) formation by suppressing iNOS and COX-2 expression thus serving as a potential anti-inflammatory agent [15]. Phlorotannins extracts from *Ecklonia cava* also suppressed the levels of iNOS, COX-2 TNF-α,IL-6 and HMGB -1 thereby inhibiting the NF-KB pathway thus increasing the survival rate of LPS-induced septic shock mouse. Dieckol was the major component in the extract which was responsible for reducing mortality, tissue toxicity and serum levels of the inflammatory components in septic mouse [16]. Phlorotannins extract from the sporophyll of *Undaria pinnatifida* also exhibited anti-inflammatory activities by suppressing the production of NO at all the testing conditions in the LPS-induced RAW 264.7 cells [17]. Crude Phlorotannins extracted from *Eisenia bicyclis* exhibited anti-inflammatory effects by reducing the expression of IL-1,6,8, chemokine CXCL10, NF-κB and TNF-α in differentiated human monocytic cell line LPS-induced THP1 cells [127]. Phlorotannins isolated from *S. vulgare* also showed dose dependent inhibitory activity against high temperature-induced protein denaturation thereby contributing to its anti-inflammatory activity [128]. Through all these findings it is

clear that the Phlorotannins derived from brown algae show significant anti-inflammatory potential and thus can be used for the treatment of various inflammatory diseases.

Antimicrobial activity

Phlorotannins extracted from algae *Ecklonia kurome* demonstrated bactericidal activity against 35 tested strains and among all the strains *Campylobacter sp* were most sensitive to the crude extracts followed by *S. aureus* and only 2 strains of *Vibrio* were killed within 2 hours at twice the MBC (minimum bactericidal concentration). For all the purified Phlorotannins the MBCs were lowest for *Campylobacter jejuni* when compared to other strains. Overall the bactericidal effects of Phlorotannins was found to be stronger when compared to the standard catechins thus serving as important antimicrobial agents [18]. Fucofuroeckol-A(FFA) isolated from *Eisenia bicyclis* displayed highest anti-listerial potential against the tested *Listeria monocytogenes* LM strains with MIC (minimum inhibitory concentration) range 16-32µg/ml. FFA-streptomycin combination also showed significant cooperation against the aminoglycoside resistant clinical LM strains [19]. Phlorotannins extracted from *Cystoseria nodicaulis, Crassiphycus usneoides* and *Fucus spiralis* exhibited antifungal activity against *Candida albicans, Epidermophyton floccosum* and *Trichophyton mentagrophyte* with MIC values ranging from 3.9 to 31.4 mg/ml. FFA isolated from *Eisenia bicyclis* and dieckol isolated from *Ecklonia cava* show MIC of 512µg/ml against *C. albicans* and MIC of 200 µM against *Trichophyton rubrum* respectively [20]. The ethyl acetate fraction of the methanolic extract of *Eisenia bicyclis* exhibited strongest antibacterial activity against the acne-related bacteria. FFA with MIC ranging from 32 to 128 µg/ml showed highest antibacterial activity and also reversed the erythromycin and lincomycin resistance of *Propionibacterium acnes* [21]. The ethyl acetate fraction of the methanolic extract of *Eisenia bicyclis* contained dieckol which showed strongest anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity with MIC values ranging from 32 to 64µg/ml [22]. Low molecular weight Phlorotannins extracted from *Sargassum thunbergii* also showed antibacterial activity against *Vibrio parahaemolyticus* through cytoplasm leakage and membrane permeability caused due to damaged cell wall and membrane [23]. Extract of *Desmarestia aculeate* displayed strongest antibiotic effect with MIC values ranging from 4 (*S. cerevisiae)* to 300 (*Chlorella)* µg/ml and maximum loss of *E. coli* cells occurred after 5-h long exposure of the Phlorotannins extracts. Extract of *Ectocarpus siliculosus* had the lowest MIC values and that of *Dictyosiphon foeniculaceus* and *Chordaria flagelliformis* showed moderate antibiotic activity. Extracts of *Pylaiella littoralis* were least toxic towards all the tested microbes [24].

Anti-photoaging activity

Skin cancer and other photoaging complications occur due to continuous exposure to UV irradiation both UV-A and UV-B. Phloroglucinol isolated from *E. cava* showed strong cryoprotective effects in UVB-irradiated HaCat cells and these anti-photoaging activities of these Phlorotannins is related to their radical scavenging activity thereby inhibiting the ROS generation and damage of macromolecules. They do not cause any harmful effects thus can be used as safe anti-photoaging agents in skin care and cosmetic products [25]. Dieckol shows maximum activity against photo-oxidative stress and also decreased the generated ROS which was 100.7% at 250µM and it also exhibited 57.8% protective properties against UVB radiation-induced DNA damage at a concentration of 50µM. The brown algal polyphenols also inhibit skin cancer induced by UV-B radiations in SKH-1 hairless mouse skin model by suppressing the COX-2 expression and cell proliferation. Due to all these activities Phlorotannins can be used for the preparation of cancer treatment drugs against photocarcinogenesis and can also give protection against harmful effects of UVB radiations [5].

Anti-cancer activity

The anti-cancer activity of the Phlorotannins extract isolated from *Laminaria japonica* Aresch was evaluated through MTT assay by incubating the human hepatocellular carcinoma cell (BEL-7402) and murine leukemic cells (P388) with the extract for 48 hrs. The rate of inhibition of the extract on BEL-7402 and P388 cells was 30.20±1.16% and 43.44±1.86% respectively and the half- inhibitory concentration of extract (IC_{50}) on P388 and BEL-7402 cells was 120µg/ml and >200µg/ml respectively. The ethyl acetate fraction of extract designated as sample A was further purified to A_1 and A_2 and it was found that for A_2 the apoptosis peak was the most prominent out of all fractions used in the flow cytometry assay [26]. Crude extracts isolated from *E. bicyclis* and *E. kurome* displayed inhibitory effects against hyaluronidase enzyme which was stronger than that of catechins and DSCG, an anti-allergic drug. Further the isolated Phlorotannins Phlorofucofuroeckol A, dieckol and 8,8'-bieckol were also active and acted as competitive inhibitor of the enzyme. Among all the isolated Phlorotannins 8,8'-bieckol displayed 80% inhibition at 100µM and was the most effective against the enzyme and thus can be used to prevent cancer migration, allergy and inflammation [27]. Dieckol from *E. cava* enhanced the efficacy of cisplatin drug on the A2780 and SKOV3 ovarian cancer cell lines by enhancing the cancer cell apoptosis through the ROS/Akt/NFkB pathways and also inhibiting the cisplatin-induced nephrotoxicity [28]. Phlorethols isolated from *Costaria costata* is a direct inhibitor of α-N-acetylgalactosaminidase isolated from HiikjuTu 80 and SK-MEL- 28 cells

by inhibiting the catalytic residues of the enzyme thereby suppressing the activity of this enzyme in these cells upto 50% at concentrations of 15.2±9.5 and 5.7±1.6 µg/ml respectively [29]. Phlorethols isolated from *Costaria costata* also demonstrated cytotoxic activity against the HT-29 and HCT 116 cells at IC_{50} of 92 and 94µg/ml respectively. They significantly reduced the colony formation in colon cancer cells and also made them sensitive towards low non-toxic X-ray radiations thus demonstrating their potential as radiosensitizers to improve the radiotherapy treatment [30]. Phlorotannins from *Cystoseira sedoides* also demonstrated anti-cancer activity against MCF-7 breast cancer cell lines and also induced apoptotic death in more than a half of the cell lines at the IC_{50} value 78 µg/ml [31].

Anti-diabetic activity

Proper dietary intake and control of blood glucose levels is very essential in diabetic patients. Phlorotannins extracted from *E. stoloifera* acted as a strong inhibitor of α-glucosidase and also suppressed the blood glucose and lipid peroxidation levels in male KK-A^y mice, a genetically non- insulin dependent diabetic model [32]. Phlorotannins isolated from *Ecklonia stolonifera* and *Eisenia bicyclis* displayed significant inhibition of protein tyrosine phosphatase 1B and α-glucosidase with IC_{50} value ranging from 0.56 to 2.4 µM and 1.37 to 6.13 µM respectively which could lead to the development of therapeutic agents to control the blood glucose levels and help in preventing diabetes [33]. Phlorotannins from *Ecklonia kurome* demonstrated inhibitory effect on carbohydrate-hydrolyzing enzymes and also suppressed the postprandial blood glucose levels. They also improved the glucose tolerance and decreased fasting blood glucose and insulin levels, fructosamine and glycoalbumin levels in KK-A^y mice thus proving to be effective against diabetes mellitus type 2 [34]. Fuhalols isolated from *Cystoseira compressa* reduced the serum glucose, liver malondialdehyde and α-amylase glucosidase activities and histopathological examination showed that there was a reduction in damage to β –cells of the pancreas thereby demonstrating their anti-diabetic activities [35]. Advanced Glycation End products (AGE) are associated with diabetes and other chronic ailments. The Phlorotannins isolated from *Padina pavonica, Sargassum polycystum* and *Turbinaria ornate* exhibited anti-AGE activity when examined in-vitro by BSA-glucose assay with the extracted Phlorotannins and the results showed that the IC_{50} were lower for the extracts as compared to the control. 100µl Phlorotannins extract also displayed protective effects against the AGE formation in-vivo in hyperglycemia-induced *Caenorhabditis elegans* [36]. Phloroglucinol derivatives isolated from *E. cava* demonstrated anti-diabetic activity by showing inhibitory action against rat intestinal α-glucosidase and porcine pancreatic α-amylase and dieckol among all the derivatives had the lowest IC_{50} value –10.8 µmol/l for α-glucosidase and 124.9 µmol/l for α-amylase and also acted as a non-competitive inhibitor of α-glucosidase thus serving as a potential natural anti-diabetic agent [37]. Crude Phlorotannins extracted from *Eisenia bicyclis* exhibited increased IRS/AKT- dependent glucose absorption and also activated the AMPK pathway and also showed anti-α-glucosidase activity and promoted 2-NBDG absorption in differentiated C2C12 myotubes under both basal (16.08%) and insulin-stimulated (51.09%) conditions thereby indicating their role in treating hyperglycemia [127].

Anti-hypertensive activity

6,6'-bieckol isolated from *E. cava* exhibited inhibition of angiotensin 1-converting enzyme (ACE) and production of NO. Oral administration of the compound also down-regulated the systolic blood pressure in spontaneously hypersensitive rats thus indicating their potential application in the treatment of hypertension [38]. Dieckol from the ethanol extract of *E. cava* showed strong inhibitory effect against ACE and was also found to be a non-competitive inhibitor of ACE according to the Lineweaver-Burk plots. It also had an inducible effect on the production of NO in the endothelial cell line EAhy926 from the inner lining of the human blood vessels [39]. Phlorotannins were obtained from *Sargassum wightii* through silica column chromatography and preparative thin layer chromatography. The extracted Phlorotannins exhibited inhibition of ACE in mixed type manner with IC_{50} value of 56.96µg/ml and the inhibitor constant K_i value of 45µg/ml thus indicating potential anti-hypertensive activity [40].

Anti-allergic activity

Phlorotannins such as eckols, 6,6'-bieckol, 6,8'-bieckol, 8,8'-bieckol, Phlorofucofuroeckol-A and Phlorofucofuroeckol-B were isolated from *Eisenia arborea* and it was observed that most of them exhibited similar to or even greater than the typical inhibitor epigallocatechin gallate (inhibiting the β—hexosaminidase release from the rat basophilic leukemia-2H3 cells). Among all the tested Phlorotannins Phlorofucofuroeckol-B demonstrated greatest activity which was 2.8 times greater than that of the standard inhibitor epigallocatechin gallate [41]. Fucophlorethol -G and Phlorofucofuroeckol- A were isolated from *Ecklonia cava* and were tested for their anti-allergic effect on human basophilic leukemia ($KU8_{12}$) and rat basophilic leukemia (RBL-2H3) cell lines via histamine release assay. Both the compounds displayed potential inhibition of histamine release by suppression of the binding activity between IgE and FcεRI and thus can be used in the drug and cosmetic industries [42].

Hepatoprotective activity

Hepatoprotective activity of dieckol-rich Phlorotannins (DRP) isolated from *Ecklonia cava* was tested on ethanol-induced hepatic damage in BALB/c mice liver. After administering 5 and 25mg/kg mouse of DRP and 4g/kg mice ethanol, the body weight and survival rates were increased when compared to control group which was ethanol-treated and without DRP. DRP also demonstrated reduced levels of total cholesterol, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase when compared to the control group thus indicating protection of liver against ethanol-induced liver injury [43]. Active ethyl acetate fraction from ethanolic extract of *E. stolonifera* resulted in isolation of various Phlorotannins and among them eckstolonol and Phlorofucofuroeckol- A protected the Hep G2 cells against the cytotoxic effects of tacrine with EC_{50} values of 62.0 and 79.2 µg/ml thereby demonstrating their hepatoprotective function [44]. Phlorotannins extracted from *E. bicyclis* were tested for their hepatoprotective activity against tert-butyl hyperoxide injured HepG2 cells. Phlorofucofuroeckol- A exhibited strongest protective activity (45.54%) at a 10µM concentration. At a dose level of 40µM the protective activities of 6,6'bieckol, dieckol and Phlorofucofuroeckol- A was higher than that of quercetin treatment at 10µM concentration. Thus, due to these activities the isolated Phlorotannins can act as natural hepatoprotective agents [45]. Extracts isolated from *Saccharina japonica* exhibited hepatoprotective activity in rat liver during carbon tetrachloride poisoning and the extracts also reduced the level of free radicals, eliminated tissue hypoxia and also restored the quantity of total lipids to normal levels in the liver [46]. Phloroglucinol isolated form *E. bicyclis* successfully inhibited the LPS-induced inflammatory responses in HepG2 cell lines by suppressing the production of inflammatory cytokines such as IL-1β, IL-6 and TNF-α and reducing the expression of COX-2 and iNOS. These activities suggest that the Phlorotannins (phloroglucinol) isolated from *E. bicyclis* are having hepatoprotective properties and can prevent inflammatory responses [47].

Anti - Adipogenic Activity:

Obesity is one of the most prevailing health issues and it leads to several diseases like type 2 diabetes, cardiovascular problems and hypertension. Increase in the number of mature adipocytes is the main cause of obesity [93-94]. Phlorotannins from brown algae are effective in reducing adipogenesis and obesity. Phlorotannins like triphlorethol-A, eckols and dieckol extracted from *E. cava* significantly increased the glycerol secretion and reduced the regulation of adipogenic transcription factors, peroxisome proliferator-activated receptor-γ (PRAR-γ), CCAAT/enhancer binding protein α (C/EBPα) and TNFα and also reduced the glucose consumption levels of 3T3-L1 adipocytes. They also reduced the expression levels of differentiation-dependent factor/sterol regulatory element-binding protein 1c, downstream genes such as fatty acid binding protein-4, fatty acid transport protein-1, fatty acid synthase, leptin and acyl-CoA synthetase 1 [95-96]. Phlorotannins like triphlorethol-A, eckols and dieckol suppressed adipogenesis in preadipocytes and also reduced lipid accumulation and suppressed the adipogenic differentiation markers [97]. Dieckol from *E. cava* reduced lipid accumulation in dieckol-supplemented mice group. LDL cholesterol level was reduced by 55% and late adipogenic factors were downregulated resulting in decrease in triacylglycerol content. Dieckol activated AMP-activated protein kinase α signaling to stop the lipid synthesis in 3T3-L1 and mouse model [98]. In another study phloroglucinol, eckols, dieckol, dioxinodehydroeckol and Phlorofucofuroeckol A isolated from *E. stolonifera* significantly reduced the lipid accumulation in 3T3-L1 cells in a dose dependent manner without affecting the cell viability. These compounds also reduced the levels of PRAR-γ and CCAAT/enhancer binding protein α (C/EBPα) [99]. Dieckol from *E. cava* displayed adipogenesis inhibition and downregulation of the expression of PRAR-γ, CCAAT/enhancer binding protein α (C/EBPα), sterol regulatory element binding protein 1 (SREBP1) and fatty acid binding protein 4 (FABP4) in a dose dependent manner [100].

Anti-HIV activity:

8,4"-dieckol isolated from *E. cava* was successful in inhibiting HIV-1 induced syncytia formation, lytic effects and viral p24 production at non-cytotoxic concentrations. It was also reported that the compound selectively inhibited the activity of HIV-1 reverse transcriptase (RT) enzyme with 91% inhibition ratio at 50µM concentration. HIV-1 entry was also stopped by 8,4"-dieckol [120]. In another study five species of phaeophyta (*E. cava, Ishige okamurae, Sargassum confusum, Sargassum hemiphyllum, Sargassum ringgoldianum* displayed inhibitory activities against 3'-processing activity of HIV-1 integrase. 8,8'-bieckol and 8,4"-dieckol displayed inhibitory effect on HIV-1 reverse transcriptase and protease and the inhibitory effect of 8,8'-bieckol at IC_{50} 0.51µM against HIV-1 RT was comparable to that of the standard compound nevirapine (IC_{50} 0.28µM). Diphlorethohydroxycarmalol obtained from *Ishige okamurae* exhibited inhibitory effects on HIV-1 RT and integrase with IC_{50} values of 9.1µM and 25.2 µM respectively. 6,6"-dieckol isolated from *E. cava* was also successful in inhibiting HIV-1 induced syncytia formation (EC_{50} 1.72µM), lytic effects (EC_{50} 1.23µM) and viral p24 antigen production (EC_{50} 1.26µM) at non-cytotoxic concentrations. It was also reported that the compound selectively inhibited the activity of HIV-1 reverse transcriptase (RT) enzyme with EC_{50} 1.07µM. All these activities of the Phlorotannins make them potential

candidates for the development of drugs against HIV [121-125]. Another study was done on the viral protein U (Vpu) which is responsible for the dissemination of the HIV viral particles and it was observed that Phlorotannins like bisfucotriphlorethol B, tetrafuhalol B, bisfucotetraphlorethol A, hexaphlorethol A and 6,8'-bieckol demonstrated inhibitory effect against Vpu thus exhibiting a novel approach to combat HIV by using marine natural products [126].

Other activities:

Other activities of the Phlorotannins that have been reported are sleep induction, arousal inhibitory effect, inhibition of SARS-CoV 3CL replication, antiviral activity, Alzheimer disease treatment, inhibitory effect against melanin synthesis, neuro-protective activity, osteogenesis, inhibitory effect on neuraminidase, anti-arthritis activity, glycosidase inhibition, antiplasmin inhibitor, carbolytic enzyme inhibition and high glucose-induced oxidative stress inhibition. [94], [101-119]

CONCLUSION

The review work done on Phlorotannins of brown algae made it clear that these large groups of marine algae are not only used for food production but are also a rich source of various secondary metabolites. Among all the secondary metabolites Phlorotannins are the most prominent because of their various pharmacological activities which play a vital role not only in algae but as well as in improving the human health and nutrition. Nowadays human beings are relying more on natural resources for producing drugs as they have better efficacy, easy availability and minimum or negligible side effects and that's why Phlorotannins from brown algae have become subjects of intense research and they serve as promising candidates for designing new functional foods, cosmetics and medicines for betterment of mankind.

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