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REVIEW

Phlorotannins are Polyphenolic Metabolites of Brown Algae

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Abstract—This review is devoted to the analysis of publications on studies of phlorotannins, which are polyphenolic metabolites of brown algae. Their properties, the pathway of biosynthesis, and the structural diversity and classification of phlorotannins, as well as the methods for their isolation and determination of their metabolic profiles, are examined. The antioxidant, antitumor, and antimicrobial activities of phlorotannins and their role in the regulation of enzyme activity are discussed. These properties of phlorotannins determine the prospects of using phlorotannins in pharmacology.

Keywords: brown algae, phlorotannins, fucols, phlorethols, eckols, fucophlorethols, biological activity

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INTRODUCTION

Polyphenolic secondary metabolites are a large group of chemical compounds found in terrestrial plants [72] and in algae [1, 49]. Tannins are a widespread group of phenolic metabolites that contain a large number of hydroxyl groups. Tannins are divided into three groups. Condensed tannins (based on flavonoids) are found mainly in woody plants, as well as in red wine and in tea [53]. Hydrolysable tannins formed by polyhydric alcohol, in which hydroxyl groups are partially or completely etherified with gallic acid or related compounds, are found in some green algae and are widely distributed in angiosperms [72]. Phlorotannins are polymeric derivatives of phloroglucinol, which are found only in brown algae and are the least-studied group.

Despite the more than 40-year study of phlorotannins, interest in these compounds has been increasing, as shown by the many recent publications [22, 28, 73]. Practical interest in phlorotannins is explained by their low toxicity and their biological activity, primarily antioxidant action [10, 37]. This review focuses on the development of methods for the isolation of phlorotannins, their structural diversity, functions in plants, and the biological activities manifested by phlorotannins.

PROPERTIES, BIOSYNTHETIC PATHWAY, STRUCTURE AND CLASSIFICATION OF BROWN ALGAL PHLOROTANNINS

Phlorotannins are phenolic metabolites of brown algae. Like tannins of terrestrial plants, these phenolic compounds contain a great number of hydroxyl groups, are highly soluble in water, bind strongly to proteins, polysaccharides, and other biopolymers, chelate divalent metals, and have a polymeric structure. Compared to tannins, phlorotannins have a wider mass range (from 126 to 1×10^5 Da and higher) and a different structure [38, 44, 69]. The monomeric unit of phlorotannins is phloroglucinol (1,3,5-trihydroxybenzene). It is assumed that the biosynthesis of phloroglucinol is developed along the acetate–malonate (polyketide) pathway. Two molecules of acetyl-CoA in the presence of carbon dioxide are converted into malonyl-CoA. The polyketomethylene precursor formed by the three malonyl-CoA blocks is subjected to a "Claisen type" cyclization reaction, which leads to the formation of a hexacyclic ring system. A thermodynamically more stable molecule of phloroglucin is formed upon tautomerization of this system (Fig. 1). An enzyme complex that includes polyketide synthases and polyketide cyclases (it converts acetyl-CoA and malonyl-CoA to the final product without any intermediate products [2, 62]) catalyzes the sequence of these reactions.

The phloroglucinol residues connect through C–C and/or C–O–C oxidative couplings, to form polymeric molecules of florotannins with diverse structures. In terms of the type of the linkage of monomers, phlorotannins can be divided into four classes [38]: fuhalols and phlorethols (an ether bond), fucols (a phenyl bond), fucophlorethols (ether and phenyl bonds), as well as eckols and carmalols (a dibenzo-dioxin bond). Within each class, the binding of monomers to each other can take place at different positions of the phloroglucinol ring, resulting in the formation of structural isomers in addition to conformational ones.

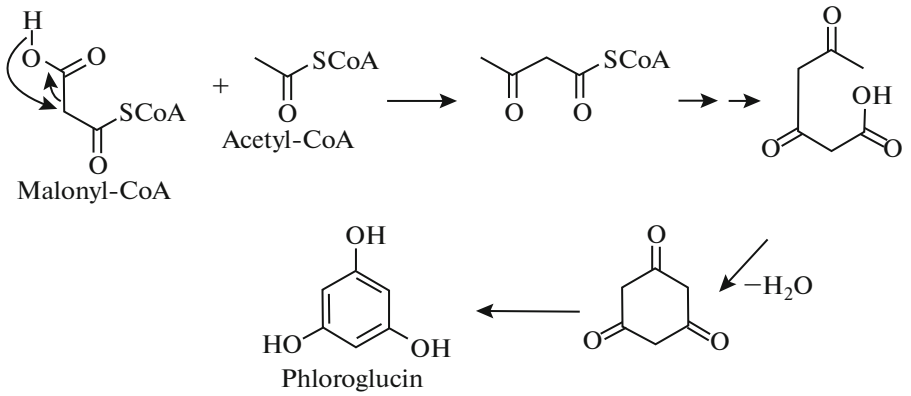


Fig. 1. The scheme of the biosynthesis of phloroglucinol (after: [62]).

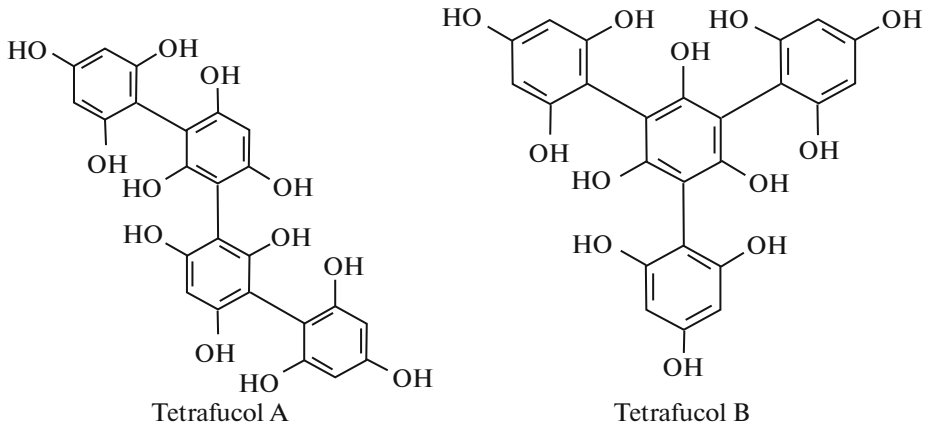


Fig. 2. Examples of the structures of linear and branched fucols.

With an increase in the degree of polymerization of phlorotannins, their structural diversity also increases; thus, it becomes necessary to use other criteria for classification. The compounds of each class can be grouped into linear phlorotannins (the C–C and/or C–O–C oxidative couplings have only two terminal phloroglucinol residues), or branched phlorotannins if they are bound to three or more monomers. In fucols, the phloroglucinol units can only be in the meta-position, as in tetrafucol A (linear) and tetrafucol B (branched) (Fig. 2) isolated from *Fucus vesiculosus* [13]. Longer oligomers (penta- and heptafucols) are isolated from *Scytothamnus australis* and *Analipus japonicus* [12, 18]. Linear phlorethols can have ortho-, meta-, and para-oriented C–O–C oxidative phenolic couplings or their combinations (Fig. 3), as in tetraplorethols A and B, isolated from *Laminaria ochroleuca* [29]. Branched phlorethols (tetraphlorethols C and E) are isolated from *Ecklonia maxima* [17]. In fuhalols, the end monomer unit of phlorethols has an additional hydroxyl group, for example, bifuhalol [13, 15], trifuhalol A with paraphenyl, and ether bridges or ortho-ordered trifuhalol B [11] (Fig. 4). Some fuhalols with more than one additional hydroxyl group isolated from *Sargassum spinuligerum* have been named hydroxyfuhalols [24].

Another subgroup of phlorethols is formed by eckols, which contain a 1,4-dibenzodioxin element in their structure. Examples of such structures are the trimers eckol and dioxinodehydroeckol, as isolated from *E. maxima* [17] (Fig. 5). The next group of phlorotannins is fucophlorethols; these are formed by combinations of C–C and C–O–C oxidative phenolic couplings between monomer residues; this leads to a high level of structural diversity of compounds in linear, branched, and heterocyclic variants. Trifucotriphlorethol A, isolated from *F. vesiculosus* [42], is an example of branched fucophlorethols; fucophlorethols B and C isolated from *L. ochroleuca* [29] and *Eisenia bicyclis* [27] are examples of linear oligomers. Heterocyclic fucophlorethols contain dibenzo dioxin and furan rings in the structure; these are fucofuroeckols A, B, and C; phlorofucofuroeckol A [9, 35, 37]; and 6,6'-bieckol [27] (Fig. 6).

It was shown based on the example of the algae *E. bicyclis* and *F. vesiculosus* that one species of algae

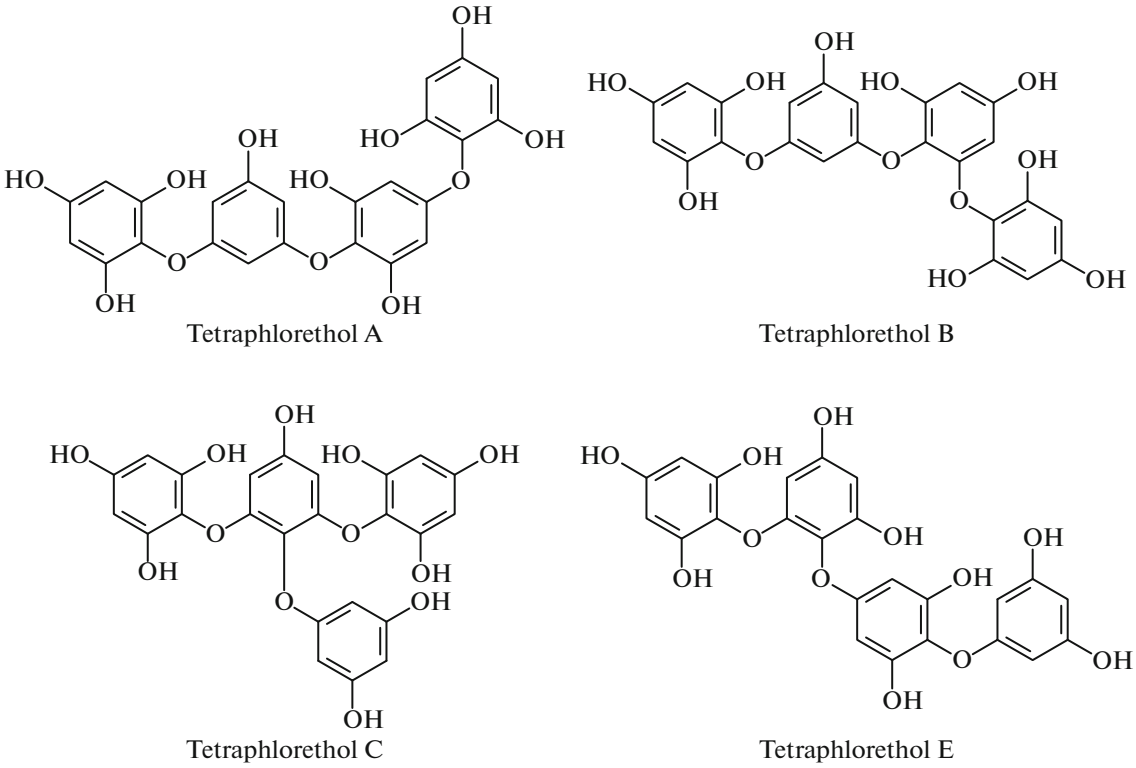


Fig. 3. Examples of the structures of linear and branched phlorethols.

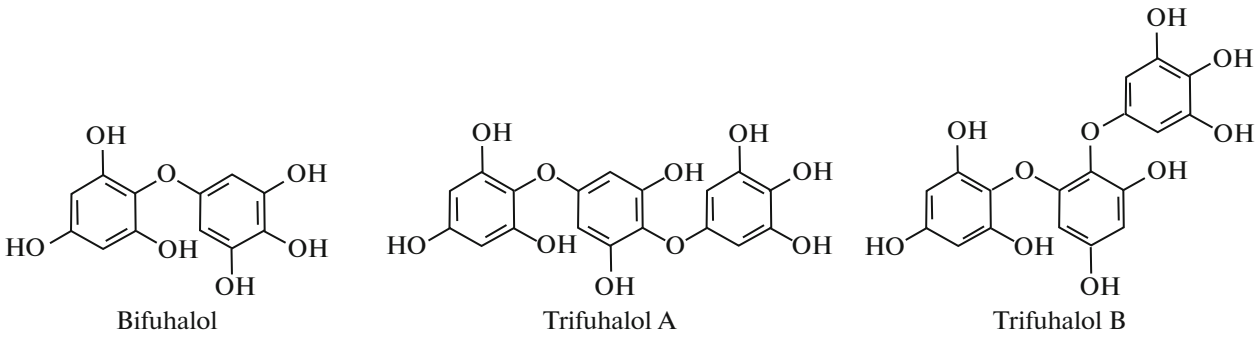


Fig. 4. Examples of fuhalol structures.

can contain phlorotannins with different structures and different degrees of polymerization. Thus, eckol, phlorofucofuroeckol, dieckol and 8,8'-bieckol [58] were isolated from *E. bicyclis;* and 15 fucophlorethols and 4 fucols with a degree of polymerization from three to eight and from two to four monomers, respectively, were obtained from *F. vesiculosus* [13, 42]. The algae *F. visiculosus* and *Ascophyllum nodosum* from the same family Fucaceae that grow under identical conditions (the surf zone and intertidal zone) had phenols with different chemical structures in their composition [63]. It is believed that fucols and fucophlorethols (phlorotannins of the "Fucus type") are characteristic of the algae of the family Fucaceae [6], while phlorethols and eckols are characteristic of algae of the families Laminariaceae and Lessoniaceae [58]. Since brown algae contain phlorotannins with different chemical structures, it was interesting to determine whether there is a connection between the specific structural group of phlorotannins and its role in the plant.

THE CONTENT AND THE FUNCTION OF PHLOROTANNINS IN BROWN ALGAE

The content of phlorotannins in brown algae reaches 15% of the dry weight [8, 49]. This value depends on the habitat of the algae, the time of their

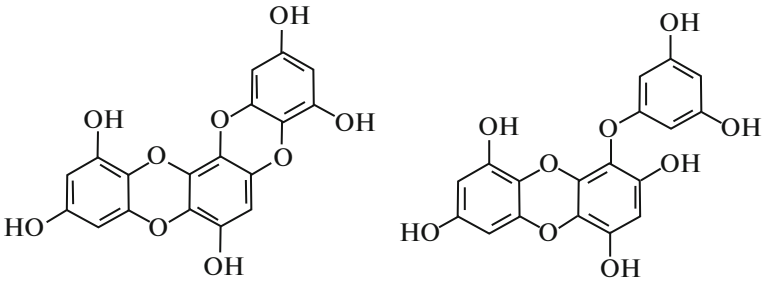


Fig. 5. Examples of eckol structures.

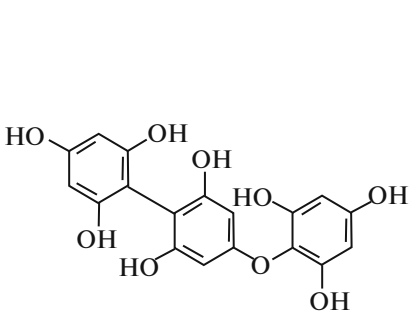
sampling, the intensity of illumination, and other factors [64, 67]. A number of studies have revealed seasonal variability in the content of phlorotannins in algae. As a rule, the maximum value is found in algae of temperate and northern latitudes in summer; this positively correlates with the reproductive status of algae [8, 43, 50]. The content of phlorotannins can vary in a single plant and among plants within the population. As an example, the content of phlorotannins in mature thalli of *Ecklonia cava* was 1.5 times higher than in young specimens [48]. The vegetative parts of *F. vesiculosus* contained more phlorotannins than reproductive parts did [51, 68]. Fertile plants of *Himanthalia elongata* [8] and *Sargassum muticum* [19] contained more phlorotannins than sterile plants have. The *E. cava* thalli contained more phlorotannins than petioles or rhizoids have [7].

It is assumed that in brown algae phlorotannins are present within a cell vacuole, called the physode [47, 49, 54]. Physodes are the main cytoplasmic component of adult plant cells, such as gametes, zygotes, embryos, and spores [49, 54]. Pellegrini [46] detected physodes by electron microscopy in meristodermic and promeristematic cells. It was later found that phlorotannins are accumulated within the vegetative cells of the outer cortical layer of the thalli, regardless of the type of tissue, growth stage, or organ [60]. A significant number of physodes are present in cells that line the mucous channels in the cortex [60]. Physodes were not found [8] in the outer epidermal layer and in the medulla. When the content of the physodes is secreted into the cell wall, phlorotannins form a complex with alginic acid, which is the structural polysaccharide of the cell wall in brown algae. Thus, phenolic compounds are a part of the structural components of the cell walls of brown algae [55–57].

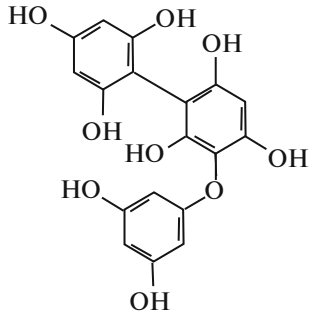
The possible functions of physodes in the plant are widely discussed. Phenols play an important role in the formation and early development of the cell wall. It was suggested that phenolic cross-linking with alginate can occur early in the formation of the cell wall during the development of fucoids [70]. In the early developmental stages of the zygote, physodes accumulate on the periphery of the zygote and are secreted into the primary cell wall. This process is catalyzed by peroxidases [70]. It is assumed that phenols are secreted in two ways: either physodes can be subject to exocytosis and their phenolic content penetrates into the cell wall, forming a phenol–alginate complex, or by detaching small phenol-containing fragments from physodes near the cell surface and further secreting them into the cell wall [54]. Schoenwaelder described participation of phenolic compounds in adhesion [54]. To provide the attachment to the substrate, zygotes are covered with a sticky brown layer consisting mainly of phenolic compounds. It was noted for the zygotes of *Cystophora paniculata* that phenols are secreted immediately after fertilization; this coincides with the process of their adhesion to the substrate [55]. It is believed that the main role of phlorotannins is to protect algae from oxidative stress [66]. The authors suggested that the occurrence of a great number of phlorotannin isomers can be caused by their oxidation and the formation of products with different degrees of oxidation during the collection of algae. This feature is promising for identifying environmental factors that affect the profile of phlorotannin metabolites in some algal species [66].

Phlorotannins exert a physiological effect on herbivores [64]; they inhibit digestive enzymes and protect algae from infections. Phlorotannins from the brown alga *E. bicyclis* were effective inhibitors of α-fuco, β-galacto, and β-mannosidase – enzymes of the digestive tract of the marine mollusk *Turbo cornutus* [58]. Phlorotannins from *Fucus evanescens* inhibited the action of fucoidan hydrolases from the marine bacterium *Formosa algae* and the bivalve mollusk *Patinopecten yessoensis*, as well as the action of β-glucosidase from the gastropod mollusk *Littorina sitkana* [61]. Inhibition of digestive glycosidases of marine invertebrates and bacteria by phlorotannins is a strategy for the survival of brown algae.

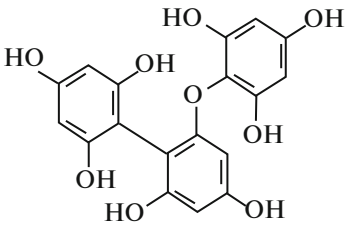
It has been suggested that phlorotannins contribute to the protection of plants from ultraviolet radiation. It is known that phlorotannins strongly absorb a portion of the UV-B spectrum [45]. The highest level of phlorotannins was found in algae of the family Fucaceae, which inhabit the intertidal zone and thus are exposed



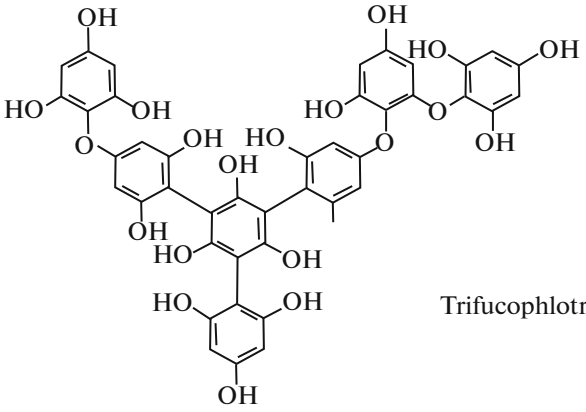
Fucophlorethol A



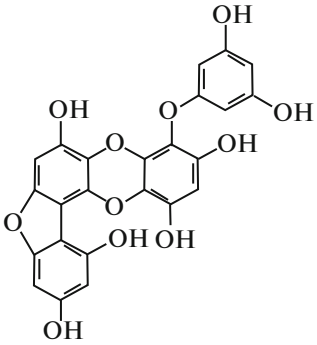
Fucophlorethol B



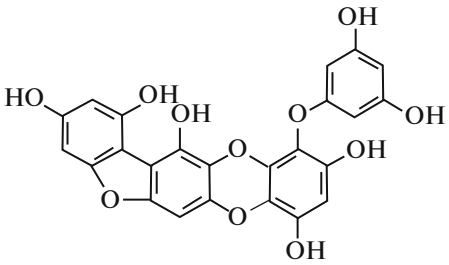
Fucophlorethol C



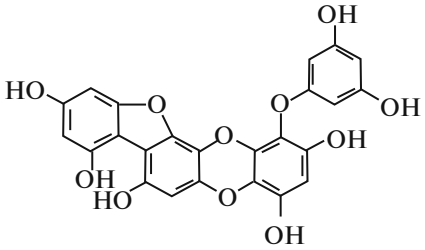
Trifucophlotrethol A



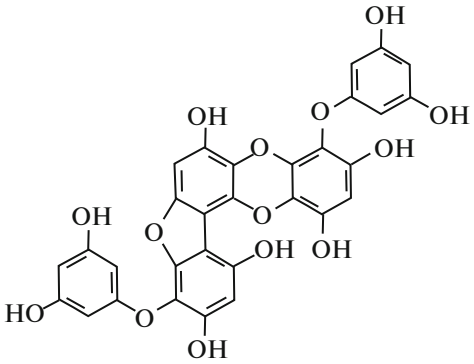
Fucofuroeckol A



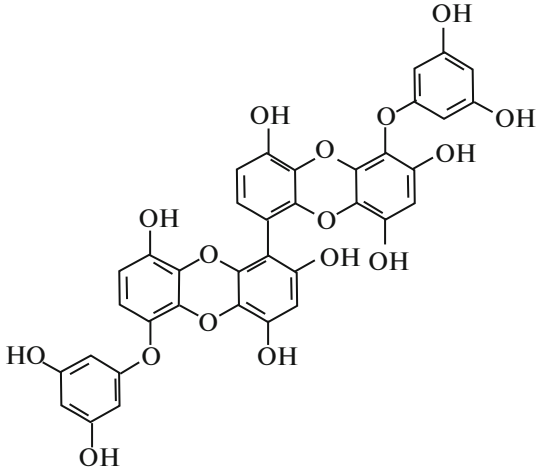
Fucofuroeckol B



Fucofuroeckol C



Phlorofucofuroeckol A



6, 6'-bieckol

Fig. 6. Examples of the structures of linear, branched, and cyclic fucoflorethols.

there for long periods to direct solar radiation [8]. It was experimentally shown for adult plants of *A. nodosum* that the content of phlorotannins increased by 30 at a 50% increase in UV-B radiation [45].

According to Schoenwaelder [54], the "multifunctionality" of phenolic compounds in Phaeophyceae convincingly demonstrates their importance and suggests that phenols belong to the main groups of compounds that are responsible for the evolutionary success of this class of algae.

METHODS FOR ISOLATING PHLOROTANNINS AND DETERMINATION OF THEIR METABOLIC PROFILES

Phlorotannins are unstable polyhydroxylated molecules, which can easily be oxidized. The structural diversity of phlorotannins is extremely high; thus, the development of methods for separation of these metabolites of brown algae is a very important aspect of their successful study. During the development of methods for the isolation of phlorotannins, it is important to consider their reactivity. The classical procedure for extracting phlorotannins involves the following procedures. Phlorotannins are extracted from lyophilized or freshly collected algal material with ethanol, or acetone, or methanol or their aqueous solutions [38]. The content of phlorotannins in the extracts is determined by colorimetric methods, e.g., with the use of the Folin–Ciocalteu reagent [43]. This is a method for quantitative determination of soluble polyphenols that are capable of reacting with the Folin–Ciocalteu reagent in a redox reaction. The subsequent separation of the extract by liquid extraction with organic solvents (most often ethyl acetate) gives an extract rich in phlorotannins. The competitive antioxidants $K_2S_2O_5$ [18] or ascorbic acid [30] are added to extraction solvents to prevent oxidation of phenols. Extraction is carried out under a nitrogen atmosphere [16]. Phlorotannins from phenol-enriched extracts are isolated as peracetates [12]. For this, the extract is acetylated with a mixture of acetic anhydride and pyridine (10 : 8). A mixture of petroleum and diethyl ether (1 : 1) is used to precipitate high-molecular-weight phlorotannins. Chromatography of the low-molecular-weight acetylated phlorotannins is performed on silica-gel columns with gradient elution. Peracetylated phlorotannins are obtained after the final purification of the fractions by high-performance liquid chromatography (HPLC); chloroform–ethanol or chloroform–hexane–ethanol gradients are used as eluents. Most of the currently known low-molecular-weight phlorotannins were isolated by this scheme; from 1974 to 2003, their structures were determined by NMR spectroscopy and mass spectrometry using fast-atom bombardment ionization (FAB-MS) and electrospray (ESI-MS) ionization methods [14, 15, 49].

Separation methods based on the size of the molecules and their polarity are used for the preliminary fractionation of phlorotannins from the phenolic extract [4, 21, 71]. Phlorotannins were fractionated into low-molecular weight, oligomeric and high-molecular-weight fractions using the membrane-separation method [65, 71]. Using chromatography on Sephadex LH-20, Lee et al. [33] identified five phlorotannins from the phenol fraction pre-purified on silica gel. Chromatography–mass spectrometry methods are an attractive option for the analysis of complex phenolic extracts. According to Koivikko [30], normal-phase liquid chromatography (NP-HPLC) is more suitable for separation of polar phlorotannins. Separation of phlorotannins from the phenolic extract of *F. vesiculosus* by HPLC on a silica gel was more effective than reverse-phase HPLC [30]. Since separation in reversed C18 phases is based on hydrophobic interaction, it is assumed that the highly polar molecules will be weakly retained or have poor resolution. However, the interaction of solvents typical for NP-HPLC can lead to a decrease in the sensitivity of the mass spectrometer because of the low degree of ionization of nonpolar solvents.

Application of the reverse-phase HPLC (RP HPLC) method allowed isolation and quantitative determination of phlorotannins in extracts and fractions without the acetylation stage. A methanol–water or acetonitrile–water gradient was usually used as the eluent; detection was carried out in the ultraviolet region of the spectrum [43]. Using RP HPLC, Parys et al. isolated the phlorotannins of trifucodiphlorethol A, trifucotriphlorethol A, and isolated fucotriphlorethol A from the phenolic extract of *F. visiculosus* and determined their potential antitumor activity [42]. The methods for isolation of native phlorotannins are not numerous but are extremely useful, primarily for studying the biological effects of phlorotannins. Acetylation facilitates the process of separation of low-molecular-weight phlorotannins; however, this approach is useful only for establishing their structure.

Methods based on chromatography–mass spectrometry using modified chromatographic phases were developed to overcome the problems of separation of phlorotannins with different molecular weights and their isomers. Enriched phlorotannin extracts from algae *Fucus spiralis*, *F. vesiculosus, Pelvetia canaliculata, A. nodosum,* and *Saccharina longicruris* were analyzed by ultra-efficient liquid chromatography–mass spectrometry (UPLC-MS), combining liquid chromatography of hydrophilic interaction (HILIC) and high-resolution mass spectrometry (HRMS) [63]. HILIC (as a variant of NP-HPLC) is used to separate strongly polar substances. It has been shown that HILIC with a phase that has alkyl fragments is an effective method of separating phlorotannins, especially low-molecular-weight phlorotannins. The use of an alkaline mobile phase enhanced ionization in the negative ion mode (ESI) to generate multiply charged ions; this allows detection of high-molecular-weight phlorotannins. The method of HRMS identified

phlorotannins with a mass of up to 6000 Da. To improve the separation of high-molecular-weight phlorotannins and to determine the level of their isomerization, Tierney et al. used a phase modified with pentafluorophenyl (PFP) [66]. PFP columns with different mechanisms of substance retention were developed to separate highly polar, aromatic, and isomeric compounds [20]. To increase the sensitivity of detection of phlorotannins (for the purpose of identifying their isomers), the authors in their study used the method of tandem mass spectrometry (MS/MS) in multiple reaction monitoring mode.

The phlorotannins from the algae *A. nodosum* and *P. canaliculata* contained 6–13 monomers. The number of the isomers was determined for each polymer molecule of phlorotannin [66]. The authors believe that the UPLC-MS/MS separation procedure allows determination of the change in the composition of algae extracts depending on the season and geographical region, as well as determination of the stability of this composition [66].

Forty-two phlorotannins with different molecular weights were isolated and characterized with high-performance chromatography and tandem mass spectrometry (UHPLC-QQQ-MS) from the brown alga *Sargassum fusiforme* [34]. The UPLC-MS and UPLC-MS/MS methods were used for complex chromatographic separation to obtain satisfactory metabolic profiles of low-molecular-weight phlorotannins consisting of 4–12 monomer units; the analysis time did not exceed 15 minutes [22]. In addition, the level of isomerization for phlorotannins with a degree of polymerization from 3 to 16 was determined. The phlorotannins of the investigated algae differed in the degree of polymerization and in the number of isomers found at each degree of polymerization. *F. vesiculosus* had the highest number of phlorotannin isomers (61 isomers) of one specific molecular weight, which corresponded to 12 phloroglucinol units [22].

The presence of complex mixtures of their structural and conformational isomers in the algae is a significant obstacle for characterization of the composition of phlorotannins. For this reason, only a selective structural characterization of phlorotannins is possible at present.

The current chromatographic and mass-spectrometric methods of analysis open the way to a more-thorough study of the isomeric complexity of phlorotannins. However, using these methods, we cannot separate complex isomeric mixtures of phlorotannins with identical molecular weights and similar structures into individual compounds.

THE BIOLOGICAL ACTIVITIES OF PHLOROTANNINS

Antioxidant Activity

Reactive oxygen forms are responsible for such cell anomalies as protein damage, enzyme deactivation, DNA alteration, and lipid peroxidation, which in turn leads to pathological conditions, carcinogenesis, reperfusion injury, rheumatoid arthritis, and diabetes [5]. To maintain the health of cells, it is important to have a specific and effective antioxidant that can absorb free radicals. As shown in a number of studies, brown algal phlorotannins and phlorotannin-enriched extracts exhibit strong antioxidant activities [10, 65, 71]. In in vitro experiments, eckol, phlorofucofuroeckol A, dieckol, and 8,8'-bieckol inhibited peroxidation of phospholipids (1 μM) in the liposome system and also inhibited the action of superoxide and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals more efficiently than ascorbic acid and α-tocopherol do [59]. The authors suggested that the anti-radical activity of phlorotannins is determined by the phenolic hydroxyl groups and their position. Phlorotannins with OH-groups in the ortho position acted more efficiently. In addition, a positive correlation occurred between antioxidant activity and the number of hydroxyl groups present in the structure of phlorotannins [36]. Three phlorotannins from *Ecklonia stolonifera* showed antioxidant activity and were effective as a chemopreventive agent [25, 37].

Antitumor Activity

Phloroglucinol is a phlorotannin component of brown algae, which suppressed the metastatic ability of breast-cancer cells [28]. Metastases are a complex clinical problem and the main cause of death in breast-cancer patients. Phloroglucinol effectively inhibited the mesenchymal phenotypes of the basal type breast-cancer cells by reducing the regulation of the SLUG transcription factor without the occurrence of a cytotoxic effect. Phloroglucinol reduced the expression of SLUG by inhibiting the PI3K/AKT and Ras/Raf-1/ERK signaling pathways. Phloroglucinol was also effective in experiments in vivo; it suppressed the metastatic ability of breast-cancer cells that spread to the lungs and increased the survival time in mice. Since there is still no suitable therapeutic agent that blocks the progression of breast cancer, these results can be of clinical importance for the treatment of metastatic breast cancer [28]. Another phlorotannin, dieckol, participated in the regulation of the expression of genes associated with metastases. Dieckol inhibited the expression of matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) associated with migration of MCF-7 human breast-cancer cells. Simultaneously, dieckol stimulated the expression of the TIMP-1 and TIMP-2 tissue inhibitors of metalloproteinases [26].

Phlorotannins are Inhibitors of Enzymes

Algal phlorotannins are known as inhibitors of glycoside hydrolases, including α-amylases and α-glucosidases, which affect the development of hyperglycemia in type 2 diabetes and obesity [31]. During inhibition of these enzymes the disintegration of oligosaccharides and disaccharides, as well as the absorption of glucose by the small intestine, slows; as a result the level of glucose in the blood falls. Phlorotannins isolated from *E. cava* inhibited the activity of α-glucosidase in rat intestinal and porcine pancreatic α-amylase (especially dieckol) with IC_{50} values of 10.8 μM/L (α–glucosidase) and 124.9 μM/L (α-amylase) [33]. Phloroglucinol and dioxinodehydroeckol, isolated from *E. stolonifera* and *E. bicyclis*, inhibited the effect of α-glucosidase (IC_{50} = 141.8 and 34.6 μM, respectively) significantly more efficiently than the acarbose commercial inhibitor [40]. The effect of phloroglucinol isolated from *E. cava* on the blood glucose level and on the regulation of glucose synthesis in the liver was investigated in experiments in vivo. Phloroglucinol significantly improved glucose tolerance in C57BL/6J male mice whose diet was high in fat and inhibited glucose synthesis in primary mouse hepatocytes [73].

Cholinesterases AChE and BChE are key enzymes that play an important role in cholinergic transmission by hydrolysis of the neurotransmitter acetylcholine [39]. Its deficiency significantly determines the clinical picture of the dangerous neurodegenerative Alzheimer's disease. Phlorotannin 6,6'-bieckol, isolated from *Ishige okamurae*, inhibited the action of acetylcholinesterase (AChE) with IC_{50} = 46.42 μM [75].

Hyaluronidase is an enzyme that depolymerizes a polysaccharide constructed from hyaluronic acid residues in the intercellular matrix of the connective tissue. It is known that this enzyme is involved in allergic reactions, cancer metastasis, and inflammatory processes. The phlorotannins eckol, phlorofucofuroeckol A, dieckol, and 8,8'-bieckol showed a stronger inhibitory effect against hyaluronidase than the commercial inhibitor catechin [58].

Phlorotannins from brown algae effectively inhibited tyrosinase activity. Phlorotannin 7-phloroeckol from *E. cava* inhibited the action of tyrosinase *in vitro* more strongly (IC_{50} = 0.85 μM) than the commercial inhibitors arbutin (IC_{50} = 243.16 μM) and kojic acid (IC_{50} = 40.28 μM) [23, 74]. Tyrosinase inhibitors are used in cosmetics in skin-whitening products, as well as for the treatment of pigmentation disorders.

Lipoxygenase is an enzyme that catalyzes the reaction of dioxygenation of polyunsaturated fatty acids. Fucophlorethol-C isolated from the brown alga *Colpomenia bullosa* inhibited soybean lipoxygenase to the same extent that the inhibitor nordihydroguaiaretic acid does [32].

Reverse transcriptase (RT) is an enzyme that catalyzes the synthesis of DNA on the RNA template during reverse transcription. Phlorotannins with a dibenzo- [1, 4]-dioxin site had an inhibitory effect on reverse transcriptase and HIV-1 protease in experiments *in vitro*. The diphenyl bond compound phlorotannin 8,8'-bieckol inhibited HIV-1 RT (IC_{50} = 0.5 μM) 10 times more efficiently than 8.4'''-dieckol, a phorotannin with a phenyl-ether linkage (IC_{50} = 5.3 μM), although both phlorotannins are dimers of eckol [3].

Antibacterial Activity

Phlorotannins have been shown to be effective against certain pathogenic bacteria. The phlorotannins dieckol and 8,8'-bieckol isolated from *Ecklonia kurome* inhibited the growth of the bacteria *Campylobacter jejuni* and *Vibrio parahaemolyticus* [41]. Fucophlorethol isolated from *F. vesiculosus* actively inhibited both gram-positive and gram-negative bacteria [52].

Thus, recent studies have shown that phlorotannins of brown algae are polyfunctional compounds. It can be assumed that due to the above biological functions phlorotannins have great potential as active ingredients for the development of pharmaceutical products. The current chromatographic and mass-spectrometric methods make it possible to study the structural diversity of phlorotannins and their isomeric complexity. In the future, this will help to create a library of metabolic profiles of phlorotannins and to establish the relationship between the structure and the function of these compounds.

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