The Applications of Phlorotannins

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Phlorotannins are a type of natural active substance extracted from brown algae, which belong to a type of important plant polyphenol. Phloroglucinol is the basic unit in its structure. Phlorotannins have a wide range of biological activities, such as antioxidant, antibacterial, antiviral, anti-tumor, anti-hypertensive, hypoglycemic, whitening, anti-allergic and anti-inflammatory, etc. Phlorotannins are mainly used in the fields of medicine, food and cosmetics.

phlorotannins extraction technology separation and purification

1. Applications in the Field of Medicine

Phlorotannins, as a role of plant polyphenols, based on its hydrophilic and hydrophobic moieties, can interact with plasma proteins in the blood by non-covalent interactions (e.g., multiple hydrogen bonding, electrostatic, and cation-π interactions) [1][2]. Based on phenol units, polyphenols have the innate ability to reduce and scavenge free radicals and have a high affinity for proteins through specific or non-specific interactions [3]. They can interact with several receptors, regulate signal transduction, regulate enzyme activity, inactivate microorganisms and cross-link biological macromolecules [4], which indicates broad application prospects in tissue engineering. In the same way as the tannins of terrestrial plants, these phenolic compounds are highly soluble in water, strongly bind to proteins, polysaccharides, and other biopolymers, chelate divalent metals and have a polymer structure. Polyphenolic compounds extracted from seaweeds are bioavailable. Polyphenolic compounds can be absorbed either directly in the upper digestive tract unchanged or in the lower intestine after being modified by the bacteria present there [5].

Related studies have shown that phlorotannins from brown seaweeds showed low toxicity in cell lines, microalgae, seaweed spores, plants, invertebrates, animals (fish, mice, rats, and dogs) and humans at a moderate dosage [6]. Mild side-effects were recorded in humans, fish and dogs. However, the safety and toxicity of phlorotannins in aquaculture fish, livestock and companion animals are limited. These findings can serve as a basis for developing these compounds into novel functional foods, animal feeds and drugs.

1.1. Cancer Prevention and Treatment

Excessive oxidative stress can cause oxidative damage to intracellular biological macromolecules, promote abnormal gene expression and DNA structural changes and block vital signaling pathways between cells [7]. Brown algae polyphenols have good anticancer activity, and their mechanism of action is mainly manifested either directly as a pro-apoptotic, antiproliferative, anti-metastatic or anti-angiogenic agent, or indirectly by inhibiting the oxidative-

stress inflammatory network closely related to tumorigenesis [8]. The anticancer activity of brown algae polyphenol crude extracts differs greatly from purified isolated components. In mouse models containing sarcoma xenografts, the in vivo antitumor effect of eckol was shown not only due to its ability to interfere with the expression of caspase-3, caspase-9, Bcl-2 and Bax genes, but also due to its ability to inhibit epidermal growth factor receptor (EGFR) expression. Thus, in addition to its antiproliferative properties, eckol exerts antitumor activity by stimulating the host immune response. Imbs et al. [9] found that among three different seaweeds, *Fucus evanescens*, *Laminaria cichorioides* and *Costaria costata*, the former with 60% ethanol extracts have highest content of polyphenols (10.1% dry matter), showed the strongest inhibitory effect on DLD-1 and HT-29 colorectal adenocarcinoma cell growth (67% and 63%).

Some studies have shown that, in the same way as plant phenolics, phlorotannins tend to degrade during their passage throughout the gastrointestinal tract, and only a small portion will reach the intestinal lumen intact and become bio-accessible for further absorption [10]. According to the work of Ahn et al. [11], carried out in xenograft mice models implanted with SKOV3 ovarian cancer cells, the oral administration of dieckol (300 mg/kg/week) was even more effective than cisplatin (9 mg/kg/week) at suppressing the tumor growth without showing any liver or kidney toxicity, while the cisplatin-treated mice revealed increased blood urea nitrogen and serum creatinine which are indicative of kidney dysfunction. *Dieckol*, derived from edible brown alga *Ecklonia cava*, can significantly enhance the inhibition of tumor growth by cisplatin with lower weight loss and kidney damage in a mouse model [12]. It also indicated that brown algae phlorotannins may improve the efficacy of platinum drugs for ovarian cancer by enhancing cancer cell apoptosis via the ROS/Akt/NFκB pathway and reduce nephrotoxicity by protecting against normal kidney cell damage.

1.2. Treatment of Neurodegenerative Diseases

The phenomenon of excitatory toxicity caused by glutamate is associated with the pathophysiology of a variety of central nervous system diseases, which can lead to neuronal dysfunction, degeneration and apoptosis [13][14][15]. Brown algae polyphenols have been found to protect brain cells from glutamate excitatory toxicity through multimodal action. The mechanism of action is as follows: the ability to inhibit central nervous system (CNS)-related enzymes (acetylcholinesterase and butyrylcholinesterase, monoaminoxidase, β-secretase, tyrosinase); Regulation of neuronal receptors; Regulation of the signaling pathways and neuroinflammation associated with oxidative stress-mediated neuronal cell death [16].

Yang et al. [17] demonstrated that phloroglucinol, the basic unit of brown algae polyphenols, regulates synaptic plasticity. With a decrease in dendritic spine density and synaptic protein levels, cognitive dysfunction in 5XFAD mouse models was alleviated. After oral administration of it, a significant decrease in the number of Aβ plaques and the level of the BACE-1 protein was also observed. In addition, resorcinol prevents lipid peroxidation, slows the reactivation of glial cells, and reduces the release of pro-inflammatory cytokines in 5XFAD mice.

Polyphenols such as phlorotannins must cross the physical barrier of the CNS to exert a neuroprotective effect: the blood–brain barrier (BBB) that separates the circulating blood from the brain extracellular fluid. Phlorotannin's

action through the BBB on gamma aminobutyric acid type A (GABAA)-benzodiazepine receptors has been demonstrated. *Dieckol* [18] and *eckol* [19] have been effectively shown to successfully penetrate the brain by the BBB via still unknown transportation mechanisms.

1.3. Development of Novel Antifungal Drugs

Polyphenolic compounds have a universal inhibitory effect on microorganisms [6]. On the one hand, phlorotannins block the synthesis of dimorphic complexes in fungal cells, resulting in an altered appearance and surface adhesion properties of *Pseudomonas*, thereby reducing the toxicity and ability of pathogenic fungi to invade host cells. On the other hand, phlorotannins induce reactive oxygen species (ROS) production and trigger early apoptosis, leading to activation of the CaMCA1 gene and destruction of cell membranes in Candida albicans. These inhibitory effects reflect the potential of phlorotannins as a novel antifungal drug [20] [21][22].

Lopes et al. [23] crushed the dried *Fucus spiralis Linnaeus*, degreased with n-hexane and extracted with acetone: water (7:3). The extract is purified with cellulose and then washed with toluene. Then, the cellulose is washed with acetone: water (7:3) to obtain phlorotannins. These phlorotannins exhibit antifungal activity against *Candida albicans*, *Aspergillus* and *Dermatophytes*. The MIC values of phlorotannins for these fungi range from 3.9 to 31.3 mg/mL.

At present, most of the antibacterial activity studies on brown seaweeds' polyphenols are in vitro activity studies, and no pharmacokinetic analysis of polyphenols exerting antibacterial effects has been found.

1.4. Development of New Blood Pressure Lowering Drugs

Angiotensin-converting enzyme (ACE) is an ideal target for the treatment of diseases such as hypertension, heart failure, diabetes mellitus and hypertension. In the study of blood pressure-lowering activity of brown algae, it has been proved that brown algae such as *Undaria pinnatifida*, *Scagassum*, *Laminaria japonica*, *Fucus vesiculosus* and *Hizikia fusifarme* contain blood pressure-lowering active substances [24].

Dieckol isolated from the ethanol extract of *Kombu* is a non-competitive inhibitor against ACE I that induces the production of nitric oxide (NO) in EA.hy926 cells and has no cytotoxic effect [25]. Ko et al. [26] extracted 6,6'-bisphenols from the *Ecklonia cava* and studied its biological activity, finding that ACE inhibitory activity was formed by the interaction of hydrogen bonds and Pi bonds between ACE and 6,6'-biphenol. The 6,6'-bisphenol significantly increased the content of NO by phosphorylation of nitric oxide synthase in human endothelial cells.

Until now, most of these ACE inhibitory activities have been observed in vitro or in mouse model systems. Therefore, further research studies are needed in order to investigate their activity in human subjects. So far, there were no clinical studies of phlorotannins in patients with hypertension.

1.5. Anti-Diabetic and Anti-Obesity Potential

In recent years, with the separation and identification of active ingredients in *Laminaria japonica*, *Undaria pinnatifida*, *Scagassum* and other brown algae, it has been proved that most brown algae contain hypoglycemic active substances [27]. Phlorotannins from the genus kombu exhibit anti-diabetic activity mainly through the inhibition of α-amylase, α-glucosidase, pancreatic lipase and aldose reductase (AR), which can promote the delay of carbohydrate and lipid digestion, followed by reducing postprandial plasma glucose levels and overall body weight, thereby helping to prevent and improve metabolic disorders such as diabetes mellitus type 2 (T2DM) and obesity [28].

Phlorotannins isolated from methanol extracts of *Ecklonia stolonifera* have inhibitory activity against α-glucosidase, which is attributed to the presence of *rhizolutin A*, dieckol and *7-rhizophericol* [29]. Lee et al. [30] extracted a phlorotannin from the *Ecklonia cava*, modeled on streptozotocin-induced diabetic mice, and after feeding, blood samples were taken from the tail vein at 0, 30, 60 and 120 min and the blood glucose amount was measured. It was found that it had strong inhibitory activity against α-glucosidase and α-amylase.

Further clinical studies have shown that the physiological effects of seaweed supplementation can reduce fasting blood glucose and two hours postprandial blood glucose levels in patients with type 2 diabetes (control: 254.4 ± 22.8 mg/dL, seaweed supplementation: 203.1 ± 12.3 mg/dL) without affecting glycated hemoglobin levels [31]. Shannon and Abu-ghannam [32] found that the daily supplementation of *Undaria pinnatifida* balanced the blood glucose levels in patients with type 2 diabetes mellitus by clinical trial.

A 24-week randomized, double-blind, placebo-controlled crossover trial was conducted to investigate the effects of brown seaweeds' polyphenols on DNA damage and antioxidant activity in overweight or obese people [33]. A total of 80 participants (BMI units: $kg/m^2 \geq 25$) aged 30–65 years consumed either a 400-mg capsule containing 100 mg seaweed (poly)phenol and 300 mg maltodextrin or a 400-mg maltodextrin placebo control capsule daily for an 8-wk period. Consumption of the seaweed (poly)phenols resulted in a modest decrease in DNA damage but only in a subset of the total population who were obese. There were no significant changes in C-reactive protein (CRP), antioxidant status or inflammatory cytokines.

1.6. SARS Virus Inhibitors

Due to its multiple functions and necessary roles in viral replication and pathogenesis, cysteine proteases can be used as an ideal target for antiviral drugs. Among them, the master protease (3CL) is a structural protein that affects the survival and reproduction of the virus by cutting the site of action of the polymer protein. The 3CL protease is also an enzyme necessary for coronavirus replication, which is a target for potential anti-SARS drugs. Of the nine phlorotannins isolated from the ethanol extract of the *Ecklonia cava*, dieckol, which is connected by diphenyl ether, exhibits the most potent SARS-CoV inhibitory activity. In addition, dieckol has the most potent inhibitory activity against cell-based 3CL, which is more potent than other phlorotannins' derivatives and natural reference inhibitors. Dieckol has a high association rate with proteins and forms strong hydrogen bonds with the catalytic binary of SARS-CoV 3CL (Cys145 and His41) and consumes the lowest binding energy [34].

To explore the pharmacokinetics of brown macroalgal polyphenols during their antiviral activity, Gunaseelan et al. [35] evaluated the potential of root tannins as multiple-target protein antagonists necessary for SARS-CoV-2 replication. Top-ranked marine brown algal phlorotannins are difucol hexaacetate, diphlorethol pentaacetate, eckol hexaacetate and fucofuroeckol.

Based on the existing studies of ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) characteristics of phlorotannins' compounds, have clearly comprehended the bioavailability of the phlorotannin ligand molecules as an oral drug candidate [35]. Followed by the first-pass metabolism, polarity, aqueous solubility and permeability of the gut–blood barrier appeared at an adequate level as compared with standard drugs. Furthermore, the metabolic reaction and blood–brain barrier are also observed under limitation as per the standard volume, which can be seen in moderate levels in all of the ligands except phlorofucofuroeckol A and B, fucodiphloroethol G, tetrafucol A, tetraphlorethol, fucotriphlorethol and diphlorethohydroxycarmalol.

Comparative studies of the route of administration were conducted by analyzing the results obtained from standard drugs used to combat COVID-19, such as remdesivir, ritonavir, favipiravir, lopinavir and hydroxychloroquine. Among them, hydroxychloroquine showed the highest human oral adsorption rate (about 91%), while the most commonly used remdesivir showed only 36% oral adsorption against COVID-19. The dioxinodehydroeckol, diphlorethol, diphlorethol pentaacetate and difucol hexacetate manifested a higher degree of oral absorption (58.0, 58.05, 58.84, 47.30, respectively) as compared with standard remdesivir [36]. At the same time, diphlorethol pentaacetate (70.56) had a higher Madin-Darby canine kidney (MDCK) permeability within the given range (25 to 500) than standard remdesivir (just 6).

1.7. Metabolomic Profiling Analysis of the Extract of Brown Seaweeds

The majority of phlorotannin metabolites were found in samples collected at late time points (6–24 h), indicating limited small intestinal absorption. Seaweed phlorotannins are metabolized and absorbed, predominantly in the large intestine, and there is a large inter-individual variation in their metabolic profile [37]. In the upper GI tract, dietary polyphenols act as substrates for a number of enzymes, and they are subjected to extensive metabolism by glucosidase enzymes, phase I enzymes (hydrolyzing and oxidizing) [38]. Thus, phlorotannin intake results in the formation of phase II conjugate metabolites (glucuronides, sulphates). Further transformations can occur in the colon, in which the enzymes of the gut microbiota act to breakdown complex polyphenolic structures to smaller units, which may also be absorbed and further metabolized in the liver [39].

In recent years, brown algae polyphenols have been a research hotspot in the field of marine compounds. However, there have been few studies into the metabolic changes following ingestion of brown algae extract. Kim et al. [40] investigated the metabolic effects of a 12-week consumption of *E. cava* polyphenol extracts (seapolynol) in subjects exposed to moderate caloric intake and physical activity and with a body mass index (BMI) higher than 25 kg/m^2 and lower than 30 kg/m^2. Urinary metabolomic profiling analysis showed that the levels of riboflavin, urocanic acid, 5-hydroxy-6-methoxyindole glucuronide and guanidino valeric acid were significantly increased in

the seapolynol intake group compared with the placebo group. These findings suggest that the decreased body fat induced by the intake of seapolynol is related to an increase in the antioxidant effect of riboflavin.

2. Applications in the Food Sector

2.1. As a Functional Food against Hypercholesterolemia

The main risk factor for coronary heart disease is excessive dietary cholesterol depletion, which, once arterial plaques form, can lead to fatal myocardial infarction, heart attack and cerebrovascular disease [41]. Currently, the intake of naturally active products can be used as a strategic therapy for the combined use of anti-hyperlipidemia drugs [42]. Studies have shown that algae compounds have the ability to bind dietary cholesterol, and brown algae have the ability to accelerate the excretion of cholesterol by the human body. Therefore, brown algae belong to a valuable food source of natural compounds that can be used to treat high cholesterol. A variety of brown algae species have shown the ability to lower blood lipid levels and total cholesterol [43].

Phlorotannins regulate serum lipid levels in most cases, reducing the risk of cardiovascular and cerebrovascular disease. The hypolipidemic effects of phlorotannins may also be associated with the antioxidant, anti-inflammatory and hepatoprotective activity of polyphenol compounds, thereby inhibiting fat-induced liver damage and ensuring lipid normalization [44][45]. Dieckol isolated from *Fucus vesiculosus* and *Ecklonia cava* has been reported to have the ability to inhibit HMG-CoA reductase, affecting cholesterol synthesis [46][47], thus demonstrating that phlorotannins have the same mode of action as statins.

2.2. As Food Antioxidants

The special phenolic hydroxyl structure endows brown algae polyphenols with antioxidant activity [48]. The phenolic hydroxyl structure can provide hydrogen donors and scavenge a variety of reactive oxygen species (ROS). On the one hand, the excited state oxygen molecules are reduced to the ground-state oxygen with lower activity, and the generation of oxygen free radicals is inhibited. On the other hand, as a free radical scavenger, brown algae polyphenol can combine with oxygen free radicals, reduce the activity of free radicals and hinder the chain-reaction of free radical scavenger [49]. The strength of the antioxidant effect of polyphenols is affected by the molecular structure and the number of hydroxyl groups, chain length and number of intramolecular hydrogen bonds [50][51]. Taking advantage of the antioxidant effects of brown algae polyphenols, it can also be used to treat degenerative diseases such as cardiovascular disease, diabetes, cancer, atherosclerosis and Alzheimer's disease [52].

Meng Tong [53] studied the effect of polyphenols from *Laminaria japonica* on the quality of emulsified intestines, and found that the brown algae polyphenols can reduce the content of carbonyl groups and the loss of sulfhydryl groups, and inhibit the oxidation of proteins [54]. In addition, when brown algae polyphenols are used to preserve oils and fats, they can act as antioxidants and color protection at the same time. Brown algae polyphenols can also undergo complex reactions with metal ions, thereby inhibiting the oxidation of food by a small amount of metal ions.

2.3. As Food Preservatives

Brown algae polyphenols are a kind of extract with both antibacterial and antioxidant activities, which can be directly used in the preparation of new edible packaging films. Studies have shown that this packaging film has the functions of antibacterial preservation and prevention of physical damage, and has played a great role in the field of food storage and preservation [55]. Low molecular weight phlorotannins extracted from *Sargassum thunbergia* damaged the cell membrane and cell wall of *Vibrio parahaemolyticus*, causing cytoplasm leakage and deconstruction of membrane permeability.

Shi [56] prepared nanoparticles embedded with algal polyphenols by the ion gel method, and found that the preservative obtained by this method had a better preservation performance and longer preservation time. Some phlorotannins derived from brown algae species have been studied in the application of antibacterial agents.

2.4. As Pesticides

The larvicidal effects of phlorotannins are mediated by multiple mechanisms, including direct inhibition of the settlement and/or survival of larvae and regulation of the growth of bacterial micropollutants, thereby affecting larval settling. Phlorotannins isolated from *Sargassum* inhibited the metamorphism of 33% of *Ciona Savignyi* and 27% of *Halocynthia roretzi* at low concentrations (25 μg/mL). These findings suggest that phlorotannins can act as antifouling agents without causing damage to other organisms [57].

The larvicidal activities of phlorotannins in mosquitoes reported by Ravikumar et al. [58] and Manilal et al. [59] suggest that they may be effective repellents. Phlorotannins have an effect on the larvae of marine invertebrates [60], suggesting that they are natural antifouling agents. Unlike heavy metals, which act as broad-spectrum toxins against both target and non-target marine organisms, the natural antifouling effect of phlorotannins is specific to target organisms.

3. Application in the Field of Cosmetics

3.1. Whitening and Beauty Effects

Tyrosinase is a key enzyme in the process of melanin formation. By adding tyrosine inhibitors to cosmetics to inhibit the formation of melanin, the whitening effect of cosmetics can be achieved. Melanin production begins by oxidation of tyrosine to dopaquinone, which is catalyzed by tyrosinase (TYR). The tyrosinase-associated protein-1 (TRP-1) and TRP-2 or dopachrome tautomerase also play an important role in all eumelanin-producing reactions [61].

Kang et al. [62] extracted and isolated five kinds of polyphenols from *Ecklonia stolonifera*. Among them, phlorofucofuroeckol A could significantly inhibit the activity of tyrosinase. *Eisenia arborea* phenols isolated from the polyphenolic compounds of the brown alga *Ecklonia cava* can significantly inhibit tyrosinase activity and prevent the formation and accumulation of melanin. Further research found that 974-A, phlorofucofuroeckol-A and eckol,

isolated from *Ecklonia stolonifera Okamura*, reduced the cellular melanin content and tyrosinase activity, and downregulated the expression of melanogenesis enzymes including tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2 in B16F10 melanoma cells [63]. These compounds also effectively scavenged radicals at the cellular level.

3.2. Treatment of Atopic Dermatitis

When the body is attacked by harmful stimuli or pathogens, the body's immune system initiates an inflammatory response to remove the harmful substances and protect itself from harm. Atopic dermatitis (AD) is a cutaneous manifestation of a systemic disorder that can lead to asthma, food allergies and allergic rhinitis [64].

Kim et al. [65] studied the activity of kombu ethanolic crude extract and found that the purified eckol can downregulate the expression of pro-inflammatory factors, tumor necrosis factor and two interleukins in mouse macrophage leukemia cells, confirming that brown algae polyphenol compounds have good anti-inflammatory activity and can be used to treat inflammation. A brand-new phlorotannin was isolated from *Ecklonia kurome Okam*, and the in vitro study of phlorofucofuroeckol-B on rat basophilic leukemia (RBL)-2H3 cells confirmed that this tannin is able to inhibit histamine release, thus guaranteeing anti-allergic properties [66].

3.3. Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are able to digest extracellular matrix components such as collagen, proteoglycans, fibronectin and laminin in vitro and in vivo. In particular, gelatinase, which effectively cuts collagen types IV and V, can degrade collagen and elastic fibers, resulting in loss of skin elasticity, promoting wrinkle formation and accelerating aging. Some studies have suggested that the effectiveness of the dieckol in downregulating the expression of MMPs preventing the cellular invasion. For example, dieckol treatment in HT-1080 cells has reduced the intracellular ROS levels, inhibited the activation of Rac1 along with expression of focal adhesion kinase (FAK) and prevented the expressions of MMP-2, MMP-9 and MMP-13 [67].

Two phlorotannins, isolated from methanolic extracts of the marine brown alga, have been reported to inhibit the protein and gene expression levels of MMP-1, MMP-3 and MMP-13 in human osteosarcoma cells (MG-63) [68]. Dieckol and Eckol, isolated from *Laminaria spp*, inhibited the expression of MMP-1 in human dermal fibroblasts [69]. These results suggested the phlorotannin could promote cell differentiation, attenuate MMP-1, MMP-3 and MMP-13 expressions, and inflammatory responses via the MAPK pathway in chronic articular diseases.

3.4. As UV Sunscreens

Under ultraviolet radiation, the human body can produce a variety of effects, such as DNA damage, inhibition of DNA replication or mutations, photosynthetic apparatus impairment, decrease in CO_2-fixation, production of (ROS) [70]. Meanwhile, a decrease in the degree of photo-inhibition is commonly observed in brown algae. Such an effect may be explained either by activation of the antioxidative response, or by the formation of UV-screening compounds [71] and an increase in the activity of repairing enzymes. Phlorotannins are able to absorb UV radiation,

mainly UV-C and partly UV-B, with maxima at 195 nm and 265 nm making them good candidates for UV protection [72][73].

Gómez et al. [74] found that the induction of phlorotannins during UV exposure can alleviate the inhibition of photosynthesis and DNA damage in the kelp *Lessonia nigrescens*, two major detrimental effects of UV. Of course, the use of phlorotannins as a sunscreen is not only due to the anti-ultraviolet radiation effect, which requires antioxidant, anti-inflammatory and antibacterial effects to work synergistically. The ethyl acetate fractions that were isolated from the brown alga *Polycladia myrica* have a greater ability to inhibit free radicals as well as inhibit the growth of Gram-positive bacteria. Soleimani et al. [75] used the ethyl acetate fraction (as a biofilter) at a concentration of 5% as F3 and studied its sun protection efficacy, physical properties and stability. It turned out that the formulation F3 with SPF = 31.8 ± 4.7, UVA/UVB ratio = 0.98, showed excellent UVR protection, compared with commercial sunscreen (SPF = 29.76 ± 5.5, UVA/UVB ratio = 0.95). During stability studies, cream was formulated with a 5% fraction of brown algae without changes in appearance and pH.

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