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Improving potential strategies for biological activities of phlorotannins derived from seaweeds

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ABSTRACT

Seaweeds have garnered considerable attention due to their capacity to serve as exceptional reservoirs of numerous bioactive metabolites possessing substantial chemical and biological significance. .Phlorotannins constitute a significant class of natural polyphenols originating from brown seaweeds, featuring a broad spectrum of bioactive attributes and demonstrating potential applicability across various sectors. The potential health advantages associated with phlorotannins, particularly concerning the prevention of conditions linked to oxidative stress, such as inflammation, diabetes, and allergies, have generated substantial interest within the food and pharmaceutical industries. Nevertheless, current research remains insufficient in providing a comprehensive understanding of their absorption, as comparisons drawn with their terrestrial counterparts remain speculative. It is commonly presumed that phenolic compounds, including phlorotannins, face challenges due to their limited solubility, instability, and extensive metabolism, all of which restrict their bioavailability. In order to circumvent these limitations and amplify their utility as components of medicinal formulations or healthcare products, researchers have explored various strategies, including the encapsulation or integration of phlorotannins into nano-/micro-particles or advanced drug delivery systems. This review offers a thorough exploration of the structural and biological attributes of phlorotannins and furnishes insights into potential strategies showing promise for their effective utilization in preclinical and clinical applications.

Introduction

The marine environment, widely recognized as a vast and unique repository, houses a multitude of organisms, including macroalgae (seaweeds), microalgae and other diverse life forms such as tunicates, sponges, soft corals, and mollusks (Victor and Sharma 2015). These organisms play a vital role within the aquatic ecosystem by providing nourishment and shelter to fish and other marine life. Furthermore, they hold significant promise as resources for the exploration of novel bioactive compounds with potential utility for human health (Ghosh et al. 2022). These bioactive compounds derived from natural sources are highly prized for their favorable characteristics, including lower toxicity and enhanced effectiveness, making them valuable for a range of therapeutic purposes (Aung et al. 2017). In contrast to terrestrial environments, the distinctive environmental factors in the marine system, such as fluctuating temperature, pressure, and light conditions, likely contribute to the production of unique metabolites (including proteins, peptides, amino acids, fatty acids, sterols, polysaccharides, oligosaccharides, phenolic compounds, photosynthetic pigments, vitamins, and minerals) by certain marine organisms (Karthikeyan, Joseph, and Nair 2022).

Phlorotannins, a distinct class of secondary metabolites belonging to polyphenolic compounds, are particularly derived from brown seaweed (Phaeophyta), primarily from the orders Laminariales (Laminariaceae) and Fucales (Fucaceae and Sargassaceae) (Nazzaro et al. 2019). Although some reviews have suggested the presence of trace amounts of phlorotannins in red algae (Pradhan et al. 2022), these claims lack support from published research articles or specific algal species. Phlorotannins are oligomers or polymers composed of the monomeric unit "phloroglucinol" (1,3,5-trihydroxybenzene) and exhibit structural dissimilarity compared to terrestrial plant polyphenols like phenolic acids or flavonoids (Shrestha, Zhang, and Smid 2021). Due to variations in size, degree of polymerization, and types of subunits, phlorotannins display structural diversity with molecular weights ranging from 126 Da to 650 kDa (Catarino et al. 2022). Moreover, different extraction and analytical techniques used in research may yield different phlorotannin profiles, adding to the complexity of identifying and quantifying specific compounds. To date, approximately 150 phlorotannins have been reported from brown seaweeds, with research into these compounds continuing to grow exponentially (Rajan et al. 2021).

Reported biological properties of phlorotannins encompass antioxidant (Kord et al. 2021), anti-inflammatory (Raja et al. 2023), and anti-diabetic (Moheimanian et al. 2023) potentials. Nevertheless, despite the increasing research interest in the therapeutic applications of phlorotannins, their limited bioavailability in the digestive tract and circulatory system remains an area requiring improvements (Corona et al. 2016). Bioavailability is a critical concept within the realm of bio-efficacy, serving as a fundamental indicator for assessing the efficacy of ingested nutrients. It pertains to the degree to which absorbed nutrient components successfully enter the systemic circulation, thereby enabling the accomplishment of highly efficient biological activities (Shahidi and Peng 2018). Like other polyphenols, phlorotannins are commonly believed to possess low bioaccessibility, ranging from approximately 2%–15% (Zhao et al. 2023). These compounds readily form crosslinks with other macromolecules, such as carbohydrates or proteins. Additionally, high molecular weight phlorotannins (up to 100 kDa) have demonstrated a propensity to interact with dietary and endogenous proteins, resulting in poor absorption in the upper gastrointestinal tract (Corona et al. 2016). Furthermore, phlorotannins are highly unstable in the acid-base environment encountered during the transition from the small intestine to the gut, undergoing rapid transformation and/or metabolism by digestive enzymes (Tong, Liu, and Yu 2021).

Given these properties, further research is warranted to explore strategies that maximize the biological activity of phlorotannins and their incorporation into clinical treatments. In recent years, encapsulation techniques, which enclose targeted materials, have gained widespread application for delivery into the system. Various carriers have been utilized for encapsulation, including microspheres, hydrogels, and nanoparticle-based drug carriers such as liposomes, niosomes, polymeric nanoparticles, and solid lipid nanoparticles (Mirchandani, Patravale, and Brijesh 2021). These carriers have demonstrated remarkable capabilities in enhancing nutrient/drug entrapment, improving bioavailability, and optimizing the pharmacokinetic profiles. However, to the best of our knowledge, there is currently no comprehensive insight into the specific digestive process of phlorotannins or the strategies to improve their bioavailability. Therefore, this review aims to shed light on the possibilities of improving the delivery and therapeutic potential of phlorotannins by exploring various strategies and considering plausible perspectives. Additionally, it offers promising opportunities for maximizing their bioavailability and harnessing their beneficial properties for targeted and controlled drug release.

Overview of seaweeds and their global utilization

Importance of seaweeds

Seaweeds, also known as marine macroalgae, constitute a foundational botanical category within marine ecology, comprising an estimated ~24,000 species, of which ~12,000 have been described (Guiry 2012). Anchoring themselves to shallow-water rocky substrates or aggregating in shallow marine waters, seaweeds are taxonomically categorized into three groups based on pigmentation: Rhodophyta (red), Phaeophyta (brown) and Chlorophyta (green) macroalgae (Xie et al. 2023). Seaweeds are renowned for their ecological significance, giving rise to benthic seascape formations that, in terms of ecological importance, can be likened to terrestrial forests, such as primarily production construction, contribution to nitrogen fixation, and cementation of reef framework, facilitation of coral settlement and creation of habitats for other reef species (El-Manaway and Rashedy 2022). Within submerged ecosystems, numerous herbivorous organisms sustain themselves by relying on seaweeds, thus facilitating energy transfer to higher trophic levels. The central role played by seaweeds in the marine food web is highlighted by their ability to capture solar energy for autotrophic nutrition, simultaneously releasing oxygen through photosynthesis. This pivotal role is exemplified by their contribution to approximately half of the total primary production, despite their representation comprising less than 1% of Earth's total photosynthetic biomass (Falkowski 2012). Beyond this, seaweeds fulfill a critical ecological function by serving as agents of nutrient and toxin regulation, actively sequestering substances deleterious to marine organisms. In this capacity, they function as a natural filtration system within the vast underwater environment, entrapping heavy metals and chemical agents (Znad, Awual, and Martini 2022).

Undoubtedly, seaweeds possess an inherent appeal due to their culinary and edible attributes. However, while over 200 species of seaweeds are globally cultivated or wild-harvested for various industries, only 21 of these have received official authorization for use as vegetables and condiments (Pereira 2016). Upon closer examination, seaweeds reveal a wealth of functional ingredients and bioactive compounds that can be harnessed for the development of food supplements and dietary health products. From a nutritional perspective, seaweeds excel in their capacity to accumulate saccharides, proteins, phenolic compounds, unsaturated fatty acids, vitamins, and minerals. Specifically, saccharides are the most prevalent constituents within seaweed species, constituting a range of 4%–76% of their dry mass (DW) (Shannon and Abu-Ghannam 2019). Primary polysaccharides found in brown algae include alginate, fucoidan, and laminarin, while red algae contain carrageenans and agarans, and green algae contain ulvans (Patel et al. 2023). Although protein, polyphenol, and lipid contents are generally modest across all species, they play indispensable roles, with proteins aiding in the synthesis of hormones, enzymes, and hemoglobin, lipids mitigating the risk of several chronic diseases, and polyphenols acting as potent antioxidants (Subbiah et al. 2023). Notably, the nutritional profiles of seaweeds exhibit multifaceted variability influenced by factors such as species, age, size, reproductive status, ecological context, and a constellation of environmental parameters, including seawater pH, depth, temperature, salinity, nutrient enrichment, oxygen levels, ultraviolet radiation exposure, light intensity, and the extent of herbivore activity (Lobine, Rengasamy, and Mahomoodally 2022; E. Park et al. 2023).

Global market of seaweeds

The global cultivation and production of seaweed have undergone significant growth in recent decades, witnessing a remarkable increase from 0.56 million tons in 1950 to 35.82 million tons in 2019 (Junning and Giulia 2021). According to the estimations by Food and Agriculture Organization (FAO), the global seaweed industry was valued at over USD $6 billion annually in 2018 (FAO 2018). This value is projected to continue its upward trajectory and reach USD $30.2 billion by 2025 (Deepika et al. 2022).

As documented by FAO (2022), Asia overwhelmingly dominates global seaweed production, accounting for ~99.54% of the total output. In contrast, Africa contributes 0.3%, America 0.07%, Europe 0.06% and Oceania 0.03% to a much lesser extent. Within Asian seaweed production, China stands as the foremost contributor, yielding over 20 million tons annually, constituting ~59.46% of the global aggregate (FAO 2022). Notable contributors following China include Indonesia, South Korea, the Philippines, North Korea, and Japan. Japan, in particular, with its archipelagic geography, has a longstanding culinary tradition rooted in the utilization of various seaweed species for sustenance. The harvesting of *Pyropia* sp. from wild populations in Japan can be traced back to the seventeenth century. Additionally, additional seaweed species such as *Undaria*, *Saccharina*, *Monostroma*, *Ulva*, and *Cladosiphon* have also undergone significant cultivation and development (Tanaka, Ohno, and Largo 2020). Likewise, Australia, benefiting from its geographical location amidst the convergence of three distinct oceanic currents, showcases a rich tapestry of algal diversity, although it represents only 0.03% of the world market. For example, native seaweeds of the Chlorophyta phylum thrive in the pristine ecosystems of the Great Barrier Reef (Deepika et al. 2022).

In the broader context of global seaweed production, brown seaweeds hold a significant share, accounting for ~62.37% in the year 2019. Within this category, noteworthy brown seaweed species such as *Laminaria*, *Saccharina*, and *Lessonia* emerge as preeminent contributors, collectively constituting ~57.06% of the total brown seaweed production worldwide. Additional species, including *Undaria*, *Sargassum*, *Macrocystis*, and various miscellaneous varieties, make more modest contributions to this sector (Junning and Giulia 2021).

Utilizations of seaweeds

Seaweeds possess a rich history of utilization, extending into both culinary and medicinal domains. They have been integral to human diets, with particularly notable prominence in the Asian region, and have also been highly regarded for their ability to yield valuable compounds (Chopin and Tacon 2021). The global seaweed industry comprises 85% of food products for human consumption, and seaweed-derived extracts make up almost 40% of the world's hydrocolloids market (Debbarma et al. 2022). For instance, agars and carrageenans extracted from red seaweeds, as well as alginates extracted from brown seaweeds, have found applications as thickening and gelling agents in various food products such as ice creams, jellies and shakes (Deepika et al. 2022). Furthermore, due to their macro- and micro-nutritional constituents, seaweeds are seen as a promising strategy to address the growing challenges associated with food supply stress resulting from the increasing global population (Duarte, Bruhn, and Krause-Jensen 2021). In addition to their culinary uses, some commercially significant seaweed species are also employed in the production of fertilizers, feed additives, biofuels, and various environmental applications, although to a lesser extent (Hessami, Rao, and Ravishankar 2019). For example, certain quaternary cations, such as NH_4^+ found in seaweed extracts from *Laminaria* sp., provide buffering capacity for the roots while acting as osmoprotectants, which are particularly beneficial in agriculture, especially in marshy lands (Blanz et al. 2019).

Brown seaweed-derived phlorotannins

Generalized structural diversity

Phlorotannins are found in various brown seaweed species, including but not limited to *Ecklonia*, *Eisenia*, and *Ishige* species (Erpel et al. 2020). They are known for their chain- and/or net-like structures with diverse molecular weights. Phlorotannins can be further classified into six subclasses based on their linkage polymorphism: phlorethols, fuhalols, fucols, fucophloroethols, eckols, and carmalols (as shown in Figure 1). These subclasses are characterized by various types of covalent bonds, including:

- Aryl-ether bonds and ether bridges (para- or ortho-arranged).
- Aryl-aryl bonds.
- Phenyl bonds.
- Dibenzo-1,4-dioxin bonds (Charoensiddhi et al. 2020; Kumar et al. 2022).

The presence of additional hydroxyl groups (–OH) accounts for the differences between fuhalols and phlorethols (Y. Li et al. 2017), as well as between eckols and carmalols (Catarino, Amarante, et al. 2021).

In addition to nonhalogenated phlorotannins, halogenated phlorotannins have also been reported. For instance, monobromo-/monoiodophloroglucinol and 4′-bromo/4′-idodoeckol were identified several decades ago by Glombitza and Gerstberger (1985) from the brown alga *Eisenia arborea*. Subsequently, four other halogenated phlorotannins were discovered and reported in 1999 from another species, *Carpophyllum angustifolium*, after per-acetylation. These include 2-chlorophloroglucinol triacetate, 2[D'] iododiphlorethol pentaacetate, 3[A] chlorobifuhalol hexaacetate, and 3[A4] chlorodifucol hexaacetate (Glombitza and Schmidt 1999). In the same year, Sailler and Glombitza (1999) isolated and characterized no fewer than 17 halogenated (brominated, chlorinated and iodinated) phlorotannins, along with 30 non-halogenated forms from the Sargassaceae *Cystophora retroflexa*.
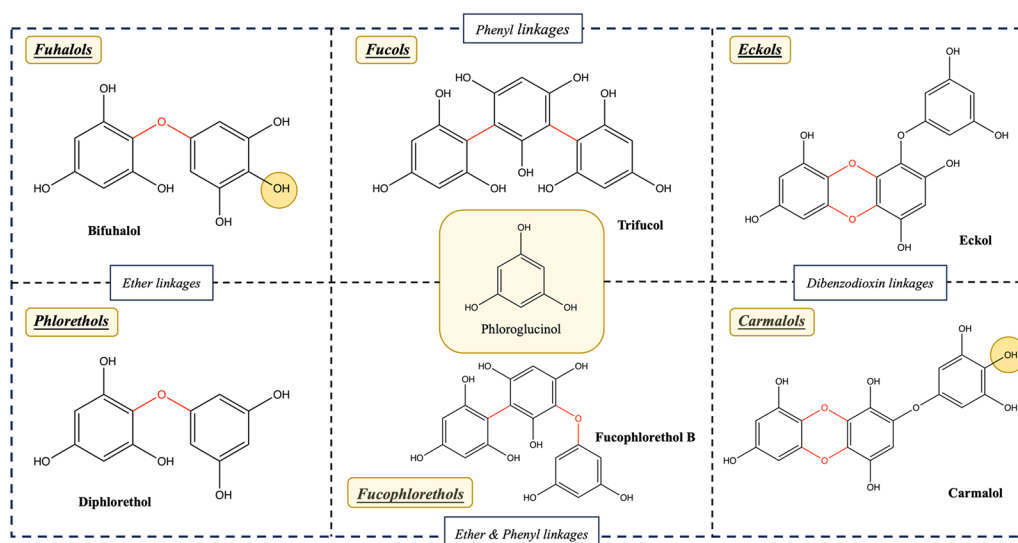
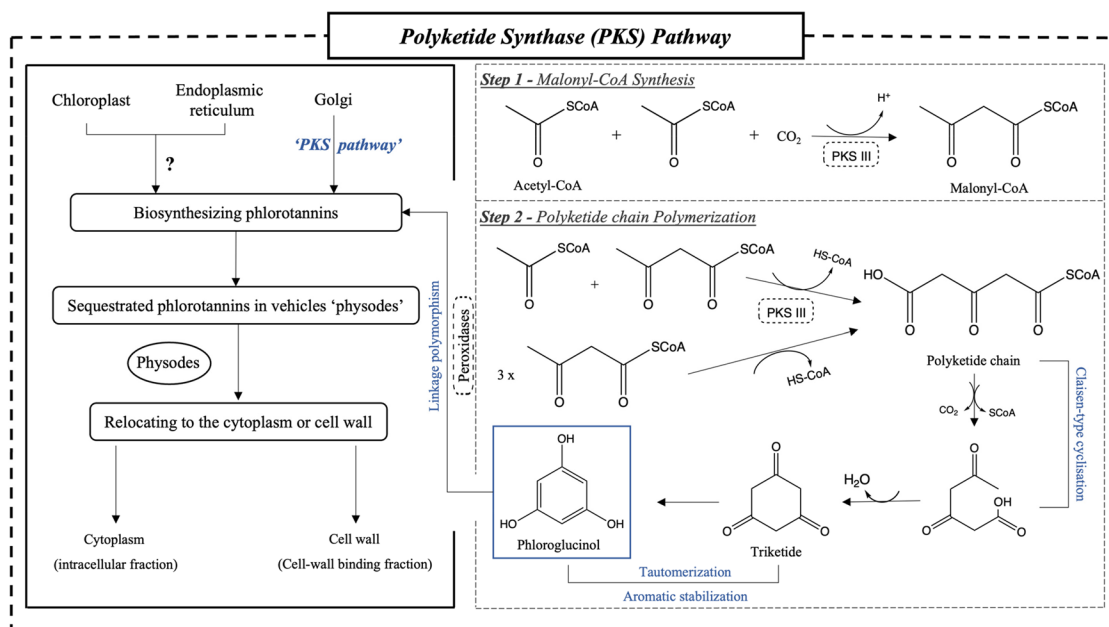**Figure 1.** The example structures of phlorotannins, divided by their linkages and functional groups.

Figure 2. Potential biosynthesis pathway of phlorotannin in brown seaweed cells (Gómez and Huovinen 2020; Phang et al. 2023). PKS: polyketide synthase; CoA: coenzyme A.

Biosynthesis of phlorotannins in brown algae

The biosynthesis of phlorotannins involves multiple steps, and although consensus on the exact mechanisms varies among scientists, a general outline of the biosynthesis process can be summarized as follows: (A) phloroglucinol formulation, (B) oxidative coupling and enzymatic modification, and (C) sub-cellular localization. For a more detailed understanding of the potential biosynthetic pathway, refer to Figure 2.

The biosynthesis of phlorotannins, which are considered the fundamental building blocks of this class of compounds, is thought to commence with the production of phloroglucinol. Three potential pathways for phloroglucinol production have been proposed, namely the shikimic acid pathway, the phenylpropanoid pathway, and/or a polyketide synthase pathway (PKS), based on existing knowledge (Pelletreau 2008). However, Siriwardhana, Lee, and Jeon (2005) have suggested that the shikimic acid pathway is more likely to serve as the metabolic pathway for condensed tannins and hydrolyzable tannins within the polyphenol category, with limited evidence specifically addressing phlorotannins. Conversely, due to the involvement of type III polyketide synthase (PKS III), the PKS pathway has gained stronger support as a more plausible and widely accepted route for phlorotannin biosynthesis, as corroborated by research studies (Bertoni 2013; Subbiah et al. 2023).

This hypothesis received support from Meslet-Cladière et al. (2013), whose genome investigation of the brown alga *Ectocarpus siliculosus* led to the discovery of a predicted key enzyme, PKS1, capable of facilitating the consecutive

condensation of acetate and malonate units. In the first step, two molecules of acetyl coenzyme A (acetyl-CoA) are converted into malonyl-CoA in the presence of carbon dioxide, catalyzed by PKS III. The resulting polyketide chain undergoes Claisen-type cyclization, generating a hexacyclic triketide. Subsequently, tautomerization and aromatic stabilization processes occur, resulting in the production of thermodynamically stable phloroglucinols (Fernando, Lee, and Ahn 2022).

Once phloroglucinol is synthesized, it undergoes oxidative coupling reactions facilitated by peroxidases, notably vanadium-dependent haloperoxidases, or phenoloxidases, as well as heme-containing glycoproteins. These enzymes play a catalytic role in the formation of end-radicals within phloroglucinol oligomers, achieved through the dehydrogenation of hydrogen atoms on –OH bonds, utilizing hydrogen peroxide (H_2O_2) as a reactant (Berglin et al. 2004; Lemesheva et al. 2020). The coupled C–C and/or C–O–C linkages contribute to the structural diversity observed among the six classes of phlorotannins mentioned above.

Regarding the localization of phlorotannin biosynthesis, it has been proposed that they are predominantly found within the chloroplast or its membrane, with potential involvement of the endoplasmic reticulum and Golgi bodies (Schoenwaelder and Clayton 2000). In general, based on their interactions with algal cells, phlorotannins exist in two distinct sub-cellular fractions: intracellular (cytoplasm) and cell wall-binding fractions (Birkemeyer et al. 2020). Polar and/or reactive-formed phlorotannins are initially sequestered in physodes, specialized secretion vesicles, which have the ability to be secreted into the extracellular compartment to form insoluble cell-wall phlorotannins that become embedded in the alginate matrix and other components of the cell wall through oxidative cross-linking (Arnold and Targett 2003; Emeline et al. 2021). The second fraction of phlorotannins is predominantly associated with carbohydrates or proteins, such as alginates, and they exhibit characteristics akin to conventional tannins, contributing to the integrity of the cell wall (Birkemeyer et al. 2020).

Quantification of phlorotannins

Quantifying phlorotannins holds significant importance across various research and industrial purposes. Researchers, for instance, employ phlorotannin quantification to enhance their understanding of the ecological roles played by brown seaweeds in marine ecosystems or to assess potential applications in the food, pharmaceutical, or cosmetic industries, along with determining the nutritional values of seaweed-based products. Common methodologies utilized for the quantification of phlorotannins encompass spectrophotometry assays (e.g., Folin-Ciocalteu assay), high-performance liquid chromatography (HPLC), and nuclear magnetic resonance (NMR).

Two spectrophotometry assays have been commonly employed to quantitatively assess the phlorotannin contents in seaweeds, including the Folin-Ciocalteu assay and the 2,4-dimethoxybenzaldehyde (DMBA) assay, which have garnered recognition due to their applicability, stemming from their distinctive interactions with the target compounds (Erpel et al. 2023; Gümüş Yılmaz et al. 2019). However, reports indicate that the Folin-Ciocalteu method has limited sensitivity. There are also concerns about its accuracy due to potential interference from other constituents in the plant matrix. Soluble sugars and proteins, for instance, can react with the Folin-Ciocalteu reagents, leading to artificially elevated values (Castro-Alves and Cordenunsi 2015). Similarly, although the DMBA assay demonstrates greater specificity as it selectively reacts with 1,3- and 1,3,5-trihydroxybenzenes, making it a more discerning option for assessing the phlorotannin structures within seaweed, some phlorotannins may exhibit branching or feature aryl linkages and fuhalols with additional –OH groups at positions 2, 4, or 6. In cases where substitutions occur at these positions, the absence of a color change may impede the detection of these particular phlorotannins (Ford et al. 2019).

The Prussian blue assay (PBA), in addition, has seen limited application in a few studies and may exhibit somewhat lower specificity compared to the other two methods (Margraf et al. 2015; Subbiah et al. 2023). Given that phlorotannins are classified as tannins, the butanol-HCl-iron method may also represent a potential means of quantifying their content, although there is currently no confirmed research validating this approach.

Proton (^1H) NMR spectroscopy indeed stands as another valuable approach for quantifying phlorotannin contents when utilizing phloroglucinol as an internal standard. However, it is essential to emphasize that NMR directly measures molar concentrations, and as such, the results obtained through NMR cannot be directly compared with those determined using spectrophotometric assays. Moreover, the quantification of phlorotannins using HPLC is impeded by the scarcity of commercially standardized reference compounds. In other words, the calibration of the sample content can only be achieved through quantification using known standards (Ford et al. 2019). Table 1 presents the phlorotannin contents as reported in various scholarly sources through the aforementioned methodologies.

Indeed, the quantification of phlorotannin content can vary significantly based on the chosen extraction method, including the selection of organic solvents or solvents ratios. In the case of brown algae, specifically *Sargassum angustifolium*, researchers have employed three distinct ratios of ethanol-aqueous solvents (30%, 50% and 70%, *v/v*), resulting in a range of phlorotannin content from 0.4 to 3.4 mg phloroglucinol equivalents (PGE)/g (Hodhodi, Babakhani, and Rostamzad 2022). It is well-established that brown algae can adjust their production of these metabolites in response to environmental cues and stress conditions. Typically, phlorotannin levels in brown algae surpass 2% DW in temperate and tropical Atlantic areas, as well as temperate Pacific regions. As noted by Ank, da Gama, and Pereira (2019), brown seaweeds from higher latitudes have demonstrated the capacity to produce phlorotannins in a broader range, often exceeding 4% DW, likely in response to environmental factors or stimuli, compared to algae found in lower latitudes, which generally contain less than 2% DW.

Table 1. Phlorotannin content among different seaweed species by different determination methods.

Seaweed species	Collection spots	Collection time	Extraction method	Contents (mg PGE/g DW)	References
Folin–Ciocalteu assay			**Spectrophotometry assays**		
Fucus vesiculosus L. *Ascophyllum nodosum* (L.) Le Jolis	Oskar Bay, Zelenetskaya Gulf, Barents Sea, Russia	August 2017	Extracted by NADES, dissolved (50–70%) in H_2O and solvents of various polarities that were used to extract the phenolic compounds (40 and 96% ethanol, Me_2CO, 70% aqueous Me_2CO) for 2 h at 50°C	8.7–61.2 7.8–50.3	(Obluchinskaya et al. 2019)
F. vesiculosus	Donegal, Ireland	(Not Specified)	30%, 50%, 70% ethanol with a sample-to-solvent ratio of 1:10 (w/v) for 4 h at 20°C with pretreated by 0, 35 and 130 kHz ultrasonic for 10 and 30 min	382.1–568.9	(Ummat et al. 2020)
F. vesiculosus	Coastal zone of the Artic: Irminger Sea, Norwegian Sea, Barents Sea, and White Sea	Fertile and sterile phases in 2019	60% methanol with a sample-to-solvent ratio of 1:25 (w/v) for 24 h at 200 rpm	72.4–158.1	(Obluchinskaya et al. 2022)
F. vesiculosus *Pelvetia canaliculata*	Donegal, Ireland	November 2017	Applied UAE, MAE, UMAE, HAE and HPAE with 50% ethanol at a sample/solvent ratio of 1:10 (w/v) by with post-treatment of 0 h and 24 h	238.7–362.9 128.3–203.9	(Garcia-Vaquero et al. 2021)
Polycladia myrica *Sirophysalis trinodis* *Dictyota spiralis* *Sargassum euryphyllum* *Turbinaria decurrens*	Hurghada, Red Sea	Winter 2020	Pre-removed lipids by adding hexane with a sample-to-solvent ratio of 1:5 (w/v), and add 50 mL of 70% acetone containing 0.3% w/v ascorbic acid to the sample for 1 h	57.52±1.2 55.58±1.6 48.75±2.1 56.13±1.4 43.75±1.2	(Ismail et al. 2023)
2,4-Dimethoxybenzaldehyde assay					
Phyllospora comosa *Ecklonia radiata* *Durvillaea* sp. *Sargassum* sp. *Cystophora* sp.	Queenscliff Harbor, Victoria, Australia	February (summer)	Conventional extracted and using UAE with 70% methanol, 70% ethanol, 70% acetone, and absolute ethyl acetate	0.33–6.65 0.59–8.29 0.29–8.22 0.54–6.32 1.02–4.15	(Subbiah, Ebrahimi, et al. 2023)
P. comosa *E. radiata* *Durvillaea* sp. *Sargassum* sp. *Cystophora* sp.	Queenscliff Harbor, Victoria, Australia	February 2022	70% ethanol (1:20, w/v) for 16 h at 120 rpm at 10°C	0.03–0.38 0.18–0.65 0.04–0.40 0.11–0.46 0.63–2.86	(Subbiah, Duan, et al. 2023)
Sargassum vulgare	Stora, Skikda, northeastern Algeria	February 2018	70% acetone solution (1:70, w/v) for 3 h at room temperature	0.4–9.4	(Chouh et al. 2022)
P. myrica *S. trinodis* *D. spiralis* *S. euryphyllum* *T. decurrens*	Hurghada, Red Sea	Winter 2020	Pre-removed lipids by adding hexane with a sample-to-solvent ratio of 1:5 (w/v), and add 50 mL of 70% acetone containing 0.3% w/v ascorbic acid to the sample for 1 h	13.44±0.4 11.22±0.6 9.05±0.3 10.92±0.2 9.94±0.4	(Ismail et al. 2023)
C. compressa	Cleopatra coast, Marsa Matruh city, Mediterranean Sea, Egypt	April 2017	Pre-removed lipids by adding hexane with a sample-to-solvent ratio of 1:5 (w/v), and add 50 mL of 70% acetone containing 0.3% w/v ascorbic acid to the sample for 1 h	140.5	(Gheda et al. 2021)
Prussian blue assay					
P. comosa *E. radiata* *Durvillaea* sp. *Sargassum* sp. *Cystophora* sp.	Queenscliff Harbor, Victoria, Australia	February (summer)	70% methanol, 70% ethanol, 70% acetone, and absolute ethyl acetate by conventional extraction and UAE	0.13–12.62 0.46–8.00 0.48–6.63 0.12–7.77 0.48–8.61	(Subbiah, Ebrahimi, et al. 2023)
P. comosa *E. radiata* *Durvillaea* sp. *Sargassum* sp. *Cystophora* sp.	Queenscliff Harbor, Victoria, Australia	February 2022	70% ethanol (1:20, w/v) for 16 h at 120 rpm at 10°C	0.17–25.35 0.06–3.33 0.20–5.31 0.34–6.01 0.56–28.77	(Subbiah, Duan, et al. 2023)
			Nuclear magnetic resonance (NMR)		
Cystoseira tamariscifolia	Penmarc'h, Brittany, France	From February 2009 to July 2010	50% methanol at 40°C	0.07%–0.46% DW	(Jégou et al. 2015)

(Continued)

Table 1. Continued.

Seaweed species	Collection spots	Collection time	Extraction method	Contents (mg PGE/g DW)	References
Laminaria digitata	Scotland	2015	80% methanol for 1.5 h under 20 °C	4.3% DW	(Vissers et al. 2017)
Laminaria hyperborea	Haugesund, Norway	March 2020, September 2020, and August 2021	50% ethanol for 30 min with pretreated by 35 kHz ultrasonic for 30 min	4.08–6.17	(Wekre, Hellesen Brunvoll, and Jordheim 2022)
L. digitata	Southern Australian coast, Melbourne, Victoria, Australia	August 2019		5.09±0.01	
F. vesiculosus	Storåkervika, Bergen, Norway	August 2019		11.0±0.0	
Saccharina latissima	Trollsøy, Vestland	June 2021		12.4±0.0	
A. nodosum	Eidsvåg, Bergen	September 2017	High-performance liquid chromatographic (HPLC)	8.57±0.0	
F. vesiculosus	Archipelago Sea, SW Finland	(Not Specified)	Soluble fraction: 70% acetone (1:50, w/v) for 1 h; Insoluble fraction: soluble fractions was further suspended in 8 mL of 1M NaOH solution (80 °C) and stirred for 2.5 h at room temperature	6.01–7.47	(Koivikko et al. 2008)
Ecklonia cava	Aewol-eup, Jeju-island, South Korea	(Not Specified)	50% ethanol (1:10, w/v) for 6 h at 60 °C	48.08±0.67 mg dieckol/g	(Petchidurai et al. 2019)
E. cava Kjellman	Busan, South Korea	2009	Methanol (1:4, w/v) for 2 h at room temperature	7.25–24.15 µg dieckol/mL 5.82–19.41 µg phlorofucofuroeckol-A/mL	(Chowdhury et al. 2011)

Note: NADES: natural deep eutectic solvents; PGE: phloroglucinol equivalents; DW: dry weight of seaweed biomass; UAE: ultrasound-assisted extraction; MAE: microwave-assisted extraction; UMAE: ultrasound–microwave-assisted extraction; HAE: hydrothermal-assisted extraction; HPAE: high-pressure-assisted extraction.

Furthermore, different seaweed parts and growth conditions also affect their phlorotannin contents. For instance, Iken et al. (2007) reported the presence of 0.5% DW of phlorotannins in the pneumatocysts of *Cystosphaera jacquinotii* (Montagne) Skottsberg and 9% DW of phlorotannins in the branches of *Desmarestia antárctica*. Singh and Sidana (2013) reported that phlorotannin concentrations can reach notable levels, sometimes as high as 25–30% DW in various algal thalli. However, it is a limitation that the specific seaweed species associated with these high phlorotannin concentrations are not specified in the provided information. This lack of information may suggest the possibility of referring to hypothetical or unidentified species, or it could indicate a potential misunderstanding or misinterpretation of the literature, thus warranting further research and investigation.

Biological activities and bioavailability of phlorotannins

Fascinating biological activities

Due to their diverse chemical structures and the presence of polyhydroxy groups, phlorotannins exhibit a wide range of biological activities. These activities, summarized in Table 2, highlight their promising potential in functional foods, nutraceuticals, and the pharmaceutical industry. These biological properties include antioxidative, anti-inflammatory, anti-allergic/histamine, anti-diabetic, and anti-bacterial/microbial effects, among others.

Antioxidant

Phlorotannins have been affirmed as excellent exogenous antioxidants that exhibit their antioxidant properties through three main mechanisms, including direct reactive oxygen species (ROS) scavenging, nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and the upregulation of antioxidant enzyme activities.

The ROS are commonly generated as natural byproducts of various metabolic processes in living organisms. When overproduced, they can lead to a state of oxidative stress, which can, in turn, cause damage to lipids, proteins, and DNA, and is associated with various diseases. The ability of phlorotannins to defend against ROS is linked to their intricately branched molecular structure, where phenol rings donate their electrons to these oxidative agents, resulting in the formation of an intermediate phenoxyl radical species that stabilizes unpaired electrons and establishes hydrogen bonds with neighboring –OH groups or engages in dimerization (phenol coupling) to create C–O or C–C linkages (Phang et al. 2023). These mechanisms have been corroborated by numerous previous studies employing colorimetric assays focused on determining radical scavenging activity. These assays encompass the assessment of radical scavenging activity against various radicals, including the 2,2-diphenyl-1-picryl-hydrazine-hydrate (DPPH) and 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radicals. For example, phlorotannins derived from *Fucus vesiculosus* and

Table 2. A brief summary of phlorotannin biological activities.

Bioactivities	Seaweeds	Phlorotannins	Models	Outcomes	References
Antioxidant	*Undaria pinnatifida* sporophyll (China)	Crude extracts	(Not Specified)	• Approximately 40 μg/mL of phlorotannin extract showed similar antioxidant capacity to positive control (80 μg/mL of epigallocatechin gallate.	(Dong et al. 2019)
	Sargassum vulgare (Algeria)	Crude extracts and liquid-liquid purification fractions	(Not Specified)	• DPPH: IC50 values ranged from 6.14 to 97.41 μg/mL. • ABTS: IC50 values ranged from 1.29 to 93.76 μg/mL.	(Chouh et al. 2022)
	Fucus vesiculosus (Denmark)	Phlorotannin-rich extracts	(Not Specified)	• EC50 of DPPH: 16.3–76.3 μg/mL.	(Hermund et al. 2022)
Anti-inflammatory	*Ascophyllum nodosum* (France)	Phlorotannin-rich extracts	Human epithelial cells (ARPE-19 and WKD cell lines)	• A concentration of 0.2% effectively prevent the overproduction of ROS. • A concentration of 0.05%, it reduced TNF-α release. • A concentration of 0.2%, it reduced TNF-α and IL-6 release.	(Dutot et al. 2012)
	U. pinnatifida Sporophyll (China)	Phlorotannin-rich extracts	RAW 264.7 Macrophages	• More efficient than epigallocatechin gallate at decreasing NO production.	(Dong et al. 2019)
	F. vesiculosus (Portugal)	Crude extracts & ethanolic extracts	RAW 264.7 Macrophages	• Inhibit the NO production in a dose-dependent manner, decreasing to 14.08±3.68 and 16.80±6.32% in 100 μg/mL crude and ethanolic extract, respectively. • However, at 200 μg/mL a decrease in cell viability indicates a cytotoxic effect. • Down-regulation of iNOS expression and reduce the expression of COX-2 and IL-1β.	(Catarino et al. 2020)
	Eisenia bicyclis (Portugal)	Crude extracts	THP1 human monocytes	• Reduce 43.5% of nitrite in the medium. • Reduce 1.2-fold in IL-8 mRNA expression, and approximately 3.7-6-fold in the expression of TNF-α, IL-1β, IL-8, and IL-6. • Increase 4-fold anti-inflammatory cytokine IL10 expression.	(Raja et al. 2023)
	Eisenia arborea (Japan)	6,6′-bieckol and 6,8′-bieckol	Mice	• Significantly suppress mice ear swelling, with 35.7%–61.8% in 6,6′-bieckol and 55.7%–77.6% in 6,8′-bieckol.	(Sugiura et al. 2017)
Anti-allergy/ histamine	*E. arborea* (Japan)	Eckol, 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, phlorofucofuroeckol-A/–B	Rat mast cell line (RBL-2H3 cells)	• Suppressed histamine release at a concentration of 100 mM, while phlorofucofuroeckol-B showing a suppressive ratio at 200 mM of 37.1%. • Suppress PGE2 release at 10, 100, 200 mM.	(Sugiura et al. 2018)
	Eckolonia cava (South Korea)	Fucodiphloroethol G, eckol, phlorofucofuroeckol-A	Human leukemia cell line (KU812) & rat basophilic leukemia cell line (RBL-2H3)	• KU812 –Reduced IgE induced stimulated histamine release to 23.97, 44.26, and 34.54% at the concentration of 100mM. • Reduced A23187 stimulated histamine release to 27.40, 61.15, and 37.05%, respectively. • RBL-2H3 –A23187 stimulated: 27.73, 50.63, and 34.18%, respectively. • Reduced β-hexosaminidase release to 18.02, 31.67, and 20.80%, respectively.	(Y. Li et al. 2008)
Anti-diabetic	*E. bicyclis* (Portugal)	Crude extracts	Mouse myoblast cell line (C2C12 cells)	• Superiorly inhibit α-glucosidase inhibitory action with an IC50 of 31.7 ± 0.84mg/mL, comparable to acarbose. • Significantly inhibit glycation, PTP1B, α-glucosidase, and α-amylase activity. • Increase glucose uptake by 51.09% (p < 0.05) under insulin-stimulated conditions.	(Raja et al. 2023)
	Sargassum linifolium (Egypt)	Phlorotannin-rich extracts	White albino male Wistar rats	• Significant decrease in serum glucose levels. • Promote the β-cell in the pancreas to secret insulin. • Reduce glucosidase, α-amylase, and CAT levels. • Lower the urea, creatinine, cholesterol and triglyceride levels. • Activate of AMPK pathway and inhibit adipogenesis.	(Gheda et al. 2023)
	1. *Cystoseira compressa*(Egypt)	Phlorotannin-rich extracts	White albino Wistar rats	• Significant reduce the blood glucose, urea, creatinine, cholesterol, and triglyceride levels compared to the diabetic control. • Increase the insulin levels. • Reduce the α-amylase and glucosidase activities. • Increase CAT activity to decrease the hepatic lipid peroxidation.	(Gheda et al. 2021)
	Sargassum tenerrimum (India)	Phlorotannin-rich extracts	Wistar albino rats	• Elevate insulin levels after 21 days of treatment (p < 0.001). • Considerably improve oral glucose tolerance by 52% and 63% at 200mg/kg and 400mg/kg (p < 0.001). • Reduced the production of the lipid oxidation product MDA level but increase SOD and CAT concentrations. • Alleviate the TNF-α level.	(Vijay and Vellapandian 2023)

(Continued)

Table 2. Continued.

Bioactivities	Seaweeds	Phlorotannins	Models	Outcomes	References
Anti-bacterial/ microbial	*Halidrys siliquosa* (France)	Phlorotannin-rich extracts	*Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538), and *E. coli* (ATCC 8739)	• Reduce higher than 5 log of the initial bacterial concentration with *Pseudomonas aeruginosa* and *E. coli* (<1 CFU/mL). • 4.5 log reduction of the initial bacterial concentration of *Staphylococcus aureus* (75 CFU/mL).	(Le Lann et al. 2016)
	Hizikia fusiforme (China)	Phlorotannin-rich extracts	*S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *P. aeruginosa* (PAO1), *Aeromonas hydrophila* (YJ-1), and *Vibrio parahaemolyticus* (X-1)	• The MIC of phlorotannins against the selected bacteria was: 0.1943 g/ml for *C. violaceum* and *E. coli*, and 0.0972 g/ml for *S. aureus*, *A. hydrophilia*, *V. parahaemolyticus*, and *P. aeruginosa*. • Inhibit the formation of biofilm.	(Tang, Wang, and Chu 2020)
	F. vesiculosus & Pelvetia canaliculate (Russia)	Cell wall extracts & intracellular phlorotannin-rich extracts	*E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), *Listeria monocytogenes* (EGD), *S. aureus* (ATCC 25923), *S. aureus* (SG-511), methicillin resistant *S. aureus* (ATCC 33591), *Micrococcus luteus* (CIP A270)	• Low or moderate antimicrobial activity for all extracts. • Cell wall extracts exhibited higher antimicrobial activity in comparison to the intracellular phlorotannin-rich extracts. • For *E. coli* and *S. aureus* (ATCC 25923) –Cell wall fraction (MIC = 31.2 µg/mL), intracellular fraction (MIC = 62.5 µg/mL).For methicillin resistant *S. aureus*–Cell wall fraction (MIC = 125 µg/mL), intracellular fraction (MIC = 500 µg/mL).	(Meshalkina et al. 2023)

Note: DPPH: 2-diphenyl1-picryl-hydrazine-hydrate; ABTS: 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid; EC50: half maximal effective concentration; ROS: reactive oxygen species; NO: nitric oxide; iNOS: inducible nitric oxide synthase; COX-2: cyclocygenase-2; IL: interleukin; PGE2: prostaglandin E2; Ig: immunoglobulin; IC50: half maximal inhibitory concentration; PTP1B: protein tyrosine phosphatase 1B; AMPK: AMP-activated protein kinase; MDA: malondialdehyde; SOD: superoxide dismutase; CAT: catalase; TNF-α: tumor necrosis factor alpha; MIC: minimum inhibitory concentration.

Ascophyllum nodosum have exhibited comparable or even superior DPPH radical scavenging activity when compared to commercially available antioxidants such as butylated hydroxytoluene and ascorbic acid (Liu et al. 2017). Similarly, stronger ABTS inhibitory effects than those observed with ascorbic acid were found in the ethyl acetate fractions of *Sargassum hemiphyllum* and *Sargassum pallidum*, with the half maximal inhibitory concentration (IC50) values of 0.11 ± 0.01 mg/mL and 0.02 ± 0.00 mg/mL, respectively, in contrast to 0.27 ± 0.00 mg/mL (Chen et al. 2023). Additionally, they include assessments of reducing power *via* ferric ion reducing antioxidant power and phosphomolybdate assay, as well as metal chelating activity. The ferrous chelating properties of phlorotannins obtained from *F. vesiculosus* were further investigated, revealing up to 95% chelation in water extracts and 55% in acetone aqueous (*v/v*, 7:3) extracts (Wang, Jonsdottir, and Ólafsdóttir 2009).

Another mechanism modulated by phlorotannins involves the activation of Nrf2, a signaling pathway that leads to the downstream production of antioxidants. Phlorotannins have been found to form quinones that act as electrophiles, interacting with the thiol group in Kelch-like ECH-associated protein 1, a crucial sensor of oxidative and electrophilic stress. With further activating quinone reductase activity that led to the reduction and detoxification of electrophilic quinones and quinone derivatives, phlorotannins help result in the formation of Michael adducts and induce a conformational change that releases the Nrf2 protein, which, in turn, promotes the translocation of Nrf2 from the cytoplasm into the nucleus, upregulating the production of antioxidant enzymes such as the heme oxygenase-1 (Hmox-1) (Jun et al. 2014). Phlorotannins can also activate the Nrf2 pathway through other mechanisms, such as the phosphorylation of several downstream pathways. Notably, the differential activation of various signaling pathways in response to phlorotannin administration, such as the induction of phosphorylated c-Jun N-terminal kinase (JNK) and phosphorylated protein kinase B (PKB) on HepG2 hepatocytes and the activation of p-Akt and phosphorylated extracellular signal-regulated kinase (ERK) pathways on V79-4 lung fibroblasts by eckol (Jun et al. 2014; K. C. Kim et al. 2010), is contingent on several factors, including the specific types of phlorotannins, the cell types involved, and the nature of the oxidative stimuli applied.

In addition to its impact on Hmox-1, phlorotannins have also been observed to reduce the expression of NADPH oxidase 2 (NOX-2), a significant source of ROS production induced by lipopolysaccharide (LPS). This findings are supported with an increased expression of glycoprotein 91^{phox}, a catalytic substrates of NOX complex (Cui et al. 2015). Meanwhile, A. D. Kim et al. (2014) reported that eckol derived from *Ecklonia cava* could enhance the expression of manganese superoxide dismutase, which serves as the primary defense mechanism against mitochondrial ROS, safeguarding cells from oxidative stress.

Anti-inflammatory

Inflammation, whether acute or chronic, can give rise to a range of health complications, including autoimmune

diseases like rheumatoid arthritis (Shrivastava and Pandey 2013), cardiovascular diseases such as high blood pressure (Botelho et al. 2021), and gastrointestinal disorders like inflammatory bowel disease (Yao et al. 2019). Researchers have posited that phlorotannins exert significant effects on three pivotal mediators, including cytokines, enzymes, and signaling pathways, drawing from observations in cell cultures and animal studies.

Besides the previously mentioned antioxidant mechanisms, phlorotannins alleviate inflammation, often associated with oxidative stress, by modulating the production of inflammation-related cytokines. For instance, treatment with eckol isolated from *E. cava* at concentrations of 50 μg/mL and 100 μg/mL in a mouse model of anaphylaxis resulted in the reduction of mRNA expression levels of proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (Han et al. 2020). They also observed the downregulation of Th2-type cytokines, specifically IL-4, IL-5, and IL-13, which led to a reduction in immunoglobulin (Ig) E and eosinophilic responses. Another study reported an amelioration of endothelial dysfunction in mouse models through the use of pyrogallol-phloroglucinol-6,6-bieckol extracted from the same species, which was attributed to the reduced expression of TNF-α and IL-6 (Son et al. 2019). The observed enhancement of transforming growth factor beta can inhibit the activation and function of various immune cells, such as T cells and macrophages, reducing their capacity to produce pro-inflammatory cytokines and mediators. Simultaneously, it promotes the development and differentiation of regulatory T cells, which are essential in maintaining immune tolerance and preventing excessive inflammation (Bierie and Moses 2010).

Several enzymes implicated in the processes of inflammation are subject to regulation by phlorotannins. Notably, inducible nitric oxide synthase (iNOS) is among the enzymes responsible for the production of nitric oxide (NO), a pivotal signaling molecule associated with a range of physiological processes, including inflammation, immune responses, and tissue damage (Spiller et al. 2019). Recent investigations have revealed that trifuhalol A, extracted from *Agarum cribrosum*, exerts a significant downregulatory effect on iNOS expression in LPS-stimulated RAW264.7 cell models, resulting in a notable decrease in NO production, estimated at 36.6%–56.8% (Phasanasophon and Kim 2019). Lopes et al. (2012) proposed that phlorotannins have the capacity to regulate NO levels not only by inhibiting related enzymes but also through direct scavenging and/or by reducing NO production *via* their influence on the inflammatory signaling cascade. Moreover, Kurihara, Konno, and Takahashi (2015) reported that fucophlorethol C, isolated from the brown seaweed *Colpomenia bullosa*, effectively inhibited lipoxygenases (LOX) to a similar extent as the known inhibitor nordihydroguaiaretic acid. LOX plays a crucial role as a rate-limiting enzyme in the conversion of arachidonic acid into leukotrienes, known mediators of inflammation (Hu and Ma 2018); therefore, compounds that inhibit LOX have the potential to decelerate this process and exert anti-inflammatory effects.

In terms of signaling pathways, Catarino et al. (2020) reported that phlorotannin derivatives from *F. vesiculosus* effectively inhibited the phosphorylation and degradation of inhibitory protein κBα, an intracellular protein that functions as a primary inhibitor of the proinflammatory transcription factor nuclear factor kappa B (NF-κB). This inhibition, in turn, prevents the activation of the NF-κB signaling pathway, thereby locking the inflammatory cascade at the transcriptional level. In line with the findings of S. Kim et al. (2019), they observed that the addition of an ethanolic extract of *E. cava*, primarily containing dieckol, induced the translocation of NF-κB to the nucleus while preventing its binding to the cell DNA, along with a dose-dependent reduction in the levels of cytokines and various enzymes. Trifuhalol A was found to significantly inhibit the expression of JNK and ERK1/2 at concentrations ranging from 5 to 20 μg/mL (Phasanasophon and Kim 2019). This inhibition further attenuated mitogen-activated protein kinases (MAPKs), serving as crucial components of a series of vital signal transduction pathways regulating processes such as cell proliferation, cell differentiation, and cell death in eukaryotes (Morrison 2012).

Anti-diabetic

Diabetes is a global health issue affecting millions of individuals, with its incidence projected to increase in the coming years. This chronic condition is associated with severe complications, including cardiovascular diseases, kidney damage, and nerve damage (Dal Canto et al. 2019). Recent advances in the study of plant polyphenols have brought attention to phlorotannins as potential candidates for modulating key enzymes, specifically α-glucosidase and α-amylase (Lopes et al. 2019), which are responsible for the elevation of postprandial glycemia. Several phlorotannins have demonstrated lower IC50 values than acarbose, a clinically approved inhibitor for type 2 diabetes treatment, indicating greater inhibitory potential. For example, fucophloroethol structures obtained from *Fucus distichus* exhibited an IC50 of 0.89 μg/mL and 13.9 μg/mL against α-glucosidase and α-amylase, respectively. In contrast, acarbose, the pharmaceutical inhibitor, showed IC50 values of 112.0 μg/mL and 137.8 μg/mL for the same enzymes (Kellogg, Grace, and Lila 2014). Consistent with the findings of H.-A. Lee, Lee, and Han (2017), oral administration of 2,7″-phloroglucinol-6,6′-bieckol led to a significant reduction in postprandial blood glucose levels in diabetic mouse models induced by streptozotocin, attributed to the delayed absorption of dietary carbohydrates through the inhibition of the related enzymes. The compound exhibited IC50 values of 23.35 μM against α-glucosidases and 6.94 μM against α-amylase, in contrast to acarbose at 130.04 and 165.12 μM, respectively. Lo Piparo et al. (2008) hypothesized that the inhibitory activity of phlorotannins is influenced by the formation of hydrogen bonds between their hydroxyl groups and the carboxylate groups of Asp_{197} and Glu_{233}, two active sites of α-amylase. This impedes the enzymatic breakdown of complex carbohydrates into simple sugars like glucose. Moreover, similar polyphenol categories,

such as flavonoids and phenolic acids, offer insight into possible inhibitory mechanisms influenced by methylation and methoxylation processes on phlorotannin structures (Guan et al. 2022). The quantity, position, and substitution pattern of these hydroxyl and methoxy groups are presumed to participate in various chemical interactions with the active sites of α-glucosidase and α-amylase, including hydrogen bonding and electrostatic interactions, further influencing binding affinity and inhibitory potency (J. Zhang et al. 2022).

Hepatic gluconeogenesis represents another critical target for diabetes modulation, involving the regulation of insulin-related enzymes, such as glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), and glucokinase. Octaphlorethol A, derived from *Ishige foliacea*, was identified as an inhibitor of hepatic gluconeogenesis in a study by S.-H. Lee et al. (2016). It significantly suppressed the upregulation of hepatic mRNA expression levels of gluconeogenic enzymes, particularly PEPCK and G6Pase, leading to a reduced hepatic glucose production and potential benefits in diabetes management. Murray et al. (2021) provided compelling evidence through a placebo-controlled randomized clinical trial, demonstrating that the administration of a polyphenol-rich seaweed extract containing 8,8′-bieckol, 6,6′-bieckol, and phlorofurofucoeckol A for 12 weeks resulted in a greater reduction in postprandial glucose levels compared to fasting glucose levels, with further support for the regulation of G6Pase and PEPCK. Conversely, S. Zhang et al. (2020) indicated that certain phlorotannins, notably trifuhalol A, did not exhibit an inhibitory effect on G6Pase, even at increased concentrations. In a randomized crossover trial, the administration of polyphenols extracted from *F. vesiculosus* demonstrated the potential to moderate glycemic responses in females by reducing peak postprandial glucose concentration (Murray et al. 2019). However, this effect was not observed in males, suggesting a gender-specific response that requires further investigation to understand the underlying mechanisms and implications of these gender differences in response to polyphenol treatment.

Oxidative stress plays a pivotal role in the development of type 2 diabetes mellitus (T2DM), resulting from an imbalance between the production of ROS and antioxidant defense. In T2DM, the decreased levels of enzymatic antioxidants contribute to the development of diabetic complications. According to a meta-analysis of 22 studies conducted by Banik and Ghosh (2021), the association between T2DM and biomarkers was emphasized, with eight studies focused on superoxide dismutase (SOD) levels and four on glutathione peroxidase levels. Administration of dieckol through intraperitoneal injections (10–20 mg/kg for 14 days) in diabetic mice resulted in a notable reduction in blood glucose and serum insulin levels, with a slight increase in the activity of the antioxidative enzyme, SOD, in the liver tissues (Kang et al. 2013). Similarly, eckol, 7-phloroeckol, and phlorofucofuroeckol-A have been identified as inhibitors of protein tyrosine phosphatase 1B (PTP1B) (Gunathilaka, Keertihirathna, and Peiris 2021), an enzyme critical for regulating insulin signaling. PTP1B overactivity can result in insulin resistance; thus, the inhibition of PTP1B is a potential therapeutic strategy to enhance efficient insulin signaling by preventing the dephosphorylation of tyrosine residues and promoting glucose uptake into cells (Koren and Fantus 2007).

Anti-allergy/histamine

Histamine, a bioactive amine released by immune cells, serves as a signaling molecule and neurotransmitter in response to allergic reactions (Mandola, Nozawa, and Eiwegger 2019). The prevalence and severity of allergic diseases have exhibited a significant rise over the past decade worldwide, particularly affecting approximately 20% of the population in developed countries (Y. Li et al. 2008). Two bioactive phloroglucinol derivatives, fucodiphloroethol G and phlorofucofuroeckol A, were initially isolated from *E. cava* by Y. Li et al. (2008), who reported their notable inhibitory activity against histamine release. This inhibition was demonstrated in human basophilic leukemia (KU812) and rat basophilic leukemia (RBL-2H3) cell lines using a histamine release assay. To support their results, Le et al. (2009) suggested that these active compounds may be useful in preventing allergen-IgE-induced allergic reactions. Likewise, G. Ahn et al. (2015) highlighted the inhibitory effects of dieckol on IgE-mediated degranulation observed in LAD2 cells. An insightful hypothesis posits that phlorotannins have the capacity to stabilize the cell membrane by reducing intracellular Ca^{2+} levels, thereby inhibiting the binding activity between IgE and its high-affinity receptor. This inhibition, in turn, disrupts downstream signaling cascades, including the activation of protein tyrosine kinases (Syk, Lyn), calcium mobilization, and protein kinase C translocation, all of which are essential for degranulation (Shim, Lee, and Lee 2016; Yoshioka et al. 2014).

Sugiura et al. (2021) discovered that the phlorotannin dieckol exhibited significant anti-allergic effects in an ear swelling test conducted on mice sensitized to arachidonic acid, 12-*O*-tetradecanoylphorbol-13-acetate and oxazolone. These effects were attributed to the suppression of degranulation, the release of chemical mediators, and the expression of mRNA, including cyclooxygenase-2 (COX-2), IL-6, and TNF-α, in rat basophilic leukemia-2H3 cells. In another study, 6,6′-bieckol and 6,8′-bieckol were found to inhibit COX-2 activity at a concentration of 500 μM, with inhibition ratios of 9.8% and 40.4%, respectively. Notably, 8,8′-bieckol (96.6%) and phlorofucofuroeckol A (96.8%) exhibited inhibitory effects comparable to that of epigallocatechin gallate (95.8%) (Sugiura et al. 2018). These findings align with the explanation that the bioactivity of phlorotannins is strongly influenced by their molecular size or the number of phenol groups. The structures of eckols and the bieckols, as presented by Sugiura et al. (2018), suggest that the positioning of the hydroxyl group at either C-4 or C-4′ in these compounds may play a crucial role in their ability to suppress degranulation and COX-2 mRNA expression.

In addition, a recent study isolated three phlorotannins from *Sargassum carpophyllum*, including 2-[2-(3,5-dihydroxyphenoxy)-3,5-dihydroxyphenoxy]-1,3,5-benzenetriol, 2,2′-[[2-(3,5 dihydroxyphenoxy)-5-hydroxy-1,3-phenylene]bis (oxy)]bis(1,3,5-benzenetriol), and 2-[2-[4-[2-(3,5-dihydroxyp

henoxy)-3,5-dihydroxyphenoxy]-3,5-dihydroxyphenoxy]-3,5 dihydroxyphenoxy]-1,3,5-benzenetriol (Matsui et al. 2022). These compounds were found to prevent immediate hypersensitivity by exhibiting a dose-dependent reduction in β-hexosaminidase secretion in vitro similar to other phlorotannins such as eckol (Han et al. 2020), with IC50 values of 50.7, 35.9, and 43.5 μM, respectively. Meanwhile, these phlorotannins exhibited a significant reduction of approximately 50% in prostaglandin D2 (PGD2) levels compared to the positive control group. PGD2 is a major prostanoid secreted by activated mast cells, and elevated PGD2 levels have been closely associated with medical conditions, including asthma and allergic reactions (Nakamura et al. 2015). However, their findings revealed no statistically significant effect on the expression of COX-2, the enzyme responsible for converting arachidonic acid to prostaglandin H2 (PGH2), the precursor of PGD2 synthesis. This contrasts with the conclusion previously reported by Sugiura et al. (2018), and as a result, they were unable to establish a definitive relationship between COX-2 expression and the levels of PGD2. It is plausible that the activity of downstream enzymes involved in PGD2 synthesis or the presence of other mediators in the cellular environment may have influenced the observed results.

Anti-microbial/viral

The hypothesis suggests that phlorotannins may exert antiviral effects through two primary mechanisms: by preventing the virus from entering host cells and by inhibiting viral replication once it has entered the host cell. J.-Y. Park et al. (2013) observed that the dieckol derived from *E. cava* competitively inhibits 3CLpro, a cysteine proteinase with similarities to chymotrypsin, which is crucial for viral replication. Other enzymes, such as reverse transcriptase and protease of human immunodeficiency virus type 1 (HIV-1), were reported to be potently inhibited by 8,4‴-dieckol and 8,8′-bieckol (M.-J. Ahn et al. 2004). Likewise, it was observed that phlorotannins extracted from *E. cava* suppressed the production of surface proteins, such as hemagglutinin and neuraminidase, which are responsible for the initial attachment of the virus to host cells and the release of newly formed virions, respectively (Cho et al. 2019). Meanwhile, phlorotannins were found to increase the activity of mitochondrial dehydrogenases, causing membrane depolarization, as well as reducing the ergosterol content of the fungal cell wall, thus demonstrating efficacy against yeast and several dermatophytes (Lopes et al. 2013). A synergistic effect was reported when using phlorotannins in conjunction with antibiotics against the *Listeria* genus (H.-J. Kim et al. 2018).

Bioavailability of phlorotannins

The concept of bioavailability refers to the proportion of an administered dose of nutrients that enters the systemic circulation (Price and Patel 2021), which is influenced by factors such as biological response (bioactivity), metabolism, absorption (bioaccessibility). While numerous biological activities of phlorotannins have been determined, research on their bioavailability is still ongoing. Scientists have

hypothesized that they exhibit similar behaviors to other polyphenols, such as phenolic acids and flavonoids. In this regard, the overall bioavailability of phlorotannins is anticipated to be limited, as Catarino, Marçal, et al. (2021) reported only a small fraction (14.1%) of phlorotannins from *F. vesiculosus* is likely to undergo absorption in the upper gastrointestinal tract. This finding aligns with the results of Corona et al. (2016), who observed that, following the ingestion of a phlorotannin-rich capsule by healthy volunteers, most of the phlorotannin metabolites were subsequently detected in their urine and plasma, indicating a low rate of absorption in the small intestine.

In detail, the low absorption rate could probably be explained by the polymeric nature of phlorotannins, as well as their molecular weight and interactions with other dietary components (Meng et al. 2021). The initial challenge in the absorption of phlorotannins is to liberate them from the seaweed matrices, because they are typically embedded or bound within the cellular and structural components that hinder their release, especially polysaccharides and proteins (Ford et al. 2020). Phlorotannins, with higher molecular weights, have a greater capacity to form bonds with proteins, which reduces their solubility and makes it more challenging for the digestive system to break them down and absorb them in the small intestine (Cáceres-Jiménez et al. 2023). Also, it is hypothesized that enzymes responsible for metabolizing them may have reduced access to the bound phlorotannins, slowing down their transformation into low molecular weight derivatives. Catarino, Marçal, et al. (2021) observed a shielding effects between bound phlorotannins and gastric enzymes that prevent their degradation during the upper gastrointestinal and therefore forcing their transportation to the colon. On the other hand, some interactions between phlorotannins and cell wall polysaccharides, such as fucoidans and alginates, would also affects their release. For example, alginates can form a three-dimensional gel-like network that captures phlorotannins, similar to the patterns seen with condensed tannins-proanthocyanidins (Liu and Bourvellec 2023).

Moreover, phlorotannins undergo various metabolic processes. Similar to terrestrial polyphenols, these metabolism processes can be categorized into three phases. Phase I reactions primarily entail intramolecular modifications, including processes such as oxidation, reduction, and hydrolysis. Meanwhile, Phase II reactions involve the conjugation of endogenous substances with ingested compounds, transforming them into water-soluble substances that can be easily excreted from the body. This process is often referred to as detoxification and is achieved through main processes like acetylation, methylation, glucuronidation, and sulfation (also known as sulfonation) (Schaffenburg, Lockshin, and DeKlotz 2021). It is worth noting that recent emphasis has been placed on a term "Phase III reaction" in the context of drug or nutrient metabolism, which is responsible for the final elimination of toxins and metabolic products from cells (Phang-Lyn and Llerena 2019). Together, these processes influence their stability during transit. In their pioneering work, Corona et al. (2016) investigated the possibility of the relationship between ingested seaweed and their colonic

biotransformation by gut microbiota. This study successfully identified a variety of unconjugated and conjugated metabolites of phlorotannins, including glucuronides and/or sulfates, in urine and plasma samples. During Phase II detoxification, phlorotannins undergo transformations that cause them to form larger and more polar conjugates, which hampers their passive diffusion across biological membranes, ultimately diminishing their bioavailability and facilitating their elimination from the body (Corona et al. 2017). This possibility found further support in a clinical experiment conducted on obese individuals, where the analysis of their urine revealed the presence of various phlorotannin conjugates, including phloroglucinol sulfate, hydroxytrifurahol A-sulfate, dioxinodehydroeckol, fucophloroethol glucuronide, diphlorethol sulfates, and dioxinodehydroeckol glucuronide (Baldrick et al. 2018).

Safety and stability of phlorotannins

When considering phlorotannins for medical or health-promoting purposes, addressing their safety concerns is imperative. However, the majority of the available studies are conducted in vitro based on cell models, with limited in vivo animal or human research. Indeed, phlorotannins have been shown to be nontoxic or not significantly toxic to several cell lines in most of the studies.

For example, diphlorethohydroxycarmalol from *Ishige okamurae* was reported to increase cell viability against H_2O_2-induced oxidative stress in murine hippocampal neuronal cells. The highest cell survival rate reached 77.21% at a dose of 50 µM, compared to the blank control, which only had a survival rate of 17.18% (Heo et al. 2012). This assessment was conducted using the 2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, a widely used test in cell biology and toxicology for evaluating cell viability and proliferation, enabling the indirect assessment of substance toxicity. However, there were some controversial results, such as dieckol (20–100 µg/mL) decreasing cell viability and increasing prostaglandin E2 (PGE2) release on HaCaT cells exposed to particulate matter (PM_{10}) (Ha et al. 2019), which could potentially lead to cardiovascular conditions, respiratory symptoms, chronic inflammation and tissue damage. These results suggest that the response patterns may vary depending on the cell line models and the specific doses applied.

In terms of animal studies, the safety and toxicity of phlorotannins have been extensively investigated using zebrafish, mice, rats and dogs. These studies have generally shown a 100% survival rate while exhibiting efficient biological activities. However, some slight symptoms have been reported, such as soft stool and diarrhea in Beagle dogs when given high-purity phlorotannin fractions at a dose of 750 mg/kg on days 3 and 13 (Yang et al. 2014). It is worth noting that these effects were only observed at high oral doses, and no adverse effects were found at doses of 250 and 500 mg/kg. Similar safety has also been demonstrated in human trials with phlorotannin-rich capsules, especially eckol from *E. cava* at a dose of 500 mg/day and treatment for one week (Um et al. 2018).

The European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) delivered a scientific report on the safety of *E. cava* products (SeaPolynol™) (Patent NO.: US10016471B2) as a phlorotannin-rich food supplements (Turck et al. 2017). They reported that there is no evidence of genotoxicity for the product and identified a low risk of allergic reactions. They suggested an intake of 163 mg/day for adolescents aged 12 to 14 years (mean body weight of 43.4 kg), 230 mg/day for adolescents above 14 years of age (mean body weight of 61.3 kg), and 263 mg/day for adults (default body weight of 70 kg).

Investigating strategies to improve bioavailability and bioactivities of phlorotannins

Research on phlorotannins is still in its early stages, and one commonly employed approach to overcome their inherent limitations involves the micro-/nano-encapsulation of phlorotannins within a carrier (Tong, Liu, and Yu 2021). Various carrier systems, such as nano-emulsions, liposomes, edible films, nanoparticles, nanogels, have been utilized for delivering terrestrial polyphenols (J. Zhang et al. 2023). In the case of phlorotannins, specific examples of targeted carriers can be observed.

Polymeric nanoparticles

To enhance the therapeutic effectiveness of phlorotannins in the human body, Bai et al. (2020) conducted a study on the encapsulation efficiency of polyvinylpyrrolidone (PVP) nanoparticles, employing various ratios in combination with phlorotannins. Among these ratios, the nanoparticles with a 1:8 ratio exhibited superior stability in water, remaining without precipitation for 5, 10, and 15 days at room temperature compared to free phlorotannins. Furthermore, the application of PVP nanoparticles at concentrations of 6.25 and 12.5 µg/mL in a HaCaT keratinocyte model resulted in a significant reduction of ROS production by 12% and 18%, respectively, without detectable irreversible cytotoxic effects. However, after discovering the carcinogenic nature of PVP, its use in health supplements and oral administration became limited. Consequently, Bai, Chen, and Qi (2022) developed an alternative approach by formulating improved protein-polysaccharide nanocomplexes using whey protein isolate and chitosan oligosaccharides, which are edible, cost-effective, and commercially available. In their experiment, Caco-2 cells exposed to hydrogen peroxide exhibited a decrease in cell viability to 68.79 ± 3.78%. However, treatment with phlorotannin-loaded nanoparticles at varying concentrations revealed a dose-dependent increase in cell viability. Notably, at a concentration of 40 µg/mL of phlorotannin-loaded nanoparticles, the cell viability significantly rose to 84.83 ± 1.92% ($p < .05$). Additionally, the administration of the nanoparticles at the aforementioned concentration effectively restrained ROS generation in H_2O_2-treated cells and NO production in LPS-induced cells, bringing them to levels comparable to the negative control

group, which further validates the enhanced anti-inflammatory and antioxidant capacity achieved through nano-encapsulation.

Another investigation employed electrospinning to prepare zein nanofiber membranes loaded with ε-polylysin e-polyphenol-polyaspartic acid for the controlled delivery of polyphenols, including phlorotannins (Yingying et al. 2022). In terms of their in vitro release profile, approximately 19.65% of the phlorotannins were released within the initial 2h under acidic conditions (pH 1.2), thereby illustrating the protective effect of zein nanofiber membranes against the acidic gastric pH environment. Moreover, a higher release of 62.35% occurred over an 8-h period at pH 6.8, which was facilitated by the electrostatic interaction between ε-polylysine and polyaspartic acid, effectively enhancing system stability and preventing burst release. Consistent with the findings reported by Amjadi et al. (2022), the investigation revealed that zein nanofiber membranes effectively preserved the activity of polyphenols and displayed favorable biocompatibility, as well as induced a higher degree of stress and apoptosis in HT-29 cells, a human colorectal adenocarcinoma cell line with epithelial morphology. Consequently, electrospinning has been validated as a highly effective method for fabricating sub-micron or nano-scale polymer fibers, which can be tailored to serve as safe and nontoxic drug delivery systems (DDSs). Moreover, Surendhiran, Cui, and Lin (2019) suggested using various biodegradable polymer-based nanofibers for food preservation purposes. In their study, they fabricated sodium alginate and poly(ethylene oxide) (PEO) blended nanofibers encapsulated with phlorotannin (50:50:10, *v/v/v*) *via* electrospinning process, which exhibited temperature-dependent antimicrobial activity. The preservation capacity of active nanofibers was assessed against *Salmonella enteritidis* on chicken at 4 and 25 °C, with cell count drastically decreasing from 6.20 to 3.28 Log CFU/g at 4 °C and from 8.80 to 2.53 Log CFU/g at 25 °C. Due to the presence of 8 interconnected rings in marine algal polyphenols, the phlorotannin encapsulated nanofibers showed higher overall acceptability scores in sensory assessment, with food preservability almost equal to sodium nitrite, a widely used synthetic preservative in meat industries (Sathya et al. 2017). Similarly, a multifunctional wound dressing using gelatin/chitosan hybrid fibers embedded with a phlorotannin-enriched extract derived from the seaweed *Undaria pinnatifida* was prepared (Ferreira et al. 2021). Electrospun meshes were created by incorporating 1 or 2 weight (wt)% of the extract, resulting in enhanced structural stability over time, as indicated by reduced in vitro degradation rates under enzymatic conditions. Initial antimicrobial assessments demonstrated the effectiveness of mesh against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, confirming its antimicrobial activity. Regarding biological characterization, none of the tested conditions showed cytotoxic effects on hDNF cells, allowing for the adhesion and proliferation of the cells over a span of 14 days, with the exception of the 2 wt% condition after 7 days exhibited some cytotoxicity effects.

Liposomes

Nano-liposomes, also known as submicron bilayer lipid vesicles, represent a novel technology for the efficient encapsulation and targeted delivery of bioactive agents, which enable the incorporation of a wide range of bioactive materials, including pharmaceuticals, cosmetics, and nutraceuticals (Mozafari 2010). This technology has opened up diverse opportunities for the development of advanced delivery systems in various fields, allowing for improved efficacy and controlled release of bioactive compounds. Savaghebi, Ghaderi-Ghahfarokhi, and Barzegar (2021) explored the potential of nano-liposomes encapsulated with brown algae extract (*Sargassum boveanum*) for their antioxidant and antimicrobial properties. Their research indicated that the ethyl acetate fraction demonstrated significant activity against gram-positive bacteria (*Bacillus cereus*), with minimum inhibitory concentration (MIC) values of 0.937 and 0.469 mg/mL before and after encapsulation in nano-liposomes. This finding was supported by the speculation made by Hierholtzer et al. (2013) that phlorotannins, present in the brown algae extract, exert antimicrobial effects by disrupting cell membranes and eliciting substantial extra- and intra-cellular responses. On the contrary, certain bacterial strains have developed resistance to a vast array of antibiotics, particularly among gram-negative species. This resistance can be attributed to the presence of an additional outer membrane within their cell wall structure, serving as a protective barrier that restricts the entry of numerous antibiotics into the bacterial cell (Breijyeh, Jubeh, and Karaman 2020). Phlorotannin extracts and their encapsulated forms exhibited MIC values of 1.875 and 0.937 mg/mL, respectively, against *P. aeruginosa* and *Escherichia coli* (Savaghebi, Ghaderi-Ghahfarokhi, and Barzegar 2021). Contrary to expectations, a previous study conducted by Savaghebi, Barzegar, and Mozafari (2020) on the same seaweed species revealed that nano-liposomes exhibited a lower antioxidant capacity compared to the free algal extract. The investigation specifically highlighted a reduction in both the radical scavenging ability and the reducing antioxidant power of the nano-liposomes when compared to the unencapsulated algal extract. Notably, the nano-liposomes displayed a notably diminished scavenging capacity on ABTS radicals, with half maximal effective concentration (EC50) values measured at 453.9 and 219.5 ppm, respectively. Zou et al. (2014) proposed that the observed phenomenon can be plausibly attributed to the structural interactions between the liposome matrix and the loaded compounds. In addition to the localization of phenolic compounds within the core of nano-liposomes, the interactions between the compounds and the lipid bilayers also play a significant role in enhancing their retention time and impeding the kinetics of their release (Karonen 2022). The balance between the biological activities of the encapsulated compounds and their release patterns within nano-liposomes introduces new challenges for their diverse applications. Undoubtedly, the attainment of an optimal release profile, which guarantees the desired biological effects while preserving stability and controlled release, constitutes a complex undertaking. Addressing these challenges holds the key to unlocking the successful utilization of nano-liposomes as efficacious delivery systems within a wide array of industries.

Composite scaffolds

The incorporation of specific compounds within a range of composite scaffolds, achieved through various mechanisms such as encapsulation, absorption, or entrapment, holds promise for advantageous utilization in osteoinductive applications within the realm of bone tissue engineering (Romagnoli, D'Asta, and Brandi 2013). Im et al. (2017) have introduced a biocomposite scaffold that incorporates collagen extracted from fish skin along with phlorotannin sourced from brown algae *E. cava*. Significantly, this composite scaffold exhibited a substantial increase in both proliferation and mineralization ($p < .05$) of osteoblast-like cells, in stark contrast to the control group lacking phlorotannins, as well as the group that was only exposed to phlorotannins. This notable enhancement can likely be attributed to the delayed and sustained release of phlorotannin facilitated by the coated components. Supported by Yeo, Jung, and Kim (2012), the utilization of phlorotannins as supplemental bioactive agents in conjunction with scaffolds has been shown to be advantageous for promoting bone tissue growth, attributed to the ability of phlorotannin to create pronounced hydrophilic sites on the composite materials, leading to enhanced wettability.

Future perspectives and possibilities

Apart from using different materials to embed phlorotannins, various chemical/physical modifications to the vehicle can achieve more targeted delivery and controlled release (Priya, Desai, and Singhvi 2023). Some of the most widely employed approaches can be summarized as follows: PEGylation (attachment or amalgamation of polyethylene glycol), surface modifications (grafting ligands, peptides and/or proteins), as well as the addition of co-solvents or co-surfactants. Moreover, significant attention has been devoted to the manipulation of microenvironments through the incorporation of magnetic fields (Hari et al. 2023; Sanadgol and Wackerlig 2020) and/or ultrasonic fields (*Wei*, Cornel, and Du 2021). These modifications alter the drug delivery environment and enhance the permeability of nutrients, ultimately leading to the desired outcomes of targeted or controlled release effects. However, it should be noted that although these strategies have been applied to several terrestrial polyphenols, no research has been conducted specifically on phlorotannins.

PEGylation

The term "PEGylation" was coined to describe the covalent and non-covalent processes that attach or merge PEG polymer chains with molecules and macrostructures (Gupta et al. 2019). PEGylation offers various benefits over non-PEGylated products in enhancing the drug circulation time and improving drug stability by reducing their immunogenicity and antigenicity (Yadav and Dewangan 2021). It has also been confirmed that PEGylation enhances the permeability and retention effects due to its unrecognizable property by the reticuloendothelial system, providing a unique opportunity to target tumors following systemic administration (Kalyane et al. 2019). Regarding specific applications of polyphenols, multifunctional PEG-mesoporous silica nanoparticles (MSNPs) loaded with curcumin (CUR), a polyphenol with a long history of use in Ayurveda medicines to treat various diseases, exhibited strong fluorescence in HepG2 and HeLa cells compared to non-PEGylated MSPNs, reflecting a high accumulation of nanocarriers within cancerous cells and an enhancement in the bioavailability of CUR (Elbialy et al. 2020). Likewise, liposomal formulations of luteolin, a naturally derived polyphenol, with or without PEG modification, were studied (Sinha and PK 2019). PEGylated liposomes carrying luteolin were the most effective in inducing caspase-3 and caspase-14 protein expressions, two proteins that modulate the cell death program of human keratinocytes. Similar results were observed with liposome containing polyphenols from the red seaweed *Kappaphycus alvarezii*, which not only increased cellular uptake efficiency but also offered site-specific targeted delivery to overexpressed folate receptors in human adenoma MCF-7 breast cancer cells (Baskararaj et al. 2020), suggesting a promising future for phlorotannins.

Recent scrutiny has raised concerns about PEGylation, making it a topic of controversy. While PEGylation reduces interactions with the mononuclear phagocyte system, it is also expected to impede interactions with tumor cells (e.g., *via* a receptor), potentially affecting uptake by the target tissue (Verhoef and Anchordoquy 2013). One critical step in DDSs is the internalization of nanoparticles by cells through endocytosis. Interestingly, evidence suggests that certain PEGylated nanocarriers may not undergo effective receptor-mediated endocytosis in cancer cells within carcinoma tissue (Magarkar et al. 2012). Through free energy analysis, Shen et al. (2018) discovered that the aggregation of PEG polymers during the membrane wrapping process of PEGylated carriers introduces a significant energy penalty of approximately 800kBT. The presence of such a substantial energy barrier and the formation of a ligand-free region on the surface of PEGylated nanoparticles can hinder the membrane-wrapping process and reduce the likelihood of internalization by tumor cells. This physically-based theory of free energy transformation was also emphasized by Y. Li, Kröger, and Liu (2014), who suggested that the grafting of PEG polymers before and after the endocytosis process had an effect comparable to or even greater than the bending energy of the membrane during endocytosis. Neglecting an investigation into this free energy gap, the delivery of PEGylated nanoparticles to diseased cells cannot be predicted. Apart from that, it has been observed that linear PEGylated nanocarriers can stimulate the production of anti-PEG IgM, resulting in significant alterations in the pharmacokinetics and biological distribution after several repeated injections, a phenomenon known as "accelerated blood clearance" (Kierstead et al. 2015).

Peptide-functionalization

Peptide-functionalization, as the name suggests, involves attaching specific peptides to the surface of co-polymer

nanoparticles or micelles. This approach is commonly used in DDSs, particularly in gene therapy, to enhance various desirable characteristics such as superior colloidal stability, enhanced cellular uptake efficiency, effective escape from endo/lysosomes, efficient nuclear import, and successful unpacking of DNA (Muhammad et al. 2019). By designing peptides that can recognize specific receptors or biomarkers on target cells or tissues, these modified copolymer carriers can improve drug delivery efficiency and minimize off-target effects. Sun et al. (2017) demonstrated the effectiveness of this strategy by coating MSPNs encapsulating CUR and doxorubicin (DOX) with an azido-peptide sequence composed of glycine (G), phenylalanine (F), leucine (L), histidine (H-H-H), arginine (R-R), aspartic acid (D), and serine (S). These MSPNs exhibited high loading efficiency and content of CUR and DOX, and they were selectively taken up by DOX-resistant MCF-7/ADR cells due to specific recognition triggered by the attached tetrapeptide R-G-D-S, allowing them to enter lysosomes. Additionally, another part of this sequence, H-H-H-R, was found to induce effective lysosomal membrane permeability, which is beneficial for drug escape from lysosomes, CUR-mediated inhibition of P-glycoprotein 1 (P-gp), and nuclear import of DOX into cells. P-gp is a type of membrane transporter primarily responsible for pumping foreign substances out of cells, which can limit the entry of drugs, reduce their bioavailability, and contribute to multidrug resistance. Another example is the TAT peptide, a short sequence derived from HIV, which can facilitate the delivery of various cargoes, including drugs, proteins, and genetic material, into cells. Sancini et al. (2013) reported that CUR-decorated nanoliposomes gained the ability to cross the blood-brain barrier (BBB), a selective barrier that restricts the entry of various molecules (e.g., drugs, toxins, and pathogens), after functionalization with a modified cell-penetrating TAT peptide. They observed a three-fold increase in the uptake of intact nanoliposomes by human brain capillary endothelial cells, with no adverse effects on cell viability.

Magnetic drug targeting

Superparamagnetic iron oxide nanoparticles (SPIONs), like maghemite (γ-Fe_2O_3), magnetite (Fe_3O_4) or hematite (α-Fe_2O_3) particles, offer the potential to encapsulate drugs or therapeutic agents for controlled release, hyperthermia therapy and BBB crossing, and targeted delivery when subjected to an external magnetic field (Mittal, Roy, and Gandhi 2022). Amanzadeh et al. (2019) demonstrated the benefits of quercetin-SPIONs, which significantly enhanced learning and memory in rats compared to free quercetin. This enhancement is likely due to the prolonged circulation of quercetin in the bloodstream and its increased concentration in the brain, facilitated by the incorporation of SPIONs. In addition to these improvements, Ramya et al. (2021) proposed a pH-responsive release behavior with silibinin-loaded Fe_2O_3 nanoparticles. They observed that less than $25 \pm 2.2\%$ of silibinin was released within 48h at pH 7.4 in phosphate-buffered saline. However, more than $54 \pm 1.6\%$ of

entrapped silibinin was released after a 48-h incubation at pH 4.5. This behavior is attributed to the deformation of the linkage between silibinin and Fe_2O_3 nanoparticles induced by the acidic pH, facilitating their efficient delivery to the tumor environment (pH 4.0–5.0). Furthermore, C. Li et al. (2020) optimized and prepared tea polyphenol-alginate/chitosan magnetic microcapsules by incorporating nano-Fe_3O_4 particles and magnetofluid. These microcapsules demonstrated a good slow-release effect lasting up to 100h and exhibited superparamagnetism with extremely low magnetic retention and coercivity, which means that there is no remanent magnetization when an external magnetic field is removed, making them excellent carriers for delivering tea polyphenols in tumor endovascular embolization therapy.

In the field of seaweed bioactive compounds, magnetic MSPNs coated with a Fe_3O_4 network have been synthesized for the delivery of fucoxanthin, a carotenoid pigment derived from brown seaweeds (Feng et al. 2022), and they can be effectively guided to the tumor site with no adverse effects. Indeed, while specific research on phlorotannins may be limited, the applications and strategies discussed in the context of other compounds provide a valuable foundation for exploring the potential delivery of phlorotannins through various nanocarriers and modifications.

Conclusion

Seaweeds exhibit remarkable versatility, holding significant importance across various sectors of the global market. They function as a valuable resource for environmental conservation, economic growth, and numerous industries. Capitalizing on their rich array of macro- and micro-nutrients, seaweeds present diverse and sustainable opportunities to enhance soil fertility, serve as constituents in animal feed, act as a renewable source of bioenergy, and contribute to the improvement of water quality. Moreover, beyond their pivotal role in environmental ecosystems, seaweeds merge as highly nutritious components, offering a broad spectrum of health benefits attributable to their distinctive composition of metabolites. This review has highlighted the generalized chemical properties of phlorotannins, a group of polyphenols derived from brown seaweeds. It covers their classification, biosynthesis pathway, and quantification among different seaweed species. Phlorotannins are promising candidates in the biomedical and nutraceutical sectors that provide safe and effective alternatives to synthetic counterparts, due to their remarkable biological activities, such as antioxidant, anti-inflammatory, anti-diabetic, anti-allergy/histamine, and anti-microbial/viral, which can be the basic mechanisms of further therapeutic applications. Despite their importance, few studies have focused on the absorption of phlorotannins. Current evidence suggests they have a bioavailability similar to terrestrial polyphenols, which hinders a comprehensive understanding of their interactions and underlying mechanisms within the human gastrointestinal tract and presenting a significant challenge for their prospective applications. To address these challenges, several innovative strategies, particularly encapsulation techniques, have been proposed to

protect phlorotannins against gastrointestinal tract biotransformation and degradation. Additionally, phlorotannins can be released in a controlled and targeted manner through additional modifications, with the goal of maximizing their therapeutic potential. However, further in-depth research and exploration of these strategies are crucial to unlock the full potential of phlorotannins in various applications, including pharmaceuticals, functional foods, and nutraceuticals.

Acknowledgments

Abbreviations

ABTS	2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid
Acetyl-CoA	acetyl coenzyme A
AMPK	AMP-activated protein kinase
BBB	blood-brain barrier
CAT	catalase
COX-2	cycloocygenase-2
CUR	curcumin
DDS	drug delivery system
DMBA	2,4-dimethoxybenzaldehyde assay
DOX	doxorubicin
DPPH	2,2-diphenyl1-picryl-hydrazine-hydrate
DW	dry mass
EC50	half maximal effective concentration
EFSA	the European Food Safety Authority
ERK	extracellular signal-regulated kinase
FAO	Food and Agriculture Organization
G6Pase	glucosde-6-phosphatase
HAE	hydrothermal-assisted extraction
HIV-1	human immunodeficiency virus type 1
Hmox-1	heme oxygenase-1
HPAE	high-pressure-assisted extraction
HPLC	high-performance liquid chromatography
H_2O_2	hydrogen peroxide
IC50	half maximal inhibitory concentration
Ig	immunoglobulin
IL	interleukin
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase
LOX	lipoxygenases
LPS	lipopolysaccharide
MAE	microwave-assisted extraction
MIC	minimum inhibitory concentration
MDA	malondialdehyde
MSPN	mesoporous silica nanoparticle
MTT	2,5-diphenyl-2H-tetrazolium bromide
NADES	natural deep eutectic solvents
NDA	the Panel on Dietetic Products, Nutrition and Allergies
NF-κB	nuclear factor kappa B
NMR	nuclear magnetic resonance
NO	nitric oxide
NOX	NADPH oxidase
Nrf2	nuclear factor erythroid 2-related factor 2
–OH	hydroxyl group
PBA	Prussian blue assay
PEG	polyethylene glycol
PEO	poly(ethylene oxide)
PEPCK	phosphoenolpyruvate carboxykinase
PGD2	prostaglandin D2
PGE2	prostaglandin E2
PGH2	prostaglandin H2
PGE	phloroglucinol equivalents
P-gp	P-glycoprotein 1
PKB	protein kinase B
PKS	polyketide synthase
PTP1B	protein tyrosine phosphatase 1B
PVP	polyvinylpyrrolidone
ROS	reactive oxygen species
SOD	superoxide dismutase
SPION	superparamagnetic iron oxide nanoparticle
T2DM	type 2 diabetes mellitus
TNF-α	tumor necrosis factor alpha
UAE	ultrasound-assisted extraction
UMAE	ultrasound–microwave-assisted extraction

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References

Ahn, G., Y. Amagai, A. Matsuda, S.-M. Kang, W. Lee, K. Jung, K. Oida, H. Jang, S. Ishizaka, K. Matsuda, et al. 2015. Dieckol, a phlorotannin of Ecklonia cava, suppresses IgE-mediated mast cell activation and passive cutaneous anaphylactic reaction. *Experimental Dermatology* 24 (12):968–70. doi:10.1111/exd.12814.

Ahn, M.-J., K.-D. Yoon, S.-Y. Min, J. S. Lee, J. H. Kim, T. G. Kim, S. H. Kim, N.-G. Kim, H. Huh, and J. Kim. 2004. Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga Ecklonia cava. *Biological & Pharmaceutical Bulletin* 27 (4):544–7. doi:10.1248/bpb.27.544.

Amanzadeh, E., A. Esmaeili, R. E. N. Abadi, N. Kazemipour, Z. Pahlevanneshan, and S. Beheshti. 2019. Quercetin conjugated with superparamagnetic iron oxide nanoparticles improves learning and memory better than free quercetin via interacting with proteins involved in LTP. *Scientific Reports* 9 (1):6876. doi:10.1038/s41598-019-43345-w.

Amjadi, S., S. Gholizadeh, A. Ebrahimi, H. Almasi, H. Hamishehkar, and R. A. Taheri. 2022. Development and characterization of the carvone-loaded zein/pullulan hybrid electrospun nanofibers for food and medical applications. *Industrial Crops and Products* 183:114964. doi:10.1016/j.indcrop.2022.114964.

Ank, G., B. A. P. da Gama, and R. C. Pereira. 2019. Latitudinal variation in phlorotannin contents from Southwestern Atlantic brown seaweeds. *PeerJ.* 7: E 7379. doi:10.7717/peerj.7379.

Arnold, T., and N. Targett. 2003. To grow and defend: Lack of tradeoffs for brown algal phlorotannins. *Oikos* 100 (2):406–8. doi:10.1034/j.1600-0706.2003.11680.x.

Aung, T. N., Z. Qu, R. D. Kortschak, and D. L. Adelson. 2017. Understanding the effectiveness of natural compound mixtures in cancer through their molecular mode of action. *International Journal of Molecular Sciences* 18 (3):656. doi:10.3390/ijms18030656.

Bai, Y., X. Chen, and H. Qi. 2022. Characterization and bioactivity of phlorotannin loaded protein-polysaccharide nanocomplexes. *Lwt* 155:112998. doi:10.1016/j.lwt.2021.112998.

Bai, Y., Y. Sun, Y. Gu, J. Zheng, C. Yu, and H. Qi. 2020. Preparation, characterization and antioxidant activities of kelp phlorotannin nanoparticles. *Molecules* 25 (19):4550. doi:10.3390/molecules25194550.

Baldrick, F. R., K. McFadden, M. Ibars, C. Sung, T. Moffatt, K. Megarry, K. Thomas, P. Mitchell, J. M. W. Wallace, L. K. Pourshahidi, et al. 2018. Impact of a (poly) phenol-rich extract from the brown algae Ascophyllum nodosum on DNA damage and antioxidant activity in an overweight or obese population: A randomized controlled trial. *The American Journal of Clinical Nutrition* 108 (4):688–700. doi:10.1093/ajcn/nqy147.

Banik, S., and A. Ghosh. 2021. The association of oxidative stress biomarkers with type 2 diabetes mellitus: A systematic review and meta-analysis. *Health Science Reports* 4 (4):e389. doi:10.1002/hsr2.389.

Baskararaj, S., T. Panneerselvam, S. Govindaraj, S. Arunachalam, P. Parasuraman, S. R. K. Pandian, M. Sankaranarayanan, U. P. Mohan, P. Palanisamy, V. Ravishankar, et al. 2020. Formulation and characterization of folate receptor-targeted PEGylated liposome encapsulating bioactive compounds from *Kappaphycus alvarezii* for cancer therapy. *3 Biotech* 10 (3):136. doi:10.1007/s13205-020-2132-7.

Berglin, M., L. Delage, P. Potin, H. Vilter, and H. Elwing. 2004. Enzymatic cross-linking of a phenolic polymer extracted from the marine alga Fucus serratus. *Biomacromolecules* 5 (6):2376–83. doi:10.1021/bm0496864.

Bertoni, G. 2013. A key step in phlorotannin biosynthesis revealed. *The Plant Cell* 25 (8):2770. doi:10.1105/tpc.113.250813.

Bierie, B., and H. L. Moses. 2010. Transforming growth factor beta (TGF-β) and inflammation in cancer. *Cytokine & Growth Factor Reviews* 21 (1):49–59. doi:10.1016/j.cytogfr.2009.11.008.

Birkemeyer, C., V. Lemesheva, S. Billig, and E. Tarakhovskaya. 2020. Composition of intracellular and cell wall-bound phlorotannin fractions in fucoid algae indicates specific functions of these metabolites dependent on the chemical structure. *Metabolites* 10 (9):369. doi:10.3390/metabo10090369.

Blanz, M., P. Ascough, I. Mainland, P. Martin, M. A. Taggart, B. Dieterich, J. Wishart, K. L. Sayle, A. Raab, and J. Feldmann. 2019. Seaweed fertilisation impacts the chemical and isotopic composition of barley: Implications for analyses of archaeological skeletal remains. *Journal of Archaeological Science* 104:34–44. doi:10.1016/j.jas.2019.02.003.

Botelho, J., V. Machado, Y. Leira, L. Proença, and J. J. Mendes. 2021. Periodontal inflamed surface area mediates the link between homocysteine and high blood pressure. *Biomolecules* 11 (6):875. doi:10.3390/biom11060875.

Breijyeh, Z., B. Jubeh, and R. Karaman. 2020. Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules* 25 (6):1340. doi:10.3390/molecules25061340.

Cáceres-Jiménez, S., J. L. Ordóñez-Díaz, J. M. Moreno-Rojas, and G. Pereira-Caro. 2023. 9 - Bioaccesibility and bioavailability of marine polyphenols. In *Marine phenolic compounds*, ed. J. R. Pérez Correa, R. Mateos, and H. Domínguez, 265–98. Netherlands: Elsevier.

Castro-Alves, V. C., and B. R. Cordenunsi. 2015. Total soluble phenolic compounds quantification is not as simple as it seems. *Food Analytical Methods* 8 (4):873–84. doi:10.1007/s12161-014-9961-0.

Catarino, M. D., S. J. Amarante, N. Mateus, A. M. Silva, and S. M. Cardoso. 2021. Brown algae phlorotannins: A marine alternative to break the oxidative stress, inflammation and cancer network. *Foods* 10 (7):1478. doi:10.3390/foods10071478.

Catarino, M. D., C. Marçal, T. Bonifácio-Lopes, D. Campos, N. Mateus, A. M. Silva, M. M. Pintado, and S. M. Cardoso. 2021. Impact of phlorotannin extracts from *Fucus vesiculosus* on human gut microbiota. *Marine Drugs* 19 (7):375. doi:10.3390/md19070375.

Catarino, M. D., S. M. Pires, S. Silva, F. Costa, S. S. Braga, D. C. Pinto, A. M. Silva, and S. M. Cardoso. 2022. Overview of phlorotannins' constituents in fucales. *Marine Drugs* 20 (12):754. doi:10.3390/md20120754.

Catarino, M. D., A. Silva, M. T. Cruz, N. Mateus, A. M. Silva, and S. M. Cardoso. 2020. Phlorotannins from *Fucus vesiculosus*: Modulation of inflammatory response by blocking NF-κB signaling pathway. *International Journal of Molecular Sciences* 21 (18):6897. doi:10.3390/ijms21186897.

Charoensiddhi, S., R. E. Abraham, P. Su, and W. Zhang. 2020. Seaweed and seaweed-derived metabolites as prebiotics. *Advances in Food and Nutrition Research* 91:97–156.

Chen, J., Z. Zhou, P. Li, S. Ye, W. Li, M. Li, L. Zhu, and Y. Ding. 2023. Investigation of the potential phlorotannins and mechanism of six brown algae in treating type II diabetes mellitus based on biological activity, UPLC-QE-MS/MS, and network pharmacology. *Foods* 12 (16):3000. doi:10.3390/foods12163000.

Cho, H. M., T. P. Doan, T. K. Q. Ha, H. W. Kim, B. W. Lee, H. T. T. Pham, T. O. Cho, and W. K. Oh. 2019. Dereplication by high-performance liquid chromatography (HPLC) with quadrupole-time-of-flight mass spectroscopy (qTOF-MS) and antiviral activities of phlorotannins from *Ecklonia cava*. *Marine Drugs* 17 (3):149. doi:10.3390/md17030149.

Chopin, T., and A. G. Tacon. 2021. Importance of seaweeds and extractive species in global aquaculture production. *Reviews in Fisheries Science & Aquaculture* 29 (2):139–48. doi:10.1080/23308249.2020.1810626.

Chouh, A., T. Nouadri, M. D. Catarino, A. M. Silva, and S. M. Cardoso. 2022. Phlorotannins of the Brown algae *Sargassum vulgare* from the Mediterranean Sea coast. *Antioxidants* 11 (6):1055. doi:10.3390/antiox11061055.

Chowdhury, M. T. H., I. Bangoura, J.-Y. Kang, N.-G. Park, D.-H. Ahn, and Y.-K. Hong. 2011. Distribution of phlorotannins in the brown alga *Ecklonia cava* and comparison of pretreatments for extraction. *Fisheries and Aquatic Sciences* 14 (3):198–204. doi:10.5657/FAS.2011.0198.

Corona, G., M. M. Coman, Y. Guo, S. Hotchkiss, C. Gill, P. Yaqoob, J. P. Spencer, and I. Rowland. 2017. Effect of simulated gastrointestinal digestion and fermentation on polyphenolic content and bioactivity of brown seaweed phlorotannin-rich extracts. *Molecular Nutrition & Food Research* 61 (11):1700223. doi:10.1002/mnfr.201700223.

Corona, G., Y. Ji, P. Anegboonlap, S. Hotchkiss, C. Gill, P. Yaqoob, J. P. Spencer, and I. Rowland. 2016. Gastrointestinal modifications and bioavailability of brown seaweed phlorotannins and effects on inflammatory markers. *The British Journal of Nutrition* 115 (7):1240–53. doi:10.1017/S0007114516000210.

Cui, Y., J.-Y. Park, J. Wu, J. H. Lee, Y.-S. Yang, M.-S. Kang, S.-C. Jung, J. M. Park, E.-S. Yoo, S.-H. Kim, et al. 2015. Dieckol attenuates microglia-mediated neuronal cell death via ERK, Akt and NADPH oxidase-mediated pathways. *The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology* 19 (3):219–28. doi:10.4196/kjpp.2015.19.3.219.

Dal Canto, E., A. Ceriello, L. Rydén, M. Ferrini, T. B. Hansen, O. Schnell, E. Standl, and J. W. Beulens. 2019. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *European Journal of Preventive Cardiology* 26 (2_suppl):25–32. doi:10.1177/2047487319878371.

Debbarma, J., P. Viji, B. M. Rao, and C. Ravishankar. 2022. Seaweeds: Potential applications of the aquatic vegetables to augment nutritional composition, texture, and health benefits of food and food products. In Sustainable *global resources of seaweeds vo*lume 2: Food, *pharmaceutical and health applicatio*ns, 3–54. Ranga Rao, A., & Ravishankar, G.A., Eds., Springer, Cham, Switzerland.

Deepika, C., J. Wolf, N. Moheimani, B. Hankamer, B. von Herzen, and A. R. Rao. 2022. Utilisation of seaweeds in the Australian market–commercialisation strategies: Current trends and future prospects. In *Sustainable global resources of seaweeds volume 1: Bioresources, cultivation, trade and multifarious applications*, 265–94. Ranga Rao, A., & Ravishankar, G.A., Ed., Springer, Cham, Switzerland.

Dong, X., Y. Bai, Z. Xu, Y. Shi, Y. Sun, S. Janaswamy, C. Yu, and H. Qi. 2019. Phlorotannins from *Undaria pinnatifida* sporophyll:

Extraction, antioxidant, and anti-inflammatory activities. *Marine Drugs* 17 (8):434. doi:10.3390/md17080434.

Duarte, C. M., A. Bruhn, and D. Krause-Jensen. 2021. A seaweed aquaculture imperative to meet global sustainability targets. *Nature Sustainability* 5 (3):185–93. doi:10.1038/s41893-021-00773-9.

Dutot, M., R. Fagon, M. Hemon, and P. Rat. 2012. Antioxidant, anti-inflammatory, and anti-senescence activities of a phlorotannin-rich natural extract from brown seaweed *Ascophyllum nodosum*. *Applied Biochemistry and Biotechnology* 167 (8):2234–40. doi:10.1007/s12010-012-9761-1.

Elbialy, N. S., S. F. Aboushoushah, B. F. Sofi, and A. Noorwali. 2020. Multifunctional curcumin-loaded mesoporous silica nanoparticles for cancer chemoprevention and therapy. *Microporous and Mesoporous Materials* 291:109540. doi:10.1016/j.micromeso.2019.06.002.

El-Manaway, I. M., and S. H. Rashedy. 2022. The ecology and physiology of seaweeds: An overview. In *Sustainable global resources of seaweeds volume 1: Bioresources, cultivation, trade and multifarious applications*, 3–16. Ranga Rao, A., & Ravishankar, G.A., Eds., Springer, Cham, Switzerland.

Emeline, C. B., D. Ludovic, V. Laurent, L. Catherine, I. Kruse, A. G. Erwan, W. Florian, and P. Philippe. 2021. Induction of phlorotannins and gene expression in the brown macroalga *Fucus vesiculosus* in response to the herbivore *Littorina littorea*. *Marine Drugs* 19 (4):185. doi:10.3390/md19040185.

Erpel, F., C. Camilo, R. Mateos, and J. R. Pérez-Correa. 2023. A macroporous resin purification process to obtain food-grade phlorotannin-rich extracts with α-glucosidase inhibitory activity from Chilean brown seaweeds: An UHPLC-MSn profiling. *Food Chemistry* 402:134472. doi:10.1016/j.foodchem.2022.134472.

Erpel, F., R. Mateos, J. Pérez-Jiménez, and J. R. Pérez-Correa. 2020. Phlorotannins: From isolation and structural characterization, to the evaluation of their antidiabetic and anticancer potential. *Food Research International* 137:109589. doi:10.1016/j.foodres.2020.109589.

Falkowski, P. 2012. Ocean science: The power of plankton. *Nature* 483 (7387):S17–S20. doi:10.1038/483S17a.

FAO. 2018. The global status of seaweed production, trade and utilization. *Globefish Research Programme* 124:120. FAO: Rome.

FAO (Food and Agriculture Organization). 2022. *The state of world fisheries and aquaculture. Towards blue transformation*. Rome: FAO.

Feng, H., M. Li, Z. Xing, X-k Ouyang, and J. Ling. 2022. Efficient delivery of fucoxanthin using metal–polyphenol network-coated magnetic mesoporous silica. *Journal of Drug Delivery Science and Technology* 77:103842. doi:10.1016/j.jddst.2022.103842.

Fernando, I. P. S., W. Lee, and G. Ahn. 2022. Marine algal flavonoids and phlorotannins; an intriguing frontier of biofunctional secondary metabolites. *Critical Reviews in Biotechnology* 42 (1):23–45. doi:10.1080/07388551.2021.1922351.

Ferreira, C. A., A. P. Januário, R. Félix, N. Alves, M. F. Lemos, and J. R. Dias. 2021. Multifunctional gelatin/chitosan electrospun wound dressing dopped with *Undaria pinnatifida* phlorotannin-enriched extract for skin regeneration. *Pharmaceutics* 13 (12):2152. doi:10.3390/pharmaceutics13122152.

Ford, L., C. Curry, M. Campbell, K. Theodoridou, G. Sheldrake, J. Dick, L. Stella, and P. J. Walsh. 2020. Effect of phlorotannins from brown seaweeds on the in vitro digestibility of pig feed. *Animals* 10 (11):2193. doi:10.3390/ani10112193.

Ford, L., K. Theodoridou, G. N. Sheldrake, and P. J. Walsh. 2019. A critical review of analytical methods used for the chemical characterisation and quantification of phlorotannin compounds in brown seaweeds. *Phytochemical Analysis: PCA* 30 (6):587–99. doi:10.1002/pca.2851.

Garcia-Vaquero, M., R. Ravindran, O. Walsh, J. O'Doherty, A. K. Jaiswal, B. K. Tiwari, and G. Rajauria. 2021. Evaluation of ultrasound, microwave, ultrasound–microwave, hydrothermal and high pressure assisted extraction technologies for the recovery of phytochemicals and antioxidants from brown macroalgae. *Marine Drugs* 19 (6):309. doi:10.3390/md19060309.

Gheda, S., R. A. Hamouda, M. A. Naby, T. M. Mohamed, T. M. Al-Shaikh, and A. Khamis. 2023. Potent effect of phlorotannins derived from *Sargassum linifolium* as antioxidant and antidiabetic in a streptozotocin-induced diabetic rats model. *Applied Sciences* 13 (8):4711. doi:10.3390/app13084711.

Gheda, S., M. A. Naby, T. Mohamed, L. Pereira, and A. Khamis. 2021. Antidiabetic and antioxidant activity of phlorotannins extracted from the brown seaweed *Cystoseira compressa* in streptozotocin-induced diabetic rats. *Environmental Science and Pollution Research* 28 (18):22886–901. doi:10.1007/s11356-021-12347-5.

Ghosh, S., T. Sarkar, S. Pati, Z. A. Kari, H. A. Edinur, and R. Chakraborty. 2022. Novel bioactive compounds from marine sources as a tool for functional food development. *Frontiers in Marine Science* 9:76. doi:10.3389/fmars.2022.832957.

Glombitza, K.-W., and G. Gerstberger. 1985. Phlorotannins with dibenzodioxin structural elements from the brown alga *Eisenia arborea*. *Phytochemistry* 24 (3):543–51. doi:10.1016/S0031-9422(00)80764-5.

Glombitza, K.-W., and A. Schmidt. 1999. Nonhalogenated and halogenated phlorotannins from the brown alga *Carpophyllum angustifolium*. *Journal of Natural Products* 62 (9):1238–40. doi:10.1021/np990076c.

Gómez, I., and P. Huovinen. 2020. Brown algal phlorotannins: An overview of their functional roles. In *Antarctic seaweeds: Diversity, adaptation and ecosystem services*, 365–88. Gómez, I., & Huovinen, P., Eds., Springer, Cham, Switzerland.

Guan, L., H. Long, F. Ren, Y. Li, and H. Zhang. 2022. A structure—Activity relationship study of the inhibition of α-amylase by benzoic acid and its derivatives. *Nutrients* 14 (9):1931. doi:10.3390/nu14091931.

Guiry, M. D. 2012. How many species of algae are there? *Journal of Phycology* 48 (5):1057–63. doi:10.1111/j.1529-8817.2012.01222.x.

Gümüş Yılmaz, G., J. L. Gómez Pinchetti, A. Cifuentes, M. Herrero, and E. Ibáñez. 2019. Comparison of extraction techniques and surfactants for the isolation of total polyphenols and phlorotannins from the brown algae *Lobophora variegata*. *Analytical Letters* 52 (17):2724–40. doi:10.1080/00032719.2019.1597878.

Gunathilaka, T., L. R. Keertihirathna, and D. Peiris. 2021. Advanced pharmacological uses of marine algae as an anti-diabetic therapy. In *Natural Medicinal Plants*, 79–95. El-Shemy, H., IntechOpen, London, UK.

Gupta, V., S. Bhavanasi, M. Quadir, K. Singh, G. Ghosh, K. Vasamreddy, A. Ghosh, T. J. Siahaan, S. Banerjee, and S. K. Banerjee. 2019. Protein PEGylation for cancer therapy: Bench to bedside. *Journal of Cell Communication and Signaling* 13 (3):319–30. doi:10.1007/s12079-018-0492-0.

Ha, J. W., H. Song, S. S. Hong, and Y. C. Boo. 2019. Marine alga *Ecklonia cava* extract and dieckol attenuate prostaglandin E2 production in HaCaT keratinocytes exposed to airborne particulate matter. *Antioxidants* 8 (6):190. doi:10.3390/antiox8060190.

Han, E. J., H.-S. Kim, K. Sanjeewa, K. Herath, Y.-J. Jeon, Y. Jee, J. Lee, T. Kim, S.-Y. Shim, and G. Ahn. 2020. Eckol from *Ecklonia cava* suppresses immunoglobulin E-mediated mast cell activation and passive cutaneous anaphylaxis in mice. *Nutrients* 12 (5):1361. doi:10.3390/nu12051361.

Hari, S. K., A. Gauba, N. Shrivastava, R. M. Tripathi, S. K. Jain, and A. K. Pandey. 2023. Polymeric micelles and cancer therapy: An ingenious multimodal tumor-targeted drug delivery system. *Drug Delivery and Translational Research* 13 (1):135–63. doi:10.1007/s13346-022-01197-4.

Heo, S.-J., S.-H. Cha, K.-N. Kim, S.-H. Lee, G. Ahn, D.-H. Kang, C. Oh, Y.-U. Choi, A. Affan, D. Kim, et al. 2012. Neuroprotective effect of phlorotannin isolated from *Ishige okamurae* against H 2 O 2-induced oxidative stress in murine hippocampal neuronal cells, HT22. *Applied Biochemistry and Biotechnology* 166 (6):1520–32. doi:10.1007/s12010-012-9545-7.

Hermund, D. B., H. Torsteinsen, J. Vega, F. L. Figueroa, and C. Jacobsen. 2022. Screening for new cosmeceuticals from brown algae *Fucus vesiculosus* with antioxidant and photo-protecting properties. *Marine Drugs* 20 (11):687. doi:10.3390/md20110687.

Hessami, M. J., A. R. Rao, and G. A. Ravishankar. 2019. Opportunities and challenges in seaweeds as feed stock for biofuel production. In *Handbook of algal technologies and phytochemicals*, 39–50. Ravishankar, G. A, & Ambati, R.R., Eds., CRC Press, USA.

Hierholtzer, A., L. Chatellard, M. Kierans, J. C. Akunna, and P. J. Collier. 2013. The impact and mode of action of phenolic compounds extracted from brown seaweed on mixed anaerobic microbial cultures. *Journal of Applied Microbiology* 114 (4):964–73. doi:10.1111/jam.12114.

Hodhodi, A., A. Babakhani, and H. Rostamzad. 2022. Effect of different extraction conditions on phlorotannin content and antioxidant activity of extract from brown algae (*Sargassum angustifolium*). *Journal of Food Processing and Preservation* 46 (3):e16307. doi:10.1111/jfpp.16307.

Hu, C., and S. Ma. 2018. Recent development of lipoxygenase inhibitors as anti-inflammatory agents. *MedChemComm* 9 (2):212–25. doi:10.1039/c7md00390k.

Iken, K., C. D. Amsler, J. M. Hubbard, J. B. McClintock, and B. J. Baker. 2007. Allocation patterns of phlorotannins in Antarctic brown algae. *Phycologia* 46 (4):386–95. doi:10.2216/06-67.1.

Im, J., C. H. Choi, F. Mun, J. Lee, H. Kim, W.-K. Jung, C. H. Jang, and G. Kim. 2017. A polycaprolactone/fish collagen/alginate biocomposite supplemented with phlorotannin for hard tissue regeneration. *RSC Advances* 7 (4):2009–18. doi:10.1039/C6RA25182J.

Ismail, M. M., G. M. El Zokm, A. M. El Sikaily, A. I. Selim, and G. A. Ismail. 2023. Chemodiversity and bioactivity assessment of phlorotannins from some *Phaeophyta* species from the Red Sea. *Journal of Applied Phycology* 35 (4):1769–88. doi:10.1007/s10811-023-03000-4.

Jégou, C., N. Kervarec, S. Cérantola, I. Bihannic, and V. Stiger-Pouvreau. 2015. NMR use to quantify phlorotannins: The case of *Cystoseira tamariscifolia*, a phloroglucinol-producing brown macroalga in Brittany (France). *Talanta* 135:1–6. doi:10.1016/j.talanta.2014.11.059.

Jun, Y.-J., M. Lee, T. Shin, N. Yoon, J.-H. Kim, and H.-R. Kim. 2014. Eckol enhances heme oxygenase-1 expression through activation of Nrf2/JNK pathway in HepG2 cells. *Molecules* 19 (10):15638–52. doi:10.3390/molecules191015638.

Junning, C., and Giulia, G. 2021. *Global seaweeds and microalgae production, 1950–2019*. Food and Agriculture Organization of the United Nations, Rome.

Kalyane, D., N. Raval, R. Maheshwari, V. Tambe, K. Kalia, and R. K. Tekade. 2019. Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. *Materials Science & Engineering. C, Materials for Biological Applications* 98:1252–76. doi:10.1016/j.msec.2019.01.066.

Kang, M.-C., W. A. J. P. Wijesinghe, S.-H. Lee, S.-M. Kang, S.-C. Ko, X. Yang, N. Kang, B.-T. Jeon, J. Kim, D.-H. Lee, et al. 2013. Dieckol isolated from brown seaweed *Ecklonia cava* attenuates type II diabetes in db/db mouse model. *Food and Chemical Toxicology* 53:294–8. doi:10.1016/j.fct.2012.12.012.

Karonen, M. 2022. Insights into polyphenol–lipid interactions: Chemical methods, molecular aspects and their effects on membrane structures. *Plants* 11 (14):1809. doi:10.3390/plants11141809.

Karthikeyan, A., A. Joseph, and B. G. Nair. 2022. Promising bioactive compounds from the marine environment and their potential effects on various diseases. *Journal of Genetic Engineering and Biotechnology* 20 (1):1–38. doi:10.1186/s43141-021-00290-4.

Kellogg, J., M. H. Grace, and M. A. Lila. 2014. Phlorotannins from Alaskan seaweed inhibit carbolytic enzyme activity. *Marine Drugs* 12 (10):5277–94. doi:10.3390/md12105277.

Kierstead, P. H., H. Okochi, V. J. Venditto, T. C. Chuong, S. Kivimae, J. M. Fréchet, and F. C. Szoka. 2015. The effect of polymer backbone chemistry on the induction of the accelerated blood clearance in polymer modified liposomes. *Journal of Controlled Release* 213:1–9. doi:10.1016/j.jconrel.2015.06.023.

Kim, A. D., K. A. Kang, M. J. Piao, K. C. Kim, J. Zheng, C. W. Yao, J. W. Cha, C. L. Hyun, H. K. Kang, N. H. Lee, et al. 2014. Cytoprotective effect of Eckol against oxidative stress-induced mitochondrial dysfunction: Involvement of the Foxo3a/Ampk pathway. *Journal of Cellular Biochemistry* 115 (8):1403–11. doi:10.1002/jcb.24790.

Kim, H.-J., C. Dasagrandhi, S.-H. Kim, B.-G. Kim, S.-H. Eom, and Y.-M. Kim. 2018. In vitro antibacterial activity of phlorotannins from edible brown algae, *Eisenia bicyclis* against streptomycin-resistant *Listeria monocytogenes*. *Indian Journal of Microbiology* 58 (1):105–8. doi:10.1007/s12088-017-0693-x.

Kim, K. C., K. A. Kang, R. Zhang, M. J. Piao, G. Y. Kim, M. Y. Kang, S. J. Lee, N. H. Lee, Y.-J. Surh, and J. W. Hyun. 2010. Up-regulation of Nrf2-mediated heme oxygenase-1 expression by eckol, a phlorotannin compound, through activation of Erk and PI3K/Akt. *The International Journal of Biochemistry & Cell Biology* 42 (2):297–305. doi:10.1016/j.biocel.2009.11.009.

Kim, S., S.-S. Kang, S.-I. Choi, G.-H. Kim, and J.-Y. Imm. 2019. Ecklonia cava extract containing dieckol suppresses RANKL-induced osteoclastogenesis via MAP kinase/NF-κB pathway inhibition and heme oxygenase-1 induction. *Journal of Microbiology and Biotechnology* 29 (1):11–20.

Koivikko, R., J. Eränen, J. Loponen, and V. Jormalainen. 2008. Variation of phlorotannins among three populations of *Fucus vesiculosus* as revealed by HPLC and colorimetric quantification. *Journal of Chemical Ecology* 34 (1):57–64. doi:10.1007/s10886-007-9410-2.

Kord, A., Y. Foudil-Cherif, M. Amiali, A. Boumechhour, and R. Benfares. 2021. Phlorotannins composition, radical scavenging capacity and reducing power of phenolics from the brown alga *Cystoseira sauvageauana*. *Journal of Aquatic Food Product Technology* 30 (4):426–38. doi:10.1080/10498850.2021.1895392.

Koren, S., and I. G. Fantus. 2007. Inhibition of the protein tyrosine phosphatase PTP1B: Potential therapy for obesity, insulin resistance and type-2 diabetes mellitus. *Best Practice & Research. Clinical Endocrinology & Metabolism* 21 (4):621–40. doi:10.1016/j.beem.2007.08.004.

Kumar, L. R., P. T. Paul, K. Anas, C. Tejpal, N. Chatterjee, T. Anupama, S. Mathew, and C. Ravishankar. 2022. Phlorotannins–Bioactivity and extraction perspectives. *Journal of Applied Phycology* 34 (4):2173–85. doi:10.1007/s10811-022-02749-4.

Kurihara, H., R. Konno, and K. Takahashi. 2015. Fucophlorethol C, a phlorotannin as a lipoxygenase inhibitor. *Bioscience, Biotechnology, and Biochemistry* 79 (12):1954–6. doi:10.1080/09168451.2015.1062716.

Le, Q.-T., Y. Li, Z.-J. Qian, M.-M. Kim, and S.-K. Kim. 2009. Inhibitory effects of polyphenols isolated from marine alga *Ecklonia cava* on histamine release. *Process Biochemistry* 44 (2):168–76. doi:10.1016/j.procbio.2008.10.002.

Lee, H.-A., J.-H. Lee, and J.-S. Han. 2017. A phlorotannin constituent of *Ecklonia cava* alleviates postprandial hyperglycemia in diabetic mice. *Pharmaceutical Biology* 55 (1):1149–54. doi:10.1080/13880209.2017.1291693.

Lee, S.-H., S.-C. Ko, M.-C. Kang, D. H. Lee, and Y.-J. Jeon. 2016. Octaphlorethol A, a marine algae product, exhibits antidiabetic effects in type 2 diabetic mice by activating AMP-activated protein kinase and upregulating the expression of glucose transporter 4. *Food and Chemical Toxicology* 91:58–64. doi:10.1016/j.fct.2016.02.022.

Le Lann, K., G. Surget, C. Couteau, L. Coiffard, S. Cérantola, F. Gaillard, M. Larnicol, M. Zubia, F. Guérard, N. Poupart, et al. 2016. Sunscreen, antioxidant, and bactericide capacities of phlorotannins from the brown macroalga *Halidrys siliquosa*. *Journal of Applied Phycology* 28 (6):3547–59. doi:10.1007/s10811-016-0853-0.

Lemesheva, V., C. Birkemeyer, D. Garbary, and E. Tarakhovskaya. 2020. Vanadium-dependent haloperoxidase activity and phlorotannin incorporation into the cell wall during early embryogenesis of *Fucus vesiculosus* (Phaeophyceae). *European Journal of Phycology* 55 (3):275–84. doi:10.1080/09670262.2019.1709131.

Li, C., B. Li, C. Zhu, and X. Meng. 2020. Modeling and optimization of tea polyphenol-alginate/chitosan magnetic microcapsules. *Journal of Molecular Structure* 1208:127827. doi:10.1016/j.molstruc.2020.127827.

Li, Y., X. Fu, D. Duan, X. Liu, J. Xu, and X. Gao. 2017. Extraction and identification of phlorotannins from the brown alga, *Sargassum fusiforme* (Harvey) Setchell. *Marine Drugs* 15 (2):49. doi:10.3390/md15020049.

Li, Y., M. Kröger, and W. K. Liu. 2014. Endocytosis of PEGylated nanoparticles accompanied by structural and free energy changes of the grafted polyethylene glycol. *Biomaterials* 35 (30):8467–78. doi:10.1016/j.biomaterials.2014.06.032.

Li, Y., S.-H. Lee, Q.-T. Le, M.-M. Kim, and S.-K. Kim. 2008. Anti-allergic effects of phlorotannins on histamine release via binding inhibition between IgE and FcεRI. *Journal of Agricultural and Food Chemistry* 56 (24):12073–80. doi:10.1021/jf802732n.

Liu, X., and C. L. Bourvellec. 2023. 7 - Interactions with other macromolecules. In *Marine phenolic compounds*, ed. J. R. Pérez-Correa, R. Mateos, and H. Domínguez, 219–38. Elsevier, Netherlands.

Liu, X., W. Yuan, R. Sharma-Shivappa, and J. van Zanten. 2017. Antioxidant activity of phlorotannins from brown algae. *International Journal of Agricultural and Biological Engineering* 10 (6):184–91. doi:10.25165/j.ijabe.20171006.2854.

Lobine, D., K. R. Rengasamy, and M. F. Mahomoodally. 2022. Functional foods and bioactive ingredients harnessed from the ocean: Current status and future perspectives. *Critical Reviews in Food Science and Nutrition* 62 (21):5794–823. doi:10.1080/10408398.2021.1893643.

Lopes, G., M. Barbosa, P. B. Andrade, and P. Valentão. 2019. Phlorotannins from Fucales: Potential to control hyperglycemia and diabetes-related vascular complications. *Journal of Applied Phycology* 31 (5):3143–52. doi:10.1007/s10811-019-01816-7.

Lopes, G., E. Pinto, P. B. Andrade, and P. Valentao. 2013. Antifungal activity of phlorotannins against dermatophytes and yeasts: Approaches to the mechanism of action and influence on *Candida albicans* virulence factor. *PLoS One* 8 (8):e72203. doi:10.1371/journal.pone.0072203.

Lopes, G., C. Sousa, L. R. Silva, E. Pinto, P. B. Andrade, J. Bernardo, T. Mouga, and P. Valentão. 2012. Can phlorotannins purified extracts constitute a novel pharmacological alternative for microbial infections with associated inflammatory conditions? *PLoS One* 7 (2):e31145. doi:10.1371/journal.pone.0031145.

Lo Piparo, E., H. Scheib, N. Frei, G. Williamson, M. Grigorov, and C. J. Chou. 2008. Flavonoids for controlling starch digestion: Structural requirements for inhibiting human α-amylase. *Journal of Medicinal Chemistry* 51 (12):3555–61. doi:10.1021/jm800115x.

Magarkar, A., E. Karakas, M. Stepniewski, T. Rog, and A. Bunker. 2012. Molecular dynamics simulation of PEGylated bilayer interacting with salt ions: A model of the liposome surface in the bloodstream. *The Journal of Physical Chemistry. B* 116 (14):4212–9. doi:10.1021/jp300184z.

Mandola, A., A. Nozawa, and T. Eiwegger. 2019. Histamine, histamine receptors, and anti-histamines in the context of allergic responses. *LymphoSign Journal* 6 (2):35–51. doi:10.14785/lymphosign-2018-0016.

Margraf, T., A. R. Karnopp, N. D. Rosso, and D. Granato. 2015. Comparison between Folin-Ciocalteu and Prussian Blue assays to estimate the total phenolic content of juices and teas using 96-well microplates. *Journal of Food Science* 80 (11):C2397–C2403. doi:10.1111/1750-3841.13077.

Matsui, T., C. Ito, M. Itoigawa, and T. Shibata. 2022. Three phlorotannins from *Sargassum carpophyllum* are effective against the secretion of allergic mediators from antigen-stimulated rat basophilic leukemia cells. *Food Chemistry* 377:131992. doi:10.1016/j.foodchem.2021.131992.

Meng, W., T. Mu, H. Sun, and M. Garcia-Vaquero. 2021. Phlorotannins: A review of extraction methods, structural characteristics, bioactivities, bioavailability, and future trends. *Algal Research* 60:102484. doi:10.1016/j.algal.2021.102484.

Meshalkina, D., E. Tsvetkova, A. Orlova, R. Islamova, M. Grashina, D. Gorbach, V. Babakov, A. Francioso, C. Birkemeyer, L. Mosca, et al. 2023. First insight into the neuroprotective and antibacterial effects of phlorotannins isolated from the cell walls of brown algae *Fucus vesiculosus* and *Pelvetia canaliculata*. *Antioxidants* 12 (3):696. doi:10.3390/antiox12030696.

Meslet-Cladière, L., L. Delage, C. J.-J. Leroux, S. Goulitquer, C. Leblanc, E. Creis, E. A. Gall, V. Stiger-Pouvreau, M. Czjzek, and P. Potin. 2013. Structure/function analysis of a type III polyketide synthase in the brown alga *Ectocarpus siliculosus* reveals a biochemical pathway in phlorotannin monomer biosynthesis. *The Plant Cell* 25 (8):3089–103. doi:10.1105/tpc.113.111336.

Mirchandani, Y., V. B. Patravale, and S. Brijesh. 2021. Solid lipid nanoparticles for hydrophilic drugs. *Journal of Controlled Release* 335:457–64. doi:10.1016/j.jconrel.2021.05.032.

Mittal, A., I. Roy, and S. Gandhi. 2022. Magnetic nanoparticles: An overview for biomedical applications. *Magnetochemistry* 8 (9):107. doi:10.3390/magnetochemistry8090107.

Moheimanian, N., H. Mirkhani, A. Purkhosrow, J. Sohrabipour, and A. R. Jassbi. 2023. In vitro and in vivo antidiabetic, α-glucosidase inhibition and antibacterial activities of three brown algae, *Polycladia myrica*, *Padina antillarum*, and *Sargassum boveanum*, and a red alga, *Palisada perforata* from the Persian Gulf. *Innovative Journal of Pharmaceutical Research* 22 (1):e133731.

Morrison, D. K. 2012. MAP kinase pathways. *Cold Spring Harbor Perspectives in Biology* 4 (11):a011254. doi:10.1101/cshperspect.a011254.

Mozafari, M. R. 2010. Nanoliposomes: Preparation and analysis. In *Liposomes: Methods and protocols, volume 1: Pharmaceutical nanocarriers*, 29–50. Weissig, V., Ed., Human Press, Totowa, NJ, USA.

Muhammad, K., J. Zhao, I. Ullah, J. Guo, X-k Ren, and Y. Feng. 2019. Ligand targeting and peptide functionalized polymers as non-viral carriers for gene therapy. *Biomaterials Science* 8 (1):64–83. doi:10.1039/c9bm01112a.

Murray, M., A. L. Dordevic, K. Cox, A. Scholey, L. Ryan, and M. P. Bonham. 2021. Twelve weeks' treatment with a polyphenol-rich seaweed extract increased HDL cholesterol with no change in other biomarkers of chronic disease risk in overweight adults: A placebo-controlled randomized trial. *The Journal of Nutritional Biochemistry* 96:108777. doi:10.1016/j.jnutbio.2021.108777.

Murray, M., A. L. Dordevic, L. Ryan, and M. P. Bonham. 2019. A single-dose of a polyphenol-rich *Fucus vesiculosus* extract is insufficient to blunt the elevated postprandial blood glucose responses exhibited by healthy adults in the evening: A randomised crossover trial. *Antioxidants* 8 (2):49. doi:10.3390/antiox8020049.

Nakamura, T., S. Maeda, K. Horiguchi, T. Maehara, K. Aritake, B-i Choi, Y. Iwakura, Y. Urade, and T. Murata. 2015. PGD2 deficiency exacerbates food antigen-induced mast cell hyperplasia. *Nature Communications* 6 (1):7514. doi:10.1038/ncomms8514.

Nazzaro, F., F. Fratianni, A. d'Acierno, V. De Feo, F. J. Ayala-Zavala, A. Gomes-Cruz, D. Granato, and R. Coppola. 2019. Effect of polyphenols on microbial cell-cell communications. In *Quorum sensing*, 195–223. Tommonaro, G., Ed., Academic Press, Netherlands.

Obluchinskaya, E. D., A. Daurtseva, O. Pozharitskaya, E. Flisyuk, and A. Shikov. 2019. Natural deep eutectic solvents as alternatives for extracting phlorotannins from brown algae. *Pharmaceutical Chemistry Journal* 53 (3):243–7. doi:10.1007/s11094-019-01987-0.

Obluchinskaya, E. D., O. N. Pozharitskaya, D. V. Zakharov, E. V. Flisyuk, I. I. Terninko, Y. E. Generalova, I. E. Smekhova, and A. N. Shikov. 2022. The biochemical composition and antioxidant properties of *Fucus vesiculosus* from the Arctic region. *Marine Drugs* 20 (3):193. doi:10.3390/md20030193.

Park, E., H. Yu, J.-H. Lim, J. H. Choi, K.-J. Park, and J. Lee. 2023. Seaweed metabolomics: A review on its nutrients, bioactive compounds and changes in climate change. *Food Research International* 163:112221. doi:10.1016/j.foodres.2022.112221.

Park, J.-Y., J. H. Kim, J. M. Kwon, H.-J. Kwon, H. J. Jeong, Y. M. Kim, D. Kim, W. S. Lee, and Y. B. Ryu. 2013. Dieckol, a SARS-CoV 3CLpro inhibitor, isolated from the edible brown algae *Ecklonia cava*. *Bioorganic & Medicinal Chemistry* 21 (13):3730–7. doi:10.1016/j.bmc.2013.04.026.

Patel, A. K., A. P. Vadrale, R. R. Singhania, P. Michaud, A. Pandey, S.-J. Chen, C.-W. Chen, and C.-D. Dong. 2023. Algal polysaccharides: Current status and future prospects. *Phytochemistry Reviews* 22 (4):1167–96. doi:10.1007/s11101-021-09799-5.

Pelletreau, K. N. 2008. *The application of molecular tools towards the study of brown algal chemical ecology and the production of phlorotannins*. University of Delaware, USA.

Pereira, L. 2016. *Edible seaweeds of the world*, CRC Press, Boca Raton, USA.

Petchidurai, G., J. A. Nagoth, M. S. John, K. Sahayaraj, N. Murugesan, and S. Pucciarelli. 2019. Standardization and quantification of total tannins, condensed tannin and soluble phlorotannins extracted from thirty-two drifted coastal macroalgae using high performance liquid chromatography. *Bioresource Technology Reports* 7:100273. doi:10.1016/j.biteb.2019.100273.

Phang, S. J., H. X. Teh, M. L. Looi, B. Arumugam, M. B. Fauzi, and U. R. Kuppusamy. 2023. Phlorotannins from brown algae: A review on their antioxidant mechanisms and applications in oxidative stress-mediated diseases. *Journal of Applied Phycology* 35 (2):867–92. doi:10.1007/s10811-023-02913-4.

Phang-Lyn, S., and V. A. Llerena. 2019. *Biochemistry, biotransformation*, StatPearls, Treasure Island, FL.

Phasanasophon, K., and S. M. Kim. 2019. Anti-inflammatory activity of the phlorotannin trifuhalol A using LPS-stimulated RAW264. 7 cells through NF-κB and MAPK main signaling pathways. *Natural Product Communications* 14 (5):1934578X19849798. doi:10.1177/1934578X19849798.

Pradhan, B., R. Nayak, P. P. Bhuyan, S. Patra, C. Behera, S. Sahoo, J.-S. Ki, A. Quarta, A. Ragusa, and M. Jena. 2022. Algal phlorotannins as novel antibacterial agents with reference to the antioxidant modulation: Current advances and future directions. *Marine Drugs* 20 (6):403. doi:10.3390/md20060403.

Price, G., and D. A. Patel. 2021. Drug bioavailability. In *StatPearls [Internet]*. Statpearls Publishing, Treasure Island, FL.

Priya, S., V. M. Desai, and G. Singhvi. 2023. Surface modification of lipid-based nanocarriers: A potential approach to enhance targeted drug delivery. *ACS Omega* 8 (1):74–86. doi:10.1021/acsomega.2c05976.

Raja, R., S. Hemaiswarya, K. Arunkumar, N. Mathiyazhagan, S. Kandasamy, A. Arun, and P. Ramasamy. 2023. Efficacy of *Eisenia bicyclis* phlorotannins in the treatment of diabetes and reducing inflammation. *Food Bioscience* 52:102381. doi:10.1016/j.fbio.2023.102381.

Rajan, D. K., K. Mohan, S. Zhang, and A. R. Ganesan. 2021. Dieckol: A brown algal phlorotannin with biological potential. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 142:111988. doi:10.1016/j.biopha.2021.111988.

Ramya, S., S. Thiruvenkataswamy, K. Kavithaa, S. Preethi, H. Winster, V. Balachander, M. Paulpandi, and A. Narayanasamy. 2021. pH dependent drug release of Silibinin, a polyphenol conjugated with magnetic nanoparticle against the human colon cancer cell. *Journal of Cluster Science* 32 (2):305–17. doi:10.1007/s10876-020-01789-5.

Romagnoli, C., F., D'Asta, and M. L. Brandi. 2013. Drug delivery using composite scaffolds in the context of bone tissue engineering. *Clinical Cases in Mineral and Bone Metabolism* 10 (3):155.

Sailler, B., and K. W. Glombitza. 1999. Halogenated phlorethols and fucophlorethols from the brown alga *Cystophora retroflexa*. *Natural Toxins* 7 (2):57–62. doi:10.1002/(SICI)1522-7189(199903/04)7:2<57::AID-NT42>3.0.CO;2-F.

Sanadgol, N., and J. Wackerlig. 2020. Developments of smart drug-delivery systems based on magnetic molecularly imprinted polymers for targeted cancer therapy: A short review. *Pharmaceutics* 12 (9):831. doi:10.3390/pharmaceutics12090831.

Sancini, G., M. Gregori, E. Salvati, I. Cambianica, F. Re, F. Ornaghi, M. Canovi, C. Fracasso, A. Cagnotto, and M. Colombo. 2013. Functionalization with TAT-peptide enhances blood-brain barrier crossing in vitro of nanoliposomes carrying a curcumin-derivative to bind amyloid-β peptide. *Journal of Nanomedicine & Nanotechnology* 04 (03):1–8. doi:10.4172/2157-7439.1000171.

Sathya, R., N. Kanaga, P. Sankar, and S. Jeeva. 2017. Antioxidant properties of phlorotannins from brown seaweed *Cystoseira trinodis* (Forsskål) C. Agardh. *Arabian Journal of Chemistry* 10:S2608–S2614. doi:10.1016/j.arabjc.2013.09.039.

Savaghebi, D., M. Barzegar, and M. R. Mozafari. 2020. Manufacturing of nanoliposomal extract from *Sargassum boveanum* algae and investigating its release behavior and antioxidant activity. *Food Science & Nutrition* 8 (1):299–310. doi:10.1002/fsn3.1306.

Savaghebi, D., M. Ghaderi-Ghahfarokhi, and M. Barzegar. 2021. Encapsulation of *Sargassum boveanum* algae extract in nano-liposomes: Application in functional mayonnaise production. *Food and Bioprocess Technology* 14 (7):1311–25. doi:10.1007/s11947-021-02638-7.

Schaffenburg, W. C., B. N. Lockshin, and C. M. C. DeKlotz. 2021. 3 - Polymorphisms: Why individual drug responses vary. In *Comprehensive dermatologic drug therapy*, ed. Stephen E. Wolverton, 21–33.e2. 4th ed. Elsevier, Netherlands.

Schoenwaelder, M. E., and M. N. Clayton. 2000. Physode formation in embryos of *Phyllospora comosa* and *Hormosira banksii* (Phaeophyceae). *Phycologia* 39 (1):1–9. doi:10.2216/i0031-8884-39-1-1.1.

Shahidi, F., and H. Peng. 2018. Bioaccessibility and bioavailability of phenolic compounds. *Journal of Food Bioactives* 4:11–68. doi:10.31665/JFB.2018.4162.

Shannon, E., and N. Abu-Ghannam. 2019. Seaweeds as nutraceuticals for health and nutrition. *Phycologia* 58 (5):563–77. doi:10.1080/00318884.2019.1640533.

Shen, Z., H. Ye, M. Kröger, and Y. Li. 2018. Aggregation of polyethylene glycol polymers suppresses receptor-mediated endocytosis of PEGylated liposomes. *Nanoscale* 10 (9):4545–60. doi:10.1039/c7nr09011k.

Shim, S. Y., M. Lee, and K. D. Lee. 2016. *Achyranthes japonica* Nakai water extract suppresses binding of IgE antibody to cell surface FcεRI. *Preventive Nutrition and Food Science* 21 (4):323–9. doi:10.3746/pnf.2016.21.4.323.

Shrestha, S., W. Zhang, and S. Smid. 2021. Phlorotannins: A review on biosynthesis, chemistry and bioactivity. *Food Bioscience* 39:100832. doi:10.1016/j.fbio.2020.100832.

Shrivastava, A. K., and A. Pandey. 2013. Inflammation and rheumatoid arthritis. *Journal of Physiology and Biochemistry* 69 (2):335–47. doi:10.1007/s13105-012-0216-5.

Singh, I. P., and J. Sidana. 2013. 5 - Phlorotannins. In *Functional ingredients from algae for foods and nutraceuticals*, ed. H. Domínguez, 181–204. Woodhead Publishing, Cambridge, UK.

Sinha, A., and S. PK. 2019. Enhanced induction of apoptosis in HaCaT cells by luteolin encapsulated in PEGylated liposomes—role of caspase-3/caspase-14. *Applied Biochemistry and Biotechnology* 188 (1):147–64. doi:10.1007/s12010-018-2907-z.

Siriwardhana, N., K.-W. Lee, and Y.-J. Jeon. 2005. Radical scavenging potential of hydrophilic phlorotannins of *Hizikia fusiformis*. *Algae* 20 (1):69–75. doi:10.4490/ALGAE.2005.20.1.069.

Son, M., S. Oh, H. S. Lee, D.-M. Chung, J. T. Jang, Y.-J. Jeon, C. H. Choi, K. Y. Park, K. H. Son, and K. Byun. 2019. Ecklonia cava extract attenuates endothelial cell dysfunction by modulation of inflammation and brown adipocyte function in perivascular fat tissue. *Nutrients* 11 (11):2795. doi:10.3390/nu11112795.

Spiller, F., R. O. Formiga, J. F. da Silva Coimbra, J. C. Alves-Filho, T. M. Cunha, and F. Q. Cunha. 2019. Targeting nitric oxide as a key modulator of sepsis, arthritis and pain. *Nitric Oxide: Biology and Chemistry* 89:32–40. doi:10.1016/j.niox.2019.04.011.

Subbiah, V., X. Duan, O. T. Agar, F. R. Dunshea, C. J. Barrow, and H. A. Suleria. 2023. Comparative study on the effect of different drying techniques on phenolic compounds in Australian beach-cast brown seaweeds. *Algal Research* 72:103140. doi:10.1016/j.algal.2023.103140.

Subbiah, V., F. Ebrahimi, O. T. Agar, F. R. Dunshea, C. J. Barrow, and H. A. Suleria. 2023. Comparative study on the effect of phenolics and their antioxidant potential of freeze-dried Australian beach-cast seaweed species upon different extraction methodologies. *Pharmaceuticals* 16 (5):773. doi:10.3390/ph16050773.

Subbiah, V., C. Xie, F. R. Dunshea, C. J. Barrow, and H. A. Suleria. 2023. The quest for phenolic compounds from seaweed: Nutrition, biological activities and applications. *Food Reviews International* 39 (8):5786–813. doi:10.1080/87559129.2022.2094406.

Sugiura, Y., M. Usui, H. Katsuzaki, K. Imai, M. Kakinuma, H. Amano, and M. Miyata. 2018. Orally administered phlorotannins from *Eisenia arborea* suppress chemical mediator release and cyclooxygenase-2 signaling to alleviate mouse ear swelling. *Marine Drugs* 16 (8):267. doi:10.3390/md16080267.

Sugiura, Y., M. Usui, H. Katsuzaki, K. Imai, and M. Miyata. 2017. Anti-inflammatory effects of 6, 6′-bieckol and 6, 8′-bieckol from *Eisenia arborea* on mouse ear swelling. *Food Science and Technology Research* 23 (3):475–80. doi:10.3136/fstr.23.475.

Sugiura, Y., M. Usui, H. Katsuzaki, K. Imai, R. Tanaka, T. Matsushita, and M. Miyata. 2021. Dieckol isolated from a brown alga, *Eisenia nipponica*, suppresses ear swelling from allergic inflammation in mouse. *Journal of Food Biochemistry* 45 (4):e13659. doi:10.1111/jfbc.13659.

Sun, X., Y. Luo, L. Huang, B.-Y. Yu, and J. Tian. 2017. A peptide-decorated and curcumin-loaded mesoporous silica nanomedicine for effectively overcoming multidrug resistance in cancer cells. *RSC Advances* 7 (27):16401–9. doi:10.1039/C7RA01128H.

Surendhiran, D., H. Cui, and L. Lin. 2019. Encapsulation of phlorotannin in alginate/PEO blended nanofibers to preserve chicken meat

from *Salmonella* contaminations. *Food Packaging and Shelf Life* 21:100346. doi:10.1016/j.fpsl.2019.100346.

Tanaka, K., M. Ohno, and D. B. Largo. 2020. An update on the seaweed resources of Japan. *Botanica Marina* 63 (1):105–17. doi:10.1515/bot-2018-0100.

Tang, J., W. Wang, and W. Chu. 2020. Antimicrobial and anti-quorum sensing activities of phlorotannins from seaweed (*Hizikia fusiforme*). *Frontiers in Cellular and Infection Microbiology* 10:586750. doi:10.3389/fcimb.2020.586750.

Tong, T., X. Liu, and C. Yu. 2021. Extraction and nano-sized delivery systems for phlorotannins to improve its bioavailability and bioactivity. *Marine Drugs* 19 (11):625. doi:10.3390/md19110625.

Turck, D., J.-L. Bresson, B. Burlingame, T. Dean, S. Fairweather-Tait, M. Heinonen, K. I. Hirsch-Ernst, I. Mangelsdorf, H. J. McArdle, A. Naska, et al. 2017. Safety of *Ecklonia cava* phlorotannins as a novel food pursuant to Regulation (EC) No 258/97. *EFSA Journal. European Food Safety Authority* 15 (10):e05003. doi:10.2903/j.efsa.2017.5003.

Um, M. Y., J. Y. Kim, J. K. Han, J. Kim, H. Yang, M. Yoon, J. Kim, S. W. Kang, and S. Cho. 2018. Phlorotannin supplement decreases wake after sleep onset in adults with self-reported sleep disturbance: A randomized, controlled, double-blind clinical and polysomnographic study. *Phytotherapy Research: PTR* 32 (4):698–704. doi:10.1002/ptr.6019.

Ummat, V., B. K. Tiwari, A. K. Jaiswal, K. Condon, M. Garcia-Vaquero, J. O'Doherty, C. O'Donnell, and G. Rajauria. 2020. Optimisation of ultrasound frequency, extraction time and solvent for the recovery of polyphenols, phlorotannins and associated antioxidant activity from brown seaweeds. *Marine Drugs* 18 (5):250. doi:10.3390/md18050250.

Verhoef, J. J., and T. J. Anchordoquy. 2013. Questioning the use of PEGylation for drug delivery. *Drug Delivery and Translational Research* 3 (6):499–503. doi:10.1007/s13346-013-0176-5.

Victor, S. P., and C. P. Sharma. 2015. Chapter 9 - Anti-inflammatory drug delivery systems using marine products. In *Functional Marine Biomaterials*, ed. S.-K. Kim, 137–47. Woodhead Publishing, Cambridge, UK.

Vijay, N. K. G., and C. Vellapandian. 2023. Ameliorative effects of phlorotannin-rich fraction of *Sargassum tenerrimum* in high-fat diet and low dose streptozotocin-induced metabolic changes and oxidative stress in diabetic rats. *Journal of Herbmed Pharmacology* 12 (3):367–79.

Vissers, A. M., A. Caligiani, S. Sforza, J. P. Vincken, and H. Gruppen. 2017. Phlorotannin composition of *Laminaria digitata*. *Phytochemical Analysis* 28 (6):487–95. doi:10.1002/pca.2697.

Wang, T., R. Jonsdottir, and G. Ólafsdóttir. 2009. Total phenolic compounds, radical scavenging and metal chelation of extracts from Icelandic seaweeds. *Food Chemistry* 116 (1):240–8. doi:10.1016/j.foodchem.2009.02.041.

Wei, P., E. J. Cornel, and J. Du. 2021. Ultrasound-responsive polymer-based drug delivery systems. *Drug Delivery and Translational Research* 11 (4):1323–39. doi:10.1007/s13346-021-00963-0.

Wekre, M. E., S. Hellesen Brunvoll, and M. Jordheim. 2022. Advancing quantification methods for polyphenols in brown seaweeds—Applying a selective qNMR method compared with the TPC assay. *Phytochemical Analysis* 33 (7):1099–110. doi:10.1002/pca.3162.

Xie, C., Z. J. Lee, S. Ye, C. J. Barrow, F. R. Dunshea, and H. A. Suleria. 2023. A review on seaweeds and seaweed-derived polysaccharides: Nutrition, chemistry, bioactivities, and applications. *Food Reviews International* 1–36. doi:10.1080/87559129.2023.2212055.

Yadav, D., and H. K. Dewangan. 2021. PEGYLATION: An important approach for novel drug delivery system. *Journal of Biomaterials Science. Polymer Edition* 32 (2):266–80. doi:10.1080/09205063.2020.1825304.

Yang, H., M. Yoon, J. Kim, and S. Cho. 2014. Acute oral toxicity of phlorotannins in beagle dogs. *Korean Journal of Fisheries and Aquatic Sciences* 47 (4):356–62. doi:10.5657/KFAS.2014.0356.

Yao, D., M. Dong, C. Dai, and S. Wu. 2019. Inflammation and inflammatory cytokine contribute to the initiation and development of ulcerative colitis and its associated cancer. *Inflammatory Bowel Diseases* 25 (10):1595–602. doi:10.1093/ibd/izz149.

Yeo, M., W.-K. Jung, and G. Kim. 2012. Fabrication, characterisation and biological activity of phlorotannin-conjugated PCL/β-TCP composite scaffolds for bone tissue regeneration. *Journal of Materials Chemistry* 22 (8):3568–77. doi:10.1039/c2jm14725d.

Yingying, M., L. Xiu-Xia, C. Luyun, and L. Jianrong. 2022. pH-Sensitive ε-polylysine/polyaspartic acid/zein nanofiber membranes for the targeted release of polyphenols. *Food & Function* 13 (12):6792–801. doi:10.1039/d1fo03051e.

Yoshioka, H., M. Ishida, K. Nishi, H. Oda, H. Toyohara, and T. Sugahara. 2014. Studies on anti-allergic activity of *Sargassum horneri* extract. *Journal of Functional Foods* 10:154–60. doi:10.1016/j.jff.2014.06.002.

Zhang, J., A. Hassane Hamadou, C. Chen, and B. Xu. 2023. Encapsulation of phenolic compounds within food-grade carriers and delivery systems by pH-driven method: A systematic review. *Critical Reviews in Food Science and Nutrition* 63 (19):4153–74. doi:10.1080/10408398.2021.1998761.

Zhang, J., L. Zhang, C. Lai, Y. Liang, L. Gao, K. Kaliaperumal, and Y. Jiang. 2022. Nutraceutical potential of navel orange peel in diabetes management: The chemical profile, antioxidant, α-glucosidase inhibitory and antiglycation effects of its flavonoids. *Food Bioscience* 49:101943. doi:10.1016/j.fbio.2022.101943.

Zhang, S., A. Taehwan Kim, X. Liu, L. Yan, and S. Moo Kim. 2020. Antioxidant and antidiabetic activities of vanadium-binding protein and trifuhalol A. *Journal of Food Biochemistry* 44 (12):e13540. doi:10.1111/jfbc.13540.

Zhao, W., V. Subbiah, C. Xie, Z. Yang, L. Shi, C. Barrow, F. Dunshea, and H. A. Suleria. 2023. Bioaccessibility and bioavailability of phenolic compounds in seaweed. *Food Reviews International* 39 (8):5729–60. doi:10.1080/87559129.2022.2094404.

Znad, H., M. R. Awual, and S. Martini. 2022. The utilization of algae and seaweed biomass for bioremediation of heavy metal-contaminated wastewater. *Molecules* 27 (4):1275. doi:10.3390/molecules27041275.

Zou, L-q., W. Liu, W-l Liu, R-h Liang, T. Li, C-m Liu, Y-l Cao, J. Niu, and Z. Liu. 2014. Characterization and bioavailability of tea polyphenol nanoliposome prepared by combining an ethanol injection method with dynamic high-pressure microfluidization. *Journal of Agricultural and Food Chemistry* 62 (4):934–41. doi:10.1021/jf402886s.