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PHLOROTANNINS AND THEIR BIOLOGICAL SIGNIFICANCES

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ABSTRACT

Marine organisms are potentially productive sources of highly bioactive secondary metabolites that might characterize useful leads in the development of new pharmaceutical agents. The reputation of food bioactive compounds as functional ingredients has been well recognized due the effectiveness in promoting health and lead to the reduction of disease risk. Especially, nutraceuticals from seaweeds have been served as a rich source of health endorsing components. Among them, mainly phlorotannins implies its potential as a functional ingredient in the food products, pharmaceuticals, and cosmeceuticals. Phlorotannins are restricted to brown seaweeds and are biosynthesised through the acetate-malonate pathway. Like other polyphenolic compounds, phlorotannins have been regarded as potential beneficial for human health. This review presents an overview of phlorotannins with their significant health beneficial biological activities.

INTRODUCTION

Marine macroalgae have been an important part of the human diet in Asia since ancient times and are traditionally well renowned for their versatile health benefits. Recent studies have revealed that marine algae not only are a good source of dietary fiber, proteins, vitamins, and minerals, but also contain a large array of secondary metabolites with valuable biological activities which cannot be found in terrestrial plants[1]. A number of potent compounds have been isolated and identified from different types of seaweeds, including phlorotannins, sulfated polysaccharides, carotenoid pigments such as fucoxanthin and astaxanthin, sterols, catechins, and mycosporine-like amino acids[2]. Phlorotannins, the dominant polyphenolic secondary metabolites found only in brown algae (Phaeophyta). There are fundamental differences in the chemical structures of polyphenols in both terrestrial& marine plants. Where as in

terrestrial plants polyphenols are derived from is Gallic acid & Ellagic acids[3] phlorotannins are group of polyphenols formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and biosynthesized via the acetate-mavalonate pathway, also known as the polyketide pathway [4].The phlorotannins are highly hydrophilic components with a wide range of molecular sizes ranging between 162Da & 650 kDa they are stored in vesicles called physodes, appearing as a colorless and refractive acidic fluid [5] as they are not normally secreted outside the cell, it is necessary for the cells to be damaged before phlorotannins release. Phlorotannins concentration in brown seaweeds can vary among species, being affected by seaweed size, age, tissue type, salinity, season, nutrient levels, intensity of herbivory, light intensity and water temperature. Their concentration can reach the maximum in temperate and tropical Atlantic (up to 20% of brown seaweed dry mass), and the minimum in tropical Pacific and Indo-Pacific regions. Species from the order Fucales are richer in this kind of compounds[6]. These phlorotannins help to protect algae from stress conditions and herbivores due to the health beneficial various biological activities of phlorotannins, marine brown algae are known to be a rich source of healthy food [7].

SOURCES

Several species of brown algae, such as *Ecklonia cava, Ecklonia kurome, Fucus vesiculosus, Hizikia fusiformis, and Sargassum ringgoldianum, Cystophora congesta, Sargassacea Cystophora retroflexa, Laminariale Laminaria ochroleuca, Sargassacea Carpophyllum angustifolium, Sargassum siliquastrum Eisenia Bicyclis, Turbinoid conoids, Turbinoid ornate, Padina gymnospora and S. polycystum, Sargassum kjellamanianum, Leathesia nana.*

ANTI-MICROBIAL AGENT

Phlorotannins in brown algae can act as potential antimicrobial agents that may be useful in food & pharmaceutical industry[8]. Dieckol purified from *E.cava* has fungicidal activity. It has shown a potent antifungal activity[9] against *T.rubrum* associated with dermatophytic nail infections in humans. In addition, it has shown a potent inhibition of cell membrane integrity as well as cell metabolism against *T.rubrum*. The minimum inhibitory concentration values for eckol from *E. cava* indicates potent anti-microbial activity against methicillin-resistant S.aureus in the range of (125-250 μg/ml)[10]. Dieckol isolated from the *E.stolonifera* may possess stronger anti-MRSA activity than eckol and the MICs of dieckol were in the range of (32-64 μg/ml),[8] although the current knowledge on the relationship between the structure and activity of the active phlorotannins is limited, the physiological activity may depends on degree of polymerization of phlorotannin derivatives[11]. In addition, comparison of other phlorotannins using catechin derivatives such as (-) – Epigallocatechin, (-) –EGCg, (+) – gallocatechin, (-)-gallocatechin from green tea (camellia sinnsis) against MRSA were 64 μg/ml[12]. thus, the anti MRSA activity of phlorotannins isolated *E. bicyclis* was superior to (or) equal to these catechins derived from green tea[11].

ANTI-ALLERGIC ACTIVITY

Food allergy has emerged as a major health problem which represents the most common disorders of the immune system, affecting about 20% of the world's population[13]. Anti-allergenic compounds usually act over mast cells which are known to play principle role in the immediate type allergic reaction, which is the major mechanism for causing allergic rhinitis and bronchial asthma[14]. Recently, it has shown that E. *cava* extract with phlorotannins could block the release of

histamine from anti-DNP IgE-sensitized rat basophile leukemia cells, RBL-2H3 cells[15]. Anti-allergic phlorotannins have been isolated from the edible marine brown alga, *Eisenia arborea*[16]. In addition, fucodiphloroethol and Phlorofucofuroeckol-A have an anti-allergic activity by reducing histamine release from human basophilic leukemia and rat basophilic leukemia cells17. The methanolic extract of E. *cava* caused a concentration-dependent reduction in the cell surface expression of FcRI in the human basophilic KU812F cells[15]. According to these findings phlorotannins may serve as potential functional candidates for functional foodstuffs with health benefits, especially for allergic prevention due to histamine.

ANTI-CANCER ACTIVITY

Chemotherapy is one of the major therapeutic approaches for cancer treatment, and several naturally obtained anticancer drugs, such as camptothecin and taxol, are used clinically. It is believed that a promising strategy to screen naturally occurring compounds in order to discover novel anticancer agents. Several studies have reported that the phlorotannin, from brown algae *E. cava*, namely, dioxinodehydroeckol can reduce the growth of human breast cancer cells (MCF-7) via induction of apoptosis[18]. Moreover, phlorotannins such as fucodiphloroethol G, dieckol, eckol, and phlorofucofuroeckol from *E.cava* have been shown to provoke potential cytotoxic effects on human cancer cell lines such as cervical cancer (HeLa), fibrosarcoma (HT1080), lung cancer (A549), and colon cancer (HT-29) cells. However, cytotoxicity to human normal lung fibroblast (MRC-5) cells has been shown to be less successful[19].

ANTI-DIABETIC ACTIVITY

Diabetes mellitus (DM) is a complex disease characterized by chronic hyperglycemia due to deficiency in insulin secretion or resistance[20]. Globally, among DM, that is type II DM accounts for more than 90% of the cases. Phlorotannins from marine brown alga E. *cava* have shown significant inhibitory activities *in vitro* against rat intestinal α -glucosidase and porcine pancreatic α -amylase, especially dieckol, with IC_{50} values at 10.8 μmol/L α-glucoidase and 124.9μmol/Lα-amylase respectively [21]. Another useful mechanism for blood glucose level maintenance on diabetic patient is by increasing glucose acquisition. Sensitive insulin will increase glucose influx in cell. Protein tyrosine phosphatase 1B (PTP 1B) is localized on the cytoplasmic surface of the endoplasmic reticulum in classical insulin-targeted tissues such as muscle, fat and liver[22] It is a negative regulator of insulin signaling and plays a key role in developing insulin resistance[23]**.** In addition, eckol, phlorofucofuroeckol A, dieckol, and 7-phloroeckol from *Ecklonia stolonifera* and *Eisenia bicyclis* inhibited protein tyrosine phosphatase 1B (PTP 1B)[24]. *Ishige foliacea* derived phlorotannin octaphlorethol A (OPA) was valuated and it was reported that OPA has successfully increased glucose uptake in differentiated L6 rat myoblast cells in a dose-dependent manner. Moreover, this study found that OPA increases Glut4-mediated glucose uptake by activating PI3-K/Akt and he AMPK signaling pathway[25].

ANTI – NEUROINFLAMMATORY ACTIVITY

Bioactivities and their potential applications of these phlorotannins have been widely discussed. In the wide range of bioactivities, the effectiveness of phlorotannins as an inhibitor of neuro-inflammation has been considerably researched, and reports indicate that use of brown algae as a food or food ingredient might have highly positive results on brain health. Ethanol extract of *Ecklonia cava* is reported to inhibit lipo-polysaccharide-induced cyclooxygenase-2 and iNOS

expression in BV_2microglia cells[26]. Detailed analysis of the extract and its constituents revealed that dieckol is the effector material responsible for the suppression of endotoxin-stimulated proinflammatory enzymes iNOS and COX-2 production in the murine BV2 microglia[27]. In addition to dieckol and several other phlorotannins present in brown algae such as phloroglucinol, eckol, 7-phloroeckol, phlorofucofuroeckolA, and dioxinodehydroeckol have also shown activity against neuro-inflammation [28].

ANTI-CHOLINESTERASE ACTIVITY

Although symptoms and features of the Alzheimer's disease are well characterized, the exact cause for the development of this devastating condition has not yet been identified. In this context, three major hypotheses have been proposed; Cholinergic hypothesis, tau hypothesis, and amyloid β hypothesis. The oldest hypothesis, cholinergic hypothesis, states that Alzheimer's is the result of a significant drop of acetylcholine, a vital neurotransmitter. The systematic biochemical investigation of the brains of patients with Alzheimer's disease showed a considerable degeneration of cholinergic neurons in the basal forebrain and the associated loss of cholinergic neurotransmission in the cerebral cortex. Moreover, detailed researches revealed that inhibition of acetylcholinesterases enzymes that breakdown acetylcholine would be an effective therapeutic intervention to restore acetylcholine concentration[29]. Various synthetic as well as natural substances have been researched as candidates for clinical treatments. Several potential acetylcholinesterase inhibitors have been identified from marine algae, although all are under experimental level. Yoon and her research team investigated cholinesterase inhibitory activity of the ethanolic extracts from27 Korean sea weed sand reported that *E.stolonifera* derived phlorofucofuroeckolA and dieckol had the highest activity against AChE, with IC_{50} value 4.89±2.28 and 17.11±3.24, respectively. Further, phlorotannins isolated from *Ishige okamurae* have shown significant inhibitory effect on acetylcholinesterase activity. Among the different phlorotannins isolated from *Ishige okamurae*, 6,6′-bieckol is known to have the highest activity, with IC50 of n46.42±1.19Mm)[30]. By contrast, a study on *Ecklonia maxima*, a brown alga that grows abundantly on the west coast of South Africa, demonstrated that eckol are the most active compounds against acetyl cholinesterase activity[31]. All these studies have shown that phlorotannins present in marine algae are mainly responsible for the cholinesterase inhibitory activity of algae. However, all phlorotannins do not show a similar inhibitor activity toward cholinesterase; particularly, low molecular weight phlorotannins, phloroglucinol, and triphlorethol-A did not show any significant activity. It has been noticed that this property is mainly because of the substrate specificity of the enzyme acetyl cholinesterase is highly specific to the substrate Ach and bulky phlorotannins may mask the acetyl cholinesterase and prevent the binding of the substrates in a noncompetitive manner[30].

ANTI-HIV ACTIVITY

Phlorotannins possess anti-HIV activity, with distinct inhibiting activities on polymerase and ribonuclease of HIV-1 life cycle. In early studies, seaweed extracts have been tested for their anti-HIV-1activity in inhibiting key viral life cycle enzymes such as RT, protease, and integrase of HIV-1[32]. Following the referred study, two phlorotannins from brown alga *Ecklonia cava* KJELLMAN have been isolated and reported to inhibit theHIV-1 protease and reverse transcriptase. These phlorotannins, 8, 8′-bieckol and 8,4‴dieckol that are dimers of eckol, were isolated from *E.cava*, which inhibited the RT and protease activity

efficiently. In addition to these, in another report, says 6, 6′-bieckol from *E.cava* reduced the cytopathic effects of HIV-1 including HIV-1-induced syncytia formation and viral p24 antigen levels, as well as inhibited RT and HIV-1entry activity[33] In this study, the lower cytotoxicity of 6,6′ bieckol compared to previous studied tannins raised the potential of this substance as a safe therapeutic agent. Another phlorotannin, diphloretho hydroxyl carmalol has been isolated from *Ishige okamurae* Yendo[32] besides the brown alga *E. cava* inhibited the RT and protease activity with IC_{50} values of 25.2μM, respectively.

ANTI-OXIDANT ACTIVITY

Several species of brown algae, such as *Ecklonia cava, Ecklonia kurome, Fucus vesiculosus, Hizikia fusiformis, and Sargassum ringgoldianum*, have been found to possess remarkably high antioxidant activity in vitro, which is well correlated with their total phlorotannin content[34,35]. The superior antioxidant properties have also been reported for individual phlorotannin compounds, including eckol, dieckol, phlorofucofuroeckol A, and 8, 8′-bieckol[36].

The scavenging activities of these phlorotannin compounds on 2, 2-diphenyl1-picrylhydrazyl (DPPH) and superoxide anion radicals were found to be around 2−10 times higher than those of catechin, α-tocopherol, and ascorbic acid[37]. Phlorotannins in *Sargassum kjellamanianum*[38], *Sargassum siliquastrum*[39], and *Ecklonia stolonifera*[40] have antioxidative activity. The isolates from the brown algae, *E. maxima* which were fully characterized are; phloroglucinol, eckol, 7-phloroeckol and 2-phloroeckol. The antioxidant radical scavenging activity of the above isolates was in the order phloroglucinol, <eckol, < 7-phloroeckol and 2-phloroeckol. Among those 7-phloroeckol was found to exert significant inhibitory effect compared to the commercial antioxidant, ascorbic acid, indicating that 7-phloroeckol could be a good candidate for food, cosmetic and pharmaceutical applications**[41].**

ANTI-AROUSAL ACTIVITY

Coffee is one of the most consumed beverages in the world and has an arousal effect on the central nervous system[42]. Caffeine, the major psychoactive constituent in coffee induces wakefulness by inhibiting adenosine A2A receptors [43]. A large amount of caffeine may lead to sleep disorders, such as insomnia[44]. Phlorotannin extracts from the brown alga *Ecklonia cava* induce sleep on caffeine induced mice. It is important that the active compounds are able to pass the blood–brain barrier to produce hypnotic or arousal activities[45]. In this study, arousal effect of caffeine via the adenosine A2A receptor was offset by hypnotic effect of high-purity phlorotannin preparation (HP-PRT) via the benzodiazepine site of the $GABA_A$ receptor.

ANTI-HYPERTENSIVE ACTIVITY

Angiotensin is a peptide hormone that can constrict the blood vessels and increase blood pressure in the cardiovascular system. Thus, inhibition of ACE is a major target when treating hypertension and cardiovascular diseases. Angiotensin-I converting enzyme plays an important physiological role in regulation of blood pressure by converting angiotensin Ito angiotensin II, in the treatment of hypertension[46]. Therefore, in the development of drugs to control high blood pressure, ACE inhibition has become an important activity. The in vitro ACE inhibitory activity of ten Korean seaweeds including five Phaeophyta (*E. cava, E. stolonifera, Pelvetiasiliqousa, H. fusiforme, and U. pinnatifida*) have been reported**[47]**. The ethanol extracts of *E. stolonifera, E. cava, P. siliquosa, and U.pinnatifida* exhibited significant inhibitory properties against ACE at more

than 50% inhibition at a concentration of 163.9 µg/ml. Moreover, have been reported that enzymatic digest of *E. cava* is a potent ACE inhibitor, exhibited an IC50 of 0.3 µg/ml in vitro and captopril, a commercial antihypertensive exhibited an IC50 of 0.05 g/ml. Polyphenolic compounds inhibit ACE activity through sequestration of the enzyme metal factor, Zn2+ ion[50]. Therefore, it has been assumed that phlorotannins in E. cava might form some type of complex associated with proteins or glycoproteins and then inhibit the ACE activity.

RADIO PROTECTIVE ACTIVITY

Ultra violet (UV) radiation has a strong oxidative component, and photo-oxidative stress has been directly linked to the onset of skin photo damage. Phlorotannins derived from *E. cava* such as dieckol and eckol reduce the intracellular reactive oxygen species generated by gamma-ray radiation [49]. Furthermore, Eckol also protects skin against radiation-induced cellular DNA damage and membrane lipid peroxidation. Therefore, phlorotannins have profound capabilities to use as functional ingredients in pharmaceutical and cosmeceuticals for skin treatment.

CYTOPROTECTIVE ACTIVITY

Eckol is a trimeric phloroglucinol with a dibenzeno-1, 4-dioxin skeleton. This compound is one of the major phlorotannins derived from *Ecklonia cava*, a brown alga belonging to the Laminariaceae family that is abundant in the subtidal regions of Jeju Island (Korea). Recently, demonstrated that eckol exerts cytoprotective properties against oxidative stress up-regulates heme oxygenase-1 via activation of extracellular signal-regulated kinase (Erk) and phosphoinositide 3-kinase[50], and inhibits the maintenance of stemness in glioma stem-like cells, along with associated malignancies. Manganese superoxide dismutase (Mn SOD), the primary antioxidant enzyme responsible for scavenging superoxide anions in the mitochondria, is essential for the survival of all aerobic organisms. On the other hand, overexpression of Mn SOD protects cells against oxidative stress-induced cell death and tissue injury. The FoxO3a mediates transcriptional up-regulation of the ROS scavenging enzymes superoxide dismutase 2 (also known as Mn SOD) and catalase. FoxO3a activity is evoked by the AMP-activated protein kinase (AMPK) pathway, an important signaling pathway involved in ROS regulation. The ability of eckol to safeguard mitochondria against oxidative stress- damaged hepatocytes in terms of the AMPK/FoxO3a/Mn SOD pathway. Therefore, the hepatoprotective activity of eckol may be useful for developing its preventive or therapeutic medicine.

PLANT GROWTH REGULATING ACTIVITY

Eckol is a derivative of phloroglucinol, eckol was obtained from 1 kg dry weight of *E. maxim*a. The high quantity of eckol extracted suggests that it may be a major component in *E. maxim*a, which acts as a potential plant growth regulator for shoot elongation, shoot tip proliferation, and root development of tissue culture plants and mangroves[51]. A recent review highlighted the potential applications of phloroglucinol in plant tissue culture with several beneficial effects such as increased shoot formation, reduced hyperhydricity, increased plant multiplication, root induction, enhancement in root frequency, improvement in auxiliary shoot proliferation, and shoot emergence. Phloroglucinol is well-known in plant tissue culture practices as it enhances growth and shoot tip proliferation and demonstrates both auxin- and cytokinin-like activity.

ANTI- TUMOR ACTIVITY

Carcinogenesis is a multistep process, often involving the appearance of several new cell populations between the initial target cells and the ultimate cancer[34]. In particular, matrix metallo proteinases (MMPs) play an important role in cancer metastasis, such as tumor migration or invasion. MMPs are a family of zinc-containing endo peptidase and degrade specific components of extracellular matrices (ECMs), which have long been considered in association with both normal tissue remodeling, pathologic conditions, and tumor metastasis. Antitumor activity in aqueous extracts of seaweed was first demonstrated by [35, 36] screened powdered tissue from 46 species of air-dried marine algae for antitumor activity. Significant activity against Ehrlich carcinoma was found in the brown alga *Scytosiphon lomentaria* (69.8% inhibition), and *E. bicyclis* showed remarkable antitumor activity with 37.5%inhibitoryactivitybyoraladministrati onof1600mgseaweedpowderper kilogram mouse per day for 28days[36] evaluated the inhibitory effects of fucofuroeckol-A and eckol, which are isolated from *E. bicyclis*, on MMP-2 and in HT1080 human fibrosarcoma cell line. Particularly, gelatinases, MMP-2 and play a role in tumor invasion and angiogenesis, and they participate in cancer progression in sever anaplasias. Moreover, fucofuroeckol-A and eckol suppressed cell migration and cell invasion in 3D culture model on HT1080 cells [9] These results suggested that *E. bicyclis* has remarkable antioxidant activity and strong potential as valuable cancer chemo preventive agents to develop nutraceuticals and pharmaceuticals.

TYROSINASE INHIBITION

Tyrosinase, which is also referred to polyphenol oxidase (PPO), is a Cu-containing enzyme and exists widely in plants and animals. Tyrosinase inhibitors have become increasingly important and used in cosmetics as skin-whitening agents and also as drugs for use in the treatment of pigmentation disturbances. Moreover, melanin is produced in the melanocytes, which is controlled by tyrosinase. Thus, inhibition of Tyrosinase activity or its production can prevent melanogenesis and darkening of the skin. Phlorotannins from marine brown algae are effective in the inhibition of tyrosinase activity and have potential to be used as functional ingredients in the cosmeceutical industry[52].7-Phloroeckol from *E. cava* has shown more potent tyrosinase inhibitory effect in vitro with an IC50 value of 0.85 M than commercial inhibitors such as arbutin (IC50, 243.16 μM) and kojic acid (IC50 is 40.28 μM), respectively[53].

ANTI-COAGULANT ACTIVITY

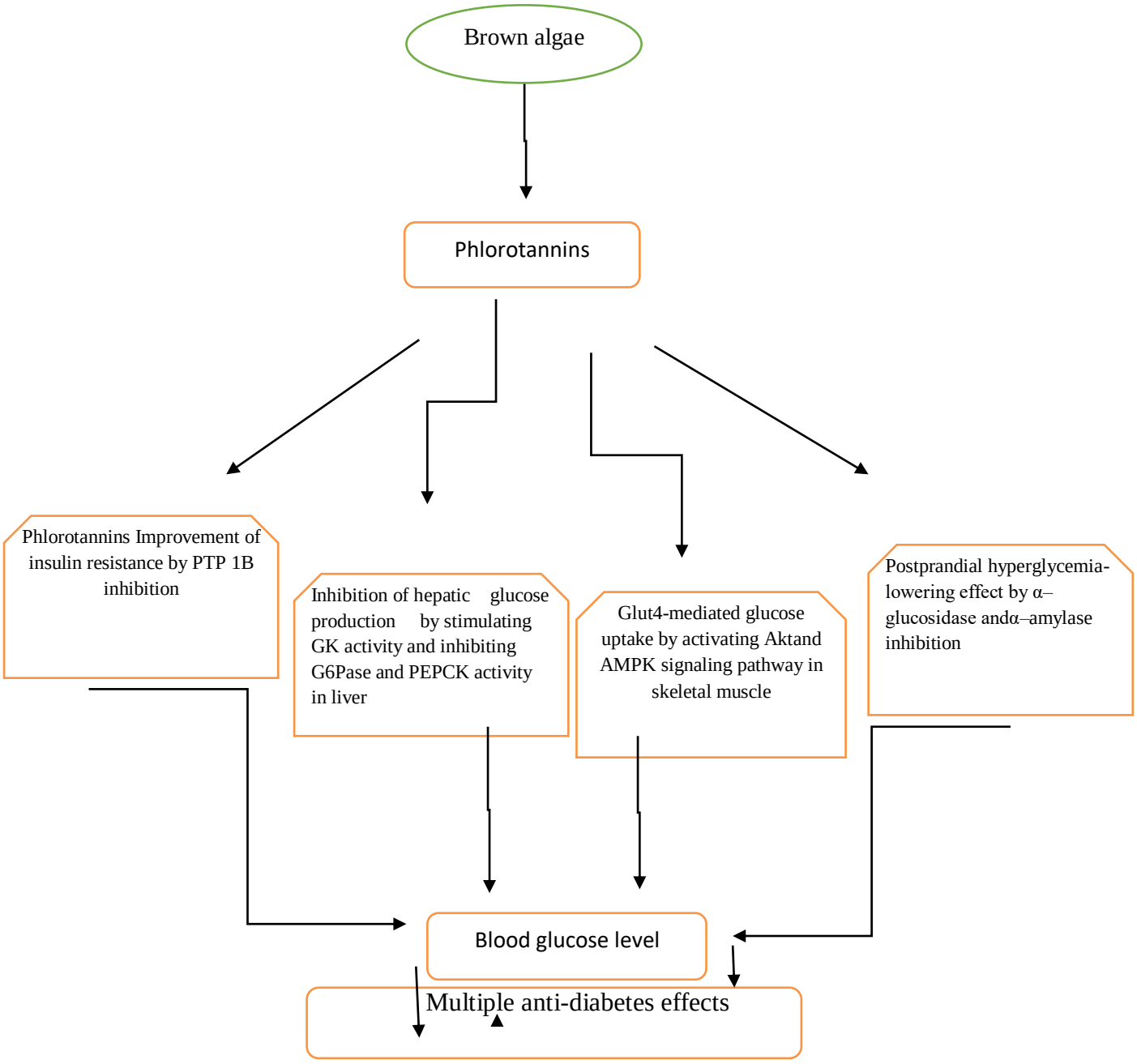
The anticoagulant activity of bioactives from marine algae has been determined by the prolongation of activated partial thromboplastin time(APTT), prothrombin time (PT), and thrombin time (TT) assays[54]. Phlorotannins from *Sargassum thunbergii* were analyzed for their potential anticoagulant activity and it has been suggested that phlorotannins are potential anticoagulants *in vitro* and *in vivo*. In addition, phlorotannins from *S. thunbergii* had a significant example, phloroglucinol can be developed as a novel anticoagulant in the pharmaceutical industry[41].

HYALURONIDASE INHIBITION

Hyaluronidase, is an enzyme that depolymerizes the polysaccharide hyaluronic acid in the extra cellular matrix of connective tissue. The enzyme is known to be involved in allergic effects, migration of cancer and inflammation. Phlorotannins such as eckol, phlorofucofuroeckol A, dieckol, and 8, 8'-bieckol have been shown a stronger inhibition effect against Hyaluronidase than well-known inhibitors such as catechin and sodium chromoglycate [42].

Table 1: Several species of brown algae

Phlorotannin	Brown algae
Phloroglucinol	*Ecklonia cava*
Eckol	*E.cava, Eisenia Bicyclis*
Fucodiphloroethol G	*E. cava*
Phlorofucofuroeckol A	*E. cava, E.stolonifera, E.kurome*
Phlorofucofuroeckol B	*E. bicyclis*
7-Phloroeckol	*E.cava, E. stolinifera*
Dieckol	*E. cav*
6,6-Bieckol	*E. cava, ishigeokamurae*
Triphloroethol B	*E. stolinifera*
2-Phloroeckol	*E. stolinifera*
6,8-Bieckol	*E. bicyclis*
8,8-Bieckol	*E. bicyclis*



BONE TISSUE REGENERATOR ACTIVITY

Many biological functions suggest phlorotannin as a possible bioactive material for bone tissue regeneration. *Ecklonia cava* is a member of the family of Laminariaceae, belonging to the order Laminariales as a perennial brown alga, producing unique phlorotannin derivatives during the lifecycle[38]. The compounds (a)dieckol and (b)1-(3′,5′-dihydroxyphenoxy)7(2″,4″,6″trihydroxyphenoxy)-2,4,9 trihydroxydibenzo-1,4,-dioxinisolatedfrom *E. cava* have promoted the osteosarcoma differentiation by increasing alkaline phosphatase (ALP)activity ,mineralization, total protein, and collagen synthesis in human osteosarcoma cell(MG-63cells)[55] Therefore this experiment data fulfill both the initiation and progression of mineralization phases[45]. Consequently, these results invariably support the osteoblast differentiation at variousstagesandfurtherensuretheapplicationasbioactivematerialin scaffold fabrication. Hence Hao *et al*, have invented a novel scaffold for bone tissue engineering through combination of phlorotannin/PCL/β-tricalcium phosphate (β-TCP) compounds.

CONCLUSION

Recent studies have provided evidence that phlorotannins from marine brown algae have a key role as bioactive ingredients and play a vital role in algae itself as well as human health and nutrition. The possibilities of designing new functional foods and pharmaceuticals to support reducing or regulating the diet related chronic malfunctions are promising. Therefore, it can be suggested that due to valuable biological functions with health beneficial effects, phlorotannins have much potential as active ingredients for preparation of nutraceuticals, cosmeceutical and pharmaceutical products.

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