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Review

Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms

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ABSTRACT

Marine algae are popular and abundant food ingredients mainly in Asian countries, and also well known for their health beneficial effects due to the presence of biologically active components. The marine algae have been studied for biologically active components and phlorotannins, marine polyphenols are among them. Among marine algae, brown algae have extensively studied for their potential anti-diabetic activities. Majority of the investigations on phlorotannins derived from brown algae have exhibited their various anti-diabetic mechanisms such as α-glucosidase and α-amylase inhibitory effect, glucose uptake effect in skeletal muscle, protein tyrosine phosphatase 1B (PTP 1B) enzyme inhibition, improvement of insulin sensitivity in type 2 diabetic *db*/*db* mice, and protective effect against diabetes complication. In this review, we have made an attempt to discuss the various anti-diabetic mechanisms associated with phlorotannins from brown algae that are confined to *in vitro* and *in vivo*.

Contents

1. Introduction

Diabetes mellitus is characterized by abnormal metabolism of glucose, due in part to resistance to the action of insulin in peripheral tissues. The characteristic symptoms are polyuria,

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polydipsia, and polyphagia. Diabetes mellitus is the most serious chronic disease that is developing prominence amidst an increasingly obese and aging world population. Diabetes mellitus is a complex disorder that is characterized by hyperglycemia. It is largely classified into insulin-dependent diabetes mellitus (type 1 diabetes) and non-insulin-dependent diabetes mellitus (type 2 diabetes). In particular, type 2 diabetes is an increasing worldwide health problem, and is the most prevalent form of diabetes [1]. Hyperglycemia plays an important role in the development of type 2 diabetes and complications associated with the disease such as micro-vascular and macro-vascular diseases [2]. Therefore, an effective control of blood glucose levels is the key to preventing or reversing diabetic complications and improving the quality of life for diabetic patients [3].

Currently available therapies for type 2 diabetes include insulin and various oral anti-diabetic drugs such as sulfonylureas, metformin, rosiglitazone, α-glucosidase inhibitors, and thiazolidinediones. However, these therapies have either limited efficacy or significant mechanism based side effects like hypoglycemia, flatulence, body weight gain and enhancement of gastrointestinal problems. Therefore, recently, there has been a growing interest in alternative therapies and in the therapeutic use of natural products for diabetes, especially those derived from herbs [4,5]. This is because plant sources are usually considered to be less toxic with fewer side effects than synthetic ones.

Marine algae are known to provide an abundance of bioactive compounds with great pharmaceutical foods and biomedical potential. In particular, the brown algae have a variety of biological compounds such as pigments, fucoidans, phycocolloids, and phlorotannins. Among them, phlorotannins have been extensively studied for their potential health benefits and reportedly they have shown promising anti-diabetic effects. Dieckol and diphlorethohydroxycarmalol (DPHC) isolated from *Ecklonia cava* and *Ishige okamurae* have been suggested to influence responses relevant to diabetes through the modulation of glucose-induced oxidative stress, as well as through the inhibition of carbohydrate-digestive enzymes [6–9]. In addition, eckol, phlorofucofuroeckol A, dieckol, and 7-phloroeckol from *Ecklonia stolonifera* and *Eisenia bicyclis* inhibited protein tyrosine phosphatase 1B (PTP 1B) [10] and phlorotannins-rich extract from *E. cava* and *I. okamurae* have shown positive effects on genetically diabetic mice [11,12]. Therefore, in this review, we have made an attempt to narrate the diverse anti-diabetic mechanisms of brown algal phlorotannins and their possible potential role in functional food and pharmaceutical areas.

2. Phlorotannins: marine polyphenols derived from brown algae

Many brown algal species are popular food ingredients and medicine mainly in Asian countries as Korea, Japan and China. And also biological activities of the brown algae are related to the presence of polyphenols, polysaccharides and pigments. Among them, polyphenols are the most significant group of biologically substances that determine the nutraceuticals and pharmaceuticals value of brown algae. Recently, several studies have demonstrated the variety of biological benefits associated with brown algal polyphenols, including antioxidant, anticoagulant, antibacterial, anti-inflammatory, and anti-cancer activities [13–15].

Polyphenols are one of the most common classes of secondary metabolites found in terrestrial plants and marine algae. There are fundamental differences in the chemical structures of polyphenols in both terrestrial and marine plants. Polyphenols from terrestrial plants are derived from gallic and ellagic acids [16], whereas the marine algae polyphenols are derived from polymerized phloroglucinol units [17]. These marine algae polyphenols are called as phlorotannins and they are suggested to be formed biosynthetically *via* acetate malonate pathway, also known as polyketide pathway [18]. The phlorotannins are highly hydrophilic components with a wide range of molecular sizes ranging between 162 Da and 650 kDa [19]. Phlorotannins are tannin derivatives composed of several phloroglucinol units linked to one another in various ways and mostly isolated from brown algae and chemical structures of few brown algal phlorotannins are shown in Fig. 1. It has been reported that phlorotannins in brown algae are richer than other marine algae. The well studied phlorotannins from *Ecklonia* species are phloroglucinol, eckol, dieckol, 6,6′-bieckol, phlorofucofuroeckol A [6,7,15,20]. Moreover, few other novel phlorotannins from other brown algae have been reported such as dioxinodehydroeckol, 7-phloroeckol from *E. bicyclis* and DPHC from *I. okamurae* [10,14].

3. Anti-diabetic effects of phlorotannins through diverse mechanisms

These brown algal phlorotannins have been extensively characterized for their possible anti-diabetic effects. A summary of brown algal phlorotannins and their possible anti-diabetic effects are shown in Table 1. This section is covering up the major anti-diabetic effects of phlorotannins isolated from brown algae.

3.1. α-Glucosidase inhibitors and postprandial hyperglycemia-lowering effect

A sudden increase in blood glucose levels, which causes hyperglycemia in type 2 diabetes patients, occurs as the result of the hydrolysis of starch by pancreatic α-amylase and glucose uptake due to intestinal α-glucosidases [21]. An effective strategy for the management of type 2 diabetes patients involved the profound inhibition of intestinal α-glucosidases and the mild inhibition of pancreatic α-amylase [22]. Several natural resources have been evaluated for their ability to suppress the production of glucose from carbohydrates in the gut or glucose absorption from the intestine [23]. α-Glucosidase is one of the glucosidases located within the brush-border surface membranes of intestinal cells, and is a key enzyme in carbohydrate digestion [24]. Similarly, α-amylase catalyzes the hydrolysis of α-1,4-glucosidic linkages of starch, glycogen, and a variety of oligosaccharides, and α-glucosidase further degrades the disaccharides into simpler sugars, which are readily available for intestinal absorption. The inhibition of their activity in the human digestive tract, is regarded as an effective method for the control of diabetes by diminishing the absorption of glucose decomposed from starch by these enzymes [25]. Therefore, effective and nontoxic inhibitors of α-glucosidase and α-amylase have long been sought.