Acta Histochemica 116 (2014) 669–674

Contents lists available at ScienceDirect

Acta Histochemica

journal homepage: www.elsevier.de/acthis

Review

Antioxidant marine algae phlorotannins and radioprotection: A review of experimental evidence

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ARTICLE INFO

Article history:
Received 5 January 2014
Received in revised form 16 March 2014
Accepted 18 March 2014

Keywords:
Gamma ray irradiation
Oxidative stress
Phlorotannin
Marine algae
Brown seaweed

ABSTRACT

Radiation has been widely used for cancer therapy in human medicine. However, the side effects of radiation are problematic and can limit its application. Radiation generates reactive oxygen species, leading to cell death *via* multiple signaling pathways. The blocking of certain signaling cascades using antioxidants represents a compensatory therapy of radiation-induced tissue injury. Although synthetic chemicals have been investigated in recent decades, anti-oxidants from natural resources have been searched for continuously. Among them, phlorotannins from marine algae, including *Ecklonia cava*, have been shown to protect cells from radiation-induced injury as well as oxidative stress. In the present review, the radioprotective capacity of phlorotannins derived from marine algae and the mechanisms involved are discussed.

Contents

Abbreviations: AP-1, activator protein-1; DRF, dose reduction factor; ERK, extracellular signal regulated kinase; *E. cava*, *Ecklonia cava*; HO-1, heme oxygenase-1; IκBα, I kappa B kinase alpha; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MKK-4, mitogen-activated protein kinase kinase-4; NF-κB, nuclear factor-kappa B; NRF2, transcription factor NF-E2-related factor 2; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; ROS, reactive oxygen species.

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http://dx.doi.org/10.1016/j.acthis.2014.03.008
0065-1281/

Introduction

Ionizing radiation is a widely studied type of oxidative stress (Mathieu et al., 1999; Miura, 2004; Cohen and Cohen, 2013) that leads to a radiation adaptive response with low-dose irradiation or induction of cell death at high-dose irradiation (Weiss and Landauer, 2003; Miura, 2004). When reactive oxygen species (ROS) are generated in stimulated cells, ROS are reduced by the activation of antioxidant enzymes, leading to redox homeostasis (Miura, 2004). Under this condition, the rates of generation and of scavenging are in balance, and high concentrations of ROS do not accumulate (Dring, 2006; Halliwell and Gutteridge, 2007). However, excess production of ROS in cells has been known to be associated with damage of cell membranes and proteins, leading to cell death (Miura, 2004), although some ROS have been shown to perform useful functions (Dring, 2006; Halliwell and Gutteridge, 2007). For the maintenance and recovery of redox balance in ROS-damaged cells, antioxidant enzymes and compounds could provide an alternative option for the amelioration of side effects caused by irradiation (Nair et al., 2001; Okunieff et al., 2008). Although the synthetic compound amifostine has been developed (Bukowski, 1996; Schuchter, 1996; Dorr, 1998; Hosseinimehr, 2007), researchers have attempted to identify antioxidants from natural resources, including marine algae, to mitigate the side effects associated with the synthetic chemicals (Hosseinimehr, 2007; Cornish and Garbary, 2010).

Marine algae contain many polyphenols, including phlorotannins, with antioxidant activities (Cornish and Garbary, 2010). Among marine algae, brown seaweeds, including *Ecklonia* species and *Ishige okamurae*, have been investigated extensively because these species contain various phlorotannins (Thomas and Kim, 2011).

Ecklonia species, including *E. cava*, *E. bicyclis*, *E. stolonifera* and *E. kurume*, are known to contain diverse phlorotannins (Thomas and Kim, 2011). These species contain many dietary fibers, carotenoids, polysaccharides and phlorotannins, which show diverse biological activities (Shim et al., 2009; Thomas and Kim, 2011; Wijesinghe and Jeon, 2012). The phytochemical characteristics and biological effects of *Ecklonia* species have been reviewed (Thomas and Kim, 2011; Wijesinghe and Jeon, 2012). The components of *Ecklonia* species are associated with antioxidant and anti-inflammatory activities (Thomas and Kim, 2011; Wijesinghe and Jeon, 2012). *I. okamurae*, a brown seaweed, was also found to contain phlorotannins, including phloroglucinol, 6,6′-bieckol and diphloroethohydroxycarmalol (Heo et al., 2008; Zou et al., 2008; Thomas and Kim, 2011). In addition to the radioprotective effects of phlorotannins from brown seaweeds, the extracts of red seaweeds, including *Polyopes lancifolia* (Jeong et al., 2011) and *Callophyllis japonica* (Kim et al., 2008; Shin et al., 2010), were found to be radioprotective in mouse models, suggesting that marine algae, including red seaweeds and brown seaweeds, have radioprotective effects.

In line with their antioxidant effects, components isolated from marine seaweeds, including *E. cava*, have been tested for their radioprotective capacity in animals and in cultured cells (Table 1). The aim of the present review is to summarize and discuss the radioprotective activities of phlorotannins, polysaccharides, and crude extracts of marine algae based on experimental evidence using gamma irradiation.

Irradiation and oxidative stress

Radiation alters the maintenance of ROS in various cells and tissues, partly inducing apoptosis depending on the radiation doses (Mikkelsen and Wardman, 2003; Corre et al., 2010). Although the underlying molecular mechanisms are complex, radiation-induced tissue damage is associated with cell death through oxidative stress (Kam and Banati, 2013). Briefly, the increased production of ROS in irradiated cells leads to lipid peroxidation in the membranes and oxidation of DNA *in vitro* and *in vivo* (Zhao and Robbins, 2009). Regarding signaling pathways involved in the response to radiation in animals, specific proteins, including lipid raft protein caveolin-1 (Kim et al., 2007), nuclear factor-kappa B(NF-κB) (Brach et al., 1993; Ha et al., 2010) and the c-Fos/c-Jun AP-1 complex (Hallahan et al., 1993) were induced *via* activation of the mitogen-activated protein kinase (MAPK) pathways, including extracellular signal regulated kinase (ERK), the c-Jun N-terminal kinase (JNK) and p38 MAPK (Ha et al., 2010). The activation of transcription factors and MAPKs induces the production of proinflammatory mediators, including cyclooxygenase-2 and inducible nitric oxide synthase (Ha et al., 2010; Kam and Banati, 2013). Moreover, tissue-protective factors, including those that mediate DNA repair and antioxidant defense, and molecular chaperones, are concurrently activated in response to irradiation, particular at low doses (Miura, 2004). Thus, the fate of irradiated cells is dependent on the levels of ROS generated by irradiation despite activation of tissue-protective enzymes. To ameliorate radiation-induced tissue injury, blocking agents for each signaling cascade after radiation injury would be necessary as part of any alternative radioprotection therapy. The molecular cascades in cells activated after irradiation and potential blockers, including antioxidants, are depicted in Fig. 1.

Phlorotannins from *Ecklonia* species and *I. okamurae*

Phlorotannins are tannin derivatives composed of several phloroglucinol units linked to each other in distinct ways (Thomas and Kim, 2011). Many phlorotannins have been isolated from edible brown algae *Ecklonia* species (including *E. cava*), and include phloroglucinol, eckol, dieckol, 6,6′-bieckol, triphlorethol A, fucodiphloroethol G, phlorofucofuroeckol A, 7-phloroeckol, dioxinodehydroeckol and 2-phloroeckol (Li et al., 2009; Park et al., 2013). The phlorotannins from *E. cava* that have radioprotective potential are phloroglucinol (Moon et al., 2008), eckol (Moon et al., 2008; Zhang et al., 2008), dieckol (Park et al., 2010) and triphlorethol A (Kang et al., 2006). Phlorotanninsfrom *I. okamurae* were identified by column chromatography as diphloroethohydroxycarmalol, phloroglucinol and 6,6′-bieckol (Zou et al., 2008). The radioprotective activities of phlorotannins and other components of marine algae are summarized in Table 1.

In the present review, marine algae-originated phlorotannins with radioprotective activity against gamma-irradiation will be discussed, particularly regarding the associated molecular changes in signaling pathways.

Molecular mechanism of phlorotannin-induced radioprotection

Phloroglucinol

Irradiation has been known to induce cell death *via* apoptotic signaling pathways, which are mediated, in part, by decreased Bcl-2 expression, increased Bax expression, and activation of caspase-3 and -9. Phloroglucinol has been demonstrated to protect Chinese hamster lung fibroblasts (V79-4) cells *in vitro* and mice *in vivo* (Kang et al., 2010). The molecular mechanism underlying the radioprotective effect of phloroglucinol is similar to that of eckol (Zhang et al., 2008; Park et al., 2010), in thatphloroglucinol inhibits mitogen-activated protein kinase kinase-4 (MKK-4/SEK1)-c-Jun NH2-terminal kinase (JNK)-activator protein 1(AP-1) cascades and restores the levels of reduced glutathione and protein expression