Marine Biotechnology
https://doi.org/10.1007/s10126-018-9820-x

REVIEW ARTICLE

Environmental Control of Vanadium Haloperoxidases and Halocarbon Emissions in Macroalgae

Thillai Punitha[1,2] · Siew-Moi Phang[1,3] · Joon Ching Juan[4,5] · John Beardall[6]

Received: 7 November 2016 / Accepted: 4 December 2017
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Vanadium-dependent haloperoxidases (V-HPO), able to catalyze the reaction of halide ions (Cl^-, Br^-, I^-) with hydrogen peroxide, have a great influence on the production of halocarbons, which in turn are involved in atmospheric ozone destruction and global warming. The production of these haloperoxidases in macroalgae is influenced by changes in the surrounding environment. The first reported vanadium bromoperoxidase was discovered 40 years ago in the brown alga *Ascophyllum nodosum*. Since that discovery, more studies have been conducted on the structure and mechanism of the enzyme, mainly focused on three types of V-HPO, the chloro- and bromoperoxidases and, more recently, the iodoperoxidase. Since aspects of environmental regulation of haloperoxidases are less well known, the present paper will focus on reviewing the factors which influence the production of these enzymes in macroalgae, particularly their interactions with reactive oxygen species (ROS).

Keywords Haloperoxidases · Macroalgae · Halocarbons · Bromoperoxidases · Iodoperoxidase · Algal biotechnology

Introduction

Halogenated natural products are widespread in the environment, and the halogen atoms are typically key to their bioactive properties. Halogenated compounds are known to have many industrial applications, including their use as biopharmaceuticals. Marine organisms (including macroalgae, sponges, and worms) are known to be good sources of halogenated organic compounds for such purposes. Until recently, research interests have focused on complex halogenated molecules, their metabolic pathways, and their possible industrial applications (Laturnus et al. 2000), but it is now recognized that small/simpler halogenated compounds play significant roles in the biology of marine organisms and in climate change.

Central to the biological synthesis of halogenated compounds is the activity of a group of enzymes known as haloperoxidases (HPOs) (Leblanc et al. 2006; Wever and Hemrika 2001). Algae produce HPO as part of their physiological responses to the environment, and this group of enzymes has attracted the attention of many researchers. There are three types of HPOs based on their cofactor requirements, namely cofactor-free haloperoxidases (HPOs), vanadium-dependent haloperoxidases (V-HPOs), and heme iron-dependent haloperoxidases (HI-HPOs), and three types of halogenating enzymes, namely nonheme iron-dependent halogenases (NI-HG), flavin-dependent halogenases (F-HG), and S-adenosyl-L-methionine (SAM)-dependent halogenases (S-HG) (Blasiak and Drennan 2009; Pang et al. 2015). Despite having similar biological functions, their structure variance suggests that they may have evolved independently. Based on phylogenetic and structural analyses, HPO, V-HPO, HI-HPO, NI-HG, F-HG, and S-HG enzyme families may have

✉ Siew-Moi Phang
phang@um.edu.my

✉ Joon Ching Juan
jcjuan@um.edu.my

[1] Institute of Ocean and Earth Sciences, University of Malaya, 50603 Kuala Lumpur, Malaysia

[2] Institute of Graduate Studies, University of Malaya, 50603 Kuala Lumpur, Malaysia

[3] Institute of Biological Sciences, University of Malaya, 50603 Kuala Lumpur, Malaysia

[4] Nanotechnology and Catalysis Research Centre (NANOCAT), University of Malaya, Level 3, IPS Building, Kuala Lumpur, Malaysia

[5] School of Science, Monash University Malaysia Campus, Bandar Sunway, 46150 Subang Jaya, Malaysia

[6] School of Biological Sciences, Monash University, Clayton, VIC 3800, Australia

Published online: 24 April 2018

evolutionary relationships to the α/β hydrolases, acid phosphatases, peroxidases, chemotaxis phosphatases, oxidoreductases, and SAM hydroxide adenosyltransferases, respectively. These halogenating enzymes have established sequence homology, structural conservation, and mechanistic features within each family (Xu and Wang 2016).

These HPOs are enzymes that catalyze the oxidation of halides by hydrogen peroxide (Leblanc et al. 2006; Wever and Hemrika 2001). HPOs occur in nature (Neidleman and Geigert 1986), inter alia in bacteria (Neidleman 1975; Suthiphongchai et al. 2008) and algae (Fenical 1975), and function as catalysts in halogenation reactions (Suthiphongchai et al. 2008). The general reaction catalyzed by HPOs is as follows (Eq. 1) (Suthiphongchai et al. 2008):

$$AH + H_2O_2 + X^- + H^+ \rightarrow^{HPO} AX + 2H_2O \quad (1)$$

where AH = organic substrate; HPO = haloperoxidases; X^- = halide ions Cl^-, Br^-, and I^-; and AX = halogenated compounds.

As shown in Fig. 1, a class of HPO enzymes found in macroalgae contains vanadium (V), as a vanadate ion located at the active site (Messerschmidt and Wever 1996). There are two types of vanadium-based enzymes, namely vanadium-nitrogenase and V-HPOs. The former enzyme will activate and reduce substrates such as molecular nitrogen (Raugei and Carloni 2006). Vanadium is an essential element in this type of enzyme, for instance as has been shown that bromoperoxidase (BPO) is inactivated after dialyzing in 1 mM EDTA at pH 3.8 and can have activity fully restored after incubation with vanadium (Vilter 1995; Sigel and Sigel 1995; Almeida et al. 2001).

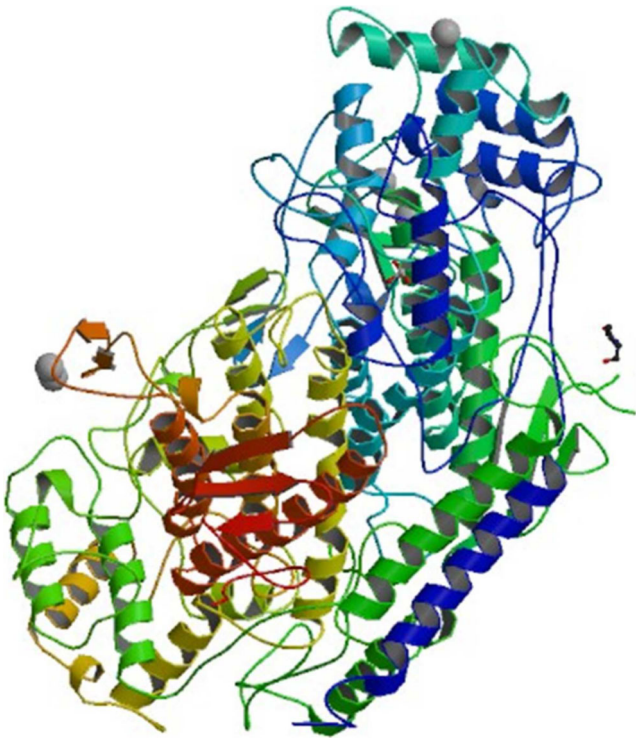

Fig. 1 X-ray SIRAS structure determination of a vanadium-dependent haloperoxidase from *Ascophyllum nodosum* at 2.0 A resolution. Reprinted from *RCSB Protein Data Bank*. Retrieved June 21, 2016, from http://www.rcsb.org/pdb/explore.do?structureId=1qi9

These enzymes contain one or more subunits of relative molecular mass around 67 kDa and all have a similar coordination of vanadium in the active site (Messerschmidt and Wever 1996; Weyand et al. 1999). After their discovery, vanadium haloperoxidases were classified as chloro-, bromo-, and iodoperoxidases. Vanadium bromo- and iodoperoxidases mostly occur in marine organisms, while terrestrial organisms produce vanadium chloroperoxidases (Kongkiattikajorna et al. 2006).

According to Leblanc et al. (2006), the naming system of haloperoxidases reflects the most electronegative halide that they can oxidize. Thus, the chloroperoxidases (CPOs) can catalyze the oxidation of chloride as well as of bromide and iodide. BPOs react with bromide and iodide, whereas iodoperoxidases (IPOs) are specific to iodide. Some studies have concluded that vanadium-iodoperoxidases (V-IPOs) play a bigger role in iodine metabolism compared to vanadium-bromoperoxidases (V-BPOs) (Colin et al. 2003). This was revealed by Wever (2012), through studies of steady-state kinetics.

Haloperoxidases act as catalysts for halogenation and oxidation of various types of organic substrates. The organic substrates include alkenes, aromatics, and thiophene (Itoh 1988), and reactions can involve bromination and cyclization of terpenes and brominative oxidation of indoles (Butler and Carter-Franklin 2004). According to Wever and van der Horst (2013), HPO catalyze the reaction of halides ($X = Cl^-$, Br^-, I^-) with hydrogen peroxide (H_2O_2) to yield hypohalous acids (Eq. 2):

$$H_2O_2 + H^+ + X^- \rightarrow HOX + H_2O \quad (2)$$

This involves using H_2O_2 as an oxidant followed by non-enzymatic halogenation of the resultant oxidized organic compounds (Maurya 2006).

For most reactions, halogenating intermediates react non-specifically with various types of organic compounds (RH). These compounds are vulnerable to electrophilic attack which eventually produces a wide array of halogenated compounds (RX) at the end of the process as described in Eq. 3 (Wever and van der Horst 2013). These organic molecules are electron-rich (Bernhardt et al. 2011).

$$HOX + R{-}H \rightarrow RX + H_2O \quad (3)$$

When a nucleophilic acceptor is absent, a reaction may also occur between HOX and H_2O_2 resulting in the formation of singlet oxygen (Eq. 4):

$$HOX + H_2O_2 \rightarrow {}^1O_2 + H_2O + HX \quad (4)$$

(Wever and van der Horst 2013).

For example, HPO-catalyzed intracellular oxidation of iodide in the presence of H_2O_2 and other reactive oxygen species releases hypoiodous acid. This acid will react with nucleophilic acceptors such as ketones to release halogenated carbons (Winter and Moore 2009; Leedham et al. 2013). Importantly, for aspects of climate change and ozone destruction in both the troposphere and stratosphere, the haloperoxidases produce short-lived and volatile brominated compounds such as methane bromoform ($CHBr_3$) and dibromomethane (CH_2Br_2). A wide variety of algae, including ice microalgae from the Arctic and Antarctic and many red, brown, and green macroalgae from the shores of temperate zones and coastal regions of the subtropics and tropics, release abundant amounts of CH_2Br_2 and $CHClBr_2$ (Wever and van der Horst 2013). These are major sources of the bromine present in the troposphere and lower stratosphere. Generally, 20–30% of stratospheric and tropospheric ozone depletion is caused by reactions with these compounds (Wever and van der Horst 2013), indicating that these halocarbons have a direct relation to global climate change.

Haloperoxidases have two main functions in algae, namely as a defense mechanism and as a way of regulating reactive oxygen species (ROS). HPOs act in defense through the production of HOBr or HOI in marine waters. These compounds act to prevent colonization of the algal thalli by microbes. HOBr in very low concentration reacts with bacterial homoserine lactones and forms inactivated brominated lactones. These lactones, which play an important role in the signaling system of bacteria, cause interference that inhibits microbial quorum sensing and thereby prevents bacterial biofilm formation (Wever and van der Horst 2013). V-BPO from *Delisea pulchra* produces bromofuranones, which are involved in the disruption of quorum sensing of epiphytic bacterial biofilms (Sandy et al. 2011).

The latter property has medical applications, where HPO is beneficial in the therapeutic or prophylactic antiseptic treatment of human and animal subjects, for example in the prevention and treatment of enveloped virus infections (herpes simplex and human immunodeficiency virus infections) (Allen 1999).

Moreover, HPOs, by consuming H_2O_2, play a role in regulating ROS production in algal cells. The overproduction of ROS, especially H_2O_2, is toxic to cells. Thus, these enzymes regulate the production of ROS by oxidation processes (La Barre et al. 2010).

HPOs are found extensively in brown algae [e.g., *Ascophyllum nodosum* (Vilter 1984), *Sacchoriza polyschides* (Almeida et al. 1998), *Pelvetia canaliculata* (Almeida et al. 2000), *Laminaria* spp. (De Boer et al. 1986; Almeida et al. 2001)] and red algae [e.g., *Corallina* spp.(Rush et al. 1995)] as well as in nonalgal species such as Gram-negative bacteria [e.g., *Pseudomonas aureofaciens* (van Pee and Lingens 1985)] and streptomycetes [e.g., *Streptomyces aureofaciens* (Krenn et al. 1988)], the marine snail *Murex trunculus* (Jannun and Coe 1987), the lichen *Xanthoria parietina* (Plat et al. 1987), and the ascomycetous fungus *Curvularia inaequalis* (Messerschmidt and Wever 1996).

Vanadium-Dependent Haloperoxidases

In 1984, the first HPO (*An*I) was identified from *Aschophyllum nodosum* (Everett et al. 1990; Butler and Walker 1993; Leblanc et al. 2015; Sigel and Sigel 1995; ten Brink et al. 1998; Walker and Butler 1996; Vilter 1984). The enzyme has vanadium (V) as cofactor, allowing it to oxidize iodide, bromide, and thiocyanide. The apoenzyme with addition of iron and other metals did not show activity (Leblanc et al. 2015). The vanadium bound to bromoperoxidase molecules has a physiological role in the chemical defense mechanism of *Ascophyllum nodosum* (De Boer et al. 1986).

Renirie et al. (2000) reported that the H_2O_2 binds firstly to vanadium, and having been activated, proceeds to oxidize the halides. Vanadium in the presence of H_2O_2 produces perhydrolases and hypohalous acid through the oxidation of halides. It has a similar function to acid phosphatases. The affinity for the vanadate cofactor is higher in the presence of H_2O_2, associated with pervanadate uptake by the apoenzyme (Renirie et al. 2000). According to Vreeland et al. (1998) and Tarakhovskaya (2014), the HPO catalytic reaction helps the adhesive attachment of fucoid zygotes to the substratum by enhancing the irreversible cross-linking of phlorotannins and alginates (Tarakhovskaya et al. 2015).

Biochemical Characterization of Vanadium Haloperoxidases

The biochemical properties of vanadium haloperoxidase have only been investigated in a few species, due to the difficultly in purifying the enzymes (Potin and Leblanc 2006). As shown in Table 1, different algae possess different types of haloperoxidases, and some studies have shown that certain species possess more than one type of V-HPO (Almeida et al. 1998, 2000; Colin et al. 2003).

According to Collén and Davison (1999a, b) and Lohrmann et al. (2004), the cellular concentration and composition of antioxidative compounds (and HPO) in seaweeds are highly species-specific and are influenced by environmental changes (Bischof and Rautenberger 2012). The optimal pH for the HPO enzyme to quench H_2O_2 ranged from 6.2 (BPO isoenzyme I, *Ascophyllum nodosum* I) to 7.2 (BPO isoenzyme II, *Ascophyllum nododsum* II) (Hartung et al. 2008). In 1989, de Boer et al. stated that increases in temperature and levels of organic co-solvents had little influence on the catalytic activity of BPO from *Ascophyllum nodosum*.

Table 1 Types of haloperoxidase found in algae. Multiple forms in the same species are indicated as, e.g., Lh1, Lh2

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
Brown algae (Phaeophyta)	*Ascophyllum nodosum*	VBPO	SDS-PAGE = 40 kDa	50 °C = Fully active 70 °C = activity decreases partially, 38% of the activity still remained At high temperature, enzyme was rapidly inactivated	BPOI pH opt = 6.0–7.6 K_m (Br^-) = 12.7 ± 3.0 mM (independent of pH) K_m (H_2O_2) = increase linearly with pH	Wever et al. (1985)
		VBPOI	97 kDa		BPOI pH opt = 6.0 K_m (Br^-) at pH 7.2 = 14.8 mM K_m (H_2O_2) at pH 7.2 = 27 μM	Tromp et al. (1990), Krenn et al. (1989)
		VBPOII	106 kDa	BPOII 50 °C = fully active 60 and 70 °C = activity decreases partially 80 °C = fully lost	BPOII pH opt = 7.2 K_m (Br^-) = 6.7 mM K_m (H_2O_2) = 27 μM	Krenn et al. (1989)
		VBPOII	67.4 kDa		BPOII pH opt = 5.9 K_{cat} = 153 s^{-1}	Wischang et al. (2012)
		VBPO	60 kDa			Weyand et al. (1999), Almeida et al. (2001)
		VBPO	Native PAGE = 90 kDa SDS-PAGE = 40 kDa		BPOII pH opt = 5.9 K_{cat} = 153 s^{-1}	De Boer et al. (1986)
	Laminaria digitata	VIPO VBPO (more dominant of iodide)	145 kDa	Full active up to 60 °C Retained highest activity up to 80 °C	pH opt = 6.2 K_m (I^-) = 2.5 mM K_{cat} (I^-) = 462 s^{-1} pH opt = 6.2 K_m (I^-) = 18.1 mM K_{cat} (I^-) = 38 s^{-1}	Colin et al. (2005), Jordan et al. (1991)
	Laminaria hyperborea (Lh)	VIPO	Native = 169 and 58 kDa SDS = 67 kDa		pH opt = 5.5 Lh1 K_{app} M (I^-) = 1.9 mM K_{app} M (H_2O_2) = 334 μM V_{max} = 0.98 μM/s Lh2 K_{app} M (I^-) = 2.3 mM	Almeida et al. (2001)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
					K_{app} M (H_2O_2) = 285 μM V_{max} = 1.21 μM/s pH = 6.1 Lh1 K_{app} M (I^-) = 3.4 mM K_{app} M (H_2O_2) = 275 μM V_{max} = 1.60 μM/s Lh2 K_{app} M (I^-) = 3.8 mM K_{app} M (H_2O_2) = 217 μM V_{max} = 1.75 μM/s pH = 6.7 Lh1 K_{app} M (I^-) = 3.5 mM K_{app} M (H_2O_2) = 166 μM V_{max} = 0.94 μM/s Lh2 K_{app} M (I^-) = 3.8 mM K_{app} M (H_2O_2) = 173 μM V_{max} = 1.08 μM/s	
	Laminaria ochroleuca	VIPO	Native = 133 kDa SDS = 65 kDa			Almeida et al. (2001)
	Laminaria saccharina (Ls)	VIPO	Ls1 = 64 kDa	Stable temperature = 25–50 °C Increased activity at temperature 30–50 °C, maximum at 40 °C Above 50 °C activity dropped drastically	pH opt = 5.5 Ls1 K_{app} M (I^-) = 1.3 mM K_{app} M (H_2O_2) = 376 μM V_{max} = 0.76 μM/s Ls2 K_{app} M (I^-) = 1.9 mM K_{app} M (H_2O_2) = 333 μM V = 1.12 μM/s pH = 6.1 Ls1 K_{app} M (I^-) = 3.4 mM	De Boer et al. (1986), Almeida et al. (2001)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
					K_{app} M (H_2O_2) = 243 μM V_{max} = 0.91 μM/s Ls2 K_{app} M (I^-) = 2.7 mM K_{app} M (H_2O_2) = 273 μM V_{max} = 1.21 μM/s pH = 6.7 Ls1 K_{app} M (I^-) = 3.7 mM K_{app} M (H_2O_2) = 120 μM V_{max} = 0.83 μM/s Ls2 K_{app} M (I^-) = 4.3 mM K_{app} M (H_2O_2) = 137 μM V_{max} = 0.71 μM/s	
			Ls2 = 66 kDa	Above 50 °C activity dropped drastically		Jordan et al. (1991), Almeida et al. (2001)
	Chorda filum					De boer et al. (1986)
	Pelvetia canaliculata	VIPOI	166 kDa	Active up to 40 °C PcI 60 °C = activity decreases 70 °C = activity fully lost	PcI pH opt = 6.0 K_m (I^-) = 2.1 mM K_m (H_2O_2) = 110 mM K_i (I^-) = 127 mM	Almeida et al. (2000)
		VIPOII	416 kDa	PcII 70 °C = 40% activity still remained	PcII pH opt = 6.5 K_m (I^-) = 2.4 mM K_m (H_2O_2) = 20 μM K_i (I^-) = 69 mM	
	Fucus distichus	VBPO	65 kDa		pH opt = 6.5 pH = 4	Soedjak and Butler (1991)
					Km (Br^-) = 0.67 (0.07) mM Km (H_2O_2) = 1.9 (0.3) mM V_{max} = 0.11 μM/s pH = 5 K_m (Br^-) = 0.72 (0.05) mM	Soedjak and Butler (1990)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
					K_m (H_2O_2) = 0.53 (0.02) mM V_{max} = 0.31 μM/s pH = 5.5 K_m (Br^-) = 0.71 (0.15) mM K_m (H_2O_2) = 0.26 (0.03) mM V_{max} = 0.42 μM/s pH = 6 K_m (Br^-) = 0.90 (0.05) mM K_m (H_2O_2) = 0.43 (0.002) mM V_{max} = 0.52 μM/s pH = 6.5 K_m (Br^-) = 1.74 (0.07) mM K_m (H_2O_2) = 0.018 (0.006) mM V_{max} = 0.56 μM/s pH = 7 K_m (Br^-) = 3.19 (0.25) mM K_m (H_2O_2) = 0.028 (0.001) mM V_{max} = 0.62 μM/s pH = 8 K_m (Br^-) = 16.54 (0.17) mM K_m (H_2O_2) = 0.019 (0.001) mM V_{max} = 0.43 μM/s	
	Macrocystis pyrifera	BPO	74 kDa		pH opt = 6.0	Soedjak and Butler (1991)
	Laminaria saccharina	BPO	108 kDa			De Boer et al. (1986)
	Ecklonia stolonifera	BPO	83 kDa	Activity completely lost at 80 °C Optimum temperature (T_m) = 68 °C	pH opt = 6.5 K_m (MCD) = 0.12 μM V_{max} = 16.67 μM/s (mg^{-1}) K_m (H_2O_2) = 52 μM V_{max} = 26.67 μM/s (mg^{-1}) K_m (Br^-) = 1.0 μM V_{max} = 18.33 μM/s (mg^{-1})	Hara and Sakurai (1998)
	Saccorhiza polyschides: Phyllariaceae	VIPOI	125 kDa	Maximum activity up to 50 °C At 70 °C half of activity remains	SpV_1 pH opt = 6.1	Almeida et al. (1998)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
					K_m (I^-) = 3.25 mM K_m (H_2O_2) = 478 μM K_{cat} = 16.2 S^{-1} SpV_2 pH opt = 6.1 K_m (I^-) = 3.35 mM K_m (H_2O_2) = 494 μM K_{cat} = 91.0 S^{-1} SpV_3 pH opt = 6.1 K_m (I^-) = 5.74 mM K_m (H_2O_2) = 84 μM K_{cat} = 91.5 S^{-1}	
	Alaria esculanta	VIPOII				Wever (unpublished work; applications for (halo) peroxidase)
Red algae (Rhodophyta)	*Corallina officinalis*	VBPO	64 kDa	Stable temperature at 80 °C Active up to 70 °C but 60% maximum activity lost Maximum activity at 65 °C	Optimal pH 6.5 K_m (Br^-) at pH 6.5 = 1.2 mM K_m (H_2O_2) at pH 6.5 = 17.0 μM Partially purified pH opt = 6.23 ± 0.01 (1 SD, n = 5) k_o = 28.0 ± 0.5 nmol μg^{-1} min^{-1} (1 SD, n = 5) K_s = 8.04 ± 0.20 μM (1 SD, n = 5) r^2 = 0.999 s = 6.23 ± 0.01 (1 SD, n = 5) r^2 = 1.09 ± 0.01 (1 SD, n = 5) n = number of days	Isupov et al. (2000) Yu and Whittaker (1989) Coupe et al. (2007) Carter et al. (2002) Rorrer et al. (2001)
	Corallina pilulifera	VBPOI (recombinant)	65,312 Da Native = 64 kDa			Littlechild and Garcia-Rodriguez (2003)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
		VBPOII				Shimonishi et al. (1998)
						Carter et al. (2002)
	C. vancouveriensis	VBPO				Everett et al. (1990)
	Cystoclonium purpureum	Heme-BPO				Pedersén (1976)
	Rhodomela larix	Heme-BPO		Optimum temperature = 32 °C	Optimum pH = ~4.4	Ahern et al. (1980)
	Gracilaria fisheri	VBPO	64 kDa	Active up to 40 °C Optimum temperature = 55 °C	Optimum pH = 6.0 pH stability = 5–10 for 24 h at 4 °C	Kongkiattikajorn and Pongdam (2006)
				Temperature stability = 50 °C at 30 min	$K_m = 2.74 \times 10^{-4}$ M $V_{max} = 8.87 \times 10^{-4}$ μM/s (ml^{-1}) Inhibitor = EDTA	
			SDS = 68 kDa			Suthiphongchai et al. (2008)
	Gracillaria edulis	BPO				
	Gracillaria firma	BPO				
	Gracillaria salicornia					
	Gracillaria tenuistipitata	VBPO1	70 kDa	Optimum temperature = 50 °C Stable temperature = 45 °C	pH opt = 5.5 K_m (Br^-) = 2.17×10^{-4} M K_m (H_2O_2) = 1.0×10^{-4} M K_m (MCD) = 2.94×10^{-5} M	Kongkiattikajorn and Pongdam (2006)
		VBPO2	48 kDa	Optimum temperature = 45 °C Stable temperature = 45 °C	pH opt = 7.0 K_m (Br^-) = 4.72×10^{-5} M K_m (H_2O_2) = 2.47×10^{-5} M K_m (MCD) = 8.52×10^{-4} M	
	Gracilaria changii (recombinant)	GCVBPO1	84 kDa		pH opt = 7 K_m (I^-) = 0.08 mM V_{max} = 12.61 μM/s (mg^{-1}) K_m (H_2O_2) = 0.71 mM V_{max} = 10.62 μM/s (mg^{-1}) K_m (Br^-) = 4.69 V_{max} = 10.62 μM/s (mg^{-1}) K_m (Cl^-) = no activity V_{max} = no activity	Baharum et al. (2013)
	Delisea pulchra	VBPO	65,458 Da			Sandy et al. (2011)

Table 1 (continued)

Sources	Species	Activity/type of enzyme	Relative molecular weight	Thermal stability (maximum stability up to)	Kinetic parameters for different types of HPO oxidation at their respective optimum pH	References
	Ceramium rubrum	VBPO	58 kDa	Remain activity = 25 °C Rapidly inactivated at = 55 °C	pH stable = 6.0–8.3 K_m (H_2O_2) = 17 μM	Krenn et al. (1987)
	Ochtodes secundiramea	VBPO	65 kDa	Temperature 22 °C	pH opt = 5.98 ± 0.35 (1 SD, n = 6) K_s = 18.1 ± 1.57 μM (1 SD, n = 4) r^2 = 0.994 s = 0.733 ± 0.234 (1 SD, n = 6) r^2 = 0.903 n = number of days	Rorrer et al. (2001)
Green algae (Chlorophyta)	*Penicillus capitatus*	BPO	Native = 97.6 kDa SDS = 55 kDa			Manthey and Hager (1981)
	Penicillus capitatus	BPO	52 kDa	Remain activity up to 60 °C	pH opt = 4 K_m (H_2O_2) = 0.125 mM K_m (Br^-) = 30 mM	Baden and Corbett (1980), Manthey and Hager (1981), Beissner et al. (1981)
	Penicillus lamourouxii	BPO	48 kDa		pH opt = 4 K_m (H_2O_2) = 0.125 mM K_m (Br^-) = 15 mM	Baden and Corbett (1980)
	Rhipocephalus phoenix	BPO	60 kDa		pH opt = 5–6 K_m (H_2O_2) = 0.25 mM K_m (Br^-) = 30 mM	Baden and Corbett (1980)
	Ulvella lens					Ohshiro et al. (1999)

VBPO, vanadium-dependent bromoperoxidase; K_i, inhibitor constant; *Lh2*, *Laminaria hyperborea* 2; *VIPO*, vanadium-dependent iodoperoxidase; K_{app} M, Apparent kinetic parameters; *PcI*, *Pelvetia canaliculata* I; *VCPO*, vanadium-dependent chloroperoxidase; *MCD*, monochlorodimedone; *PcII*, *Pelvetia canaliculata* II; *SDS*, sodium dodecyl sulfate; *pH opt*, optimum pH; SpV_1, *Saccorhiza polyschides* 1 collected at Viana do Castelo; K_m, substrate concentration at 1/2 the maximum velocity; K_o, forward rate constant; SpV_2, *Saccorhiza polyschides* 2 collected at Viana do Castelo; K_{cat}, catalyst constant; K_s, half-saturation constant; SpV_3, *Saccorhiza polyschides* 3 collected at Viana do Castelo; V_{max}, maximum reaction velocity; r^2, nonlinear regression; *Ls1*, *Laminaria saccharina* 1; *S*, substrate; *Lh1*, *Laminaria hyperborea* 1; *Ls2*, *Laminaria saccharina* 2; *()*, number in parentheses is standard error

The mechanism of V-HPO during the catalytic cycle is known as a bi-bi ping-pong mechanism and has been well described by Leblanc et al. (2015). In vitro assays have been developed for HPOs, which are based on the reactivity of the intermediates (a mixture of halogen species), and a colorimetric assay was established for IPO and BPO activities using thymolsulfonephthalein as a reagent (Verhaeghe et al. 2008b).

Two V-BPO isoenzymes that have been identified from various parts of the thallus of the brown seaweed *A. nodosum* (Tromp et al. 1990) have different biochemical and structural properties and biological roles in the physiology of the alga (Wischang et al. 2012). The purified native V-BPO isoenzyme can catalyze the bromination of pyrroles (Wischang et al. 2011) or phenols (Wischang and Hartung 2012). *Laminaria digitata* produced two isoforms of V-BPO (Colin et al. 2003) and another isoform which is specific for iodide oxidation (and leads to accumulation of iodide in outer tissues) (Colin et al. 2005). Red and brown algae have V-IPO similar to that from the marine flavobacterium *Z. galactanivorans*. V-BPO isolated or cloned from *Laurencia*, *Plocamium*, and *Corallina* (Carter-Franklin and Butler 2004) in in vitro studies showed catalysis of asymmetric bromination and cyclization of certain terpenes, including nerolidol, leading to the biosynthesis of brominated cyclic sesquiterpenes. Halogenated compounds can interfere with bacterial signaling systems, e.g., V-BPO from *L. digitata* deactivates acylated homoserine lactones (cell-to-cell signaling molecules), and control biofilm formation and growth in Gram-negative bacteria (Borchardt et al. 2001; Salaün et al. 2012).

Tissue and Cellular Localization of V-HPOs

HPOs occur naturally in different parts of the algal thallus, depending on the species. Mostly HPOs are found close to the thallus surface in regions such as near the cuticle in the external cortex in *Laminaria* (Almeida et al. 2001). Krenn et al. (1989) tested *Ascophyllum nodosum* and found the enzyme activity to be localized on the surface of the cell wall of the outer part of the thallus as well as inside the alga between the cortex and the medulla and especially around the conceptacles. In a follow- up study on another brown alga *Pelvetia canaliculata*, enzyme activity was found to be located on the surface cuticle of the thallus (Almeida et al. 2000) and, in *L. hyperborea*, around the mucilaginous channels (Bischof and Rautenberger 2012). BPO has also been found throughout the blades of *Saccharina latissima* and *L. digitata* (Bischof and Rautenberger 2012; Jordan et al. 1991; Mehrtens and Laturnus 1998).

Upregulation of Vanadium Haloperoxidases in Response to Pathogens

Molecular studies have contributed to understanding the transcriptional and transductional regulation of V-HPO in macroalgae. Higher eukaryotes release exogenous or endogenous elicitors as defense against invading pathogens. The general or exogenous elicitors, called microbe-associated molecular patterns (MAMPs), elicit an array of secondary signaling pathways and defense responses. On the other hand, endogenous elicitors are referred to as pathogen-induced molecular patterns (PIMPs) (Mackey and McFall 2006). In the marine brown alga *Laminaria digitata*, ROS production is activated by a chain of signaling events triggered by oligoguluronates (GG) derived from the alginate oligosaccharides (Küpper et al. 2001). The signaling events include modification of ion fluxes across the plasma membrane and the activation of phospholipases and kinases. This occurs along with MAMPs to trigger an oxidative burst and fatty acid oxidation in *L. digitata* (Küpper et al. 2006). PIMP and MAMP have also been observed in the red macroalgae *Gracilaria conferta* (Weinberger et al. 2005a, b; Weinberger et al. 2001), *Solieria chordalis* (Ar Gall et al. 2008), and *Chondrus crispus* (Bouarab et al. 1999, 2004).

Macroalgae are exposed to biotic stresses from viruses, bacteria, fungi, oomycetes, chytrids, and algae in the form of endo- or epiphytes. Previous studies on the responses of brown and red macroalgae to pathogens were based on models and measurements of elicitors from short-term experimental studies (Weinberger and Friedlander 2000; Küpper et al. 2001). In a recent study with *Ectocarpus siliculosus* infected with *Eurychasma dicksonii*, the host-pathogen interaction resulted in upregulated halogen metabolism in response to the stress (Strittmatter et al. 2016). Vanadium-dependent haloperoxidases are prominent brown algal stress markers in *Laminaria* and *Ectocarpus* (Crépineau et al. 2000; Roeder et al. 2005; Cosse et al. 2009) and were shown to be involved during the pathogenic infection in the study of Strittmatter et al. (2016). BPO was excreted when H_2O_2 was produced in response to the *Eurychasma* infection. The BPO removes ROS and releases antimicrobial halogenated compounds (Strittmatter et al. 2016). The production of BPO was enhanced by copper stress and with accumulation of H_2O_2 and linolenic acid (Mithöfer et al. 2004; Ritter et al. 2010; Zambounis et al. 2013). This was further supported by Cosse et al. (2009), in their study showing that V-BPO production increased by scavenging H_2O_2 resulting from *Eu. dicksonii* infection. The source of H_2O_2 in these studies appears to be from NADPH oxidase-dependent superoxide, as was reported in *Laminaria digitata* (Küpper et al. 2002). V-BPO is the only upregulated protein in *Ec. siliculosus* in response to *Eu. dicksonii*. Although this is similar to the elicitor-based transcriptome studies in *Laminaria digitata* (Cock et al. 2010), multigene haloperoxidases (IPO and BPO) were observed in the latter study (Crépineau et al. 2000; Roeder et al. 2005; Cosse et al. 2009). The ROS produced by *Ectocarpus* in response to *Eurychasma* infection has a function in defense signal transduction and intracellular communication (Orozco-Cárdenas et al. 2001).

More than 3000 expressed sequence tags (ESTs) are available from different life-cycle phases of *L. digitata* (Crépineau et al. 2000) and from protoplasts which are enriched with stress- and ROS detoxifying-related genes (Roeder et al. 2005). The EST libraries were enriched using PCR-based suppression subtractive hybridization (SSH). This is to differentiate distinctly expressed genes by responding to GG using a DNA microarray (exposed to stress responses and GG-induced defense responses). The results showed that defense responses such as antioxidant mechanisms or signaling were conserved at the molecular level along with novel defense traits that involve tight transcriptomic regulation of V-HPO gene families (Cosse et al. 2009).

Halogenation Mechanism in Macroalgae

The Production of Reactive Oxygen Species and Their Relation with Haloperoxidase Activity

Haloperoxidases use H_2O_2, generated by various cellular reactions contributing to the formation of ROS, as their substrate (Thannickal and Fanburg 2000). Given the central role of H_2O_2 in HPO-catalyzed reactions, it is thus relevant to consider here factors that supply the substrate, H_2O_2, for HPO activity. ROS are highly reactive species of molecular oxygen such as singlet oxygen (O_2), superoxide anion radicals (O_2^-), hydroxyl radicals (^-OH), and hydrogen peroxide (H_2O_2) (Maharana et al. 2015).

Marine seaweeds predominantly in intertidal zones, during tidal fluctuations, are repeatedly subjected to direct sunlight, aberrant temperatures, and emersion. In addition, precipitation also brings changes in salinity levels, ambient water quality, and mineral composition. These changes affect the normal metabolic functions in algae creating oxidative stress and increasing ROS production (Maharana et al. 2015) by noncyclic photosynthetic and Mehler reaction.

HPOs and Other ROS Scavengers in Seaweeds

ROS are scavenged through either antioxidants or enzyme systems which evolved as defense mechanisms in macroalgae (Maharana et al. 2015). Antioxidants like tocopherol, ascorbate, glutathione, and beta-carotene act as effective ROS scavengers (Apel and Hirt 2004; Gechev et al. 2006). Red algae produce mycosporine like amino acids (MAAs) in response to UV radiation stress (Bischof and Steinhoff 2012), and these compounds, in addition to their primary function as UV-screening compounds, also possess antioxidant characteristics (De la Coba et al. 2009; Bischof and Rautenberger 2012). Antioxidant systems also involve several enzymes, such as catalase (CAT), ascorbate peroxidase (APX), secretory peroxidases (POX), glutathione reductases (GR), and peroxiredoxines (Prx) (Aguilera et al. 2002; Dummermuth et al. 2003).

SOD catalyzes the conversion of O_2^- to H_2O_2. This H_2O_2 is reduced via CAT activity into water and molecular oxygen, e.g., in *Fucus vesiculosus* (Collén and Davison 2001; Maharana et al. 2015). *Glutathione peroxidase* (GPX), which rarely occurs in seaweeds (Contreras et al. 2009; Yende et al. 2014), reduces H_2O_2 to water and organic peroxides to alcohols. Glutathione [regenerated by *glutathione reductase* (GR) from oxidized glutathione] functions in various metabolic reactions involving endogenous hydroperoxides and scavengers of ROS (Aravind and Prasad 2005; Maharana et al. 2015). Thylakoid-associated ascorbate peroxidase (APX) is situated near to SOD in the neighborhood of PSI. It can thus reduce the effects of H_2O_2 diffusing across biological membranes (Dring 2005; Lesser 2012).

According to Ross and Alstyne (2007), some seaweeds have another mechanism of disposing ROS, i.e., excreting the H_2O_2 into the surrounding water. For instance, this was shown to be the case for the chlorophyte *Ulva rigida*. These authors found that H_2O_2 was expelled from the thallus into the surrounding water, where the concentration of H_2O_2 increased up to 4.0 μM (Collén et al. 1995; Collén and Pedersén 1996; Bischof and Rautenberger 2012). Meanwhile, in some brown algae, SOD and CAT do not function in scavenging ROS. In *Laminaria digitata* gametophytes, although a gene which codes for SOD has been isolated (Bartsch et al. 2008; Bischof and Rautenberger 2012), analysis of 1985 gene transcripts did not show expression of any of these ROS scavenging enzymes (Bischof and Rautenberger 2012; Roeder et al. 2005). Instead, the Phaeophyceae produce HPO enzymes to scavenge ROS (Almeida et al. 2001). In the Phaeophyceae and Rhodophyceae, H_2O_2 is scavenged by V-HPO.

Küpper et al. (2001) found that the addition of extracellular elicitors (e.g., oligoguluronates), which mimicked pathogen attack, and oxidants (e.g., H_2O_2) caused the release of iodide from Laminarian algae into the surrounding seawater within seconds. Although this iodide is not toxic to prokaryotes and eukaryotes, iodocarbons have the characteristic of preventing microbial growth (Leblanc et al. 2006). Iodocarbons such as CH_2I_2 (diiodomethane) and CH_3I (iodomethane) are generated after exposure of algae to oligoguluronate (Palmer et al. 2005). Iodide acts as an antioxidant in the apoplast of *L. digitata* and is able to scavenge ROS quickly by nonenzymatic reactions. At the end of oxidative stress exposures, those iodide molecules that were released into the seawater will be taken up again into the apoplasm and reassociated with biomolecules (Küpper et al. 2008).

Iodide has been found to be a better antioxidant than bromide (Küpper et al. 2008, 2013). High concentrations of Br^- function as an antioxidant against superoxide (formed in an oxidative burst), while both I^- and Br^- in high concentrations are useful in defense against hydroxyl radicals (synthesized

from hydrogen peroxide from Fenton chemistry). Thus, the strategy is to keep these halides in inactive forms by binding to organic entities and release them in high amounts in response to stress. The combined release of both halides would have the additional function of targeting more ROS species (Küpper et al. 2013).

Factors that Induce Uptake of Halides

Marine organisms use halides like bromine to enhance the biological activity of secondary metabolites. Brown algae such as Laminariales have developed a way to accumulate and use iodine from seawater for physiological adaptation to stress (La Barre et al. 2010). Seawater has high concentrations of halide ions which are important in geochemical cycles (Leblanc et al. 2006). The average concentrations of halides, based on Goldberg (1963), are 0.5359 mol/L for Cl^-, 8.135×10^{-4} mol/L for Br^- and 4.728×10^{-7} mol/L for I^-, and 3.431×10^{-7} mol/L IO^-_3 (Fenical 1975), and 4.57×10^{-7} mol/L of iodine (Leblanc et al. 2006).

In a study conducted on species including *Asparagopsis* and *Bonnemaisonia*, molecular iodine appeared to be in high concentration and accounted for 0.3–0.5% of the fresh weight (Fenical 1975). In another study (Burreson et al. 1975), *A. taxiformis* from the Gulf of California, Mexico, showed the presence of I_2 in large amounts in chloroform extracts of the alga (Fenical 1975). Members of the Laminariales can accumulate iodide into the apoplast to level 30,000 times greater than in natural seawater, but the extent of such accumulation depends on the age of the sporophyte and the region of the thallus, wave exposure, geographic location, and depth (Gall et al. 2004; Küpper et al. 1998). In a study conducted by Küpper et al. (2008), an approximately 1% dry weight (apoplastic concentration 20 mM) iodine content was detected in *Laminaria digitata* sporophytes collected from Helgoland (German Bight) and Roscoff (Brittany, France) with considerably higher concentrations (up to around 5% dry weight) found in young plants (Küpper et al. 1998).

Other species known to contain iodide are *Ectocarpus* and *Fucus* but at only a fraction of the concentration found in the Laminariales (Saenko et al. 1978; Bischof and Rautenberger 2012; Cock et al. 2010). In contrast, BPOs are encoded in the genome of *Ectocarpus siliculosus* (Bischof and Rautenberger 2012; Cock et al. 2010), and these use less iodine and more bromide compared to IPOs. It has been suggested that in kelp, iodide constitutes as an extracellular protection against oxidative stress, and as such, it was the first known inorganic antioxidant in living systems (Küpper et al. 2008).

Iodide ion is noncovalently bound to biomolecules such as phenolic compounds, polysaccharides, and protein in the apoplast (Küpper et al. 2008, 2013). This accumulation prepares the species to release the bound iodide as chemical defense under oxidative stress conditions during high tide (Küpper et al. 1998; Verhaeghe et al. 2008a, b). In unstressed and submerged conditions during high tide, *Laminaria digitata* takes up iodide from seawater by facilitated diffusion down the concentration gradient to the apoplast (Küpper et al. 1998). IPOs then catalyze the oxidation of iodide. However, in order for the reaction to proceed, a supply to the apoplast of H_2O_2 of at least ~ 5 μM is required (Küpper et al. 1998).

In order for HPOs to oxidize more electronegative halides, more acidic pH values are needed (Meister and Butler 1994). The IPOs specifically assimilate iodide due to their special halide-binding site topology and the fine alteration of the vanadate cofactor electronegativity (Colin et al. 2005). V-IPOs have lower affinity and a higher oxidizing rate than V-BPOs (Colin et al. 2003).

Recently, researchers have focused on the fine structure of the active site, to investigate halide selectivity according to the types of HPOs (Butler and Carter-Franklin 2004). Different HPOs have various associated amino acids which play a role when the halide does not bind to the vanadate (Wischang et al. 2012). Although site-directed mutagenesis could not identify an amino acid residue responsible for halide specificity, the answer may be obtained through other studies on the hydrogen-bonding network at the active site and the redox state and charge distribution at the vanadate center, that may influence halogen specificity (Baharum et al. 2013; Tanaka et al. 2003). The low redox potential of the peroxovanadium center in VIPO is chemically unfavorable for bromide and chloride oxidation. This clearly shows that changes in amino acid residues and stabilization of the peroxovanadium intermediate could change the redox state and prevent halide binding (Leblanc et al. 2006).

Selectivity of Halides and Vanadium by V-HPO

Halide complexes with alkali metal ions are very stable. Dissociation of complexes such as tetraiodidomercurate, $[Hg(II)I_4]^{2-}$, or tetrachloridothallate, $[Tl(III)Cl_4]^-$, is hardly detected (Küpper and Kroneck 2014). Iodide anions being weak coordinating ligands form many robust metal complexes and disproportionated hydrogen peroxide with V-HPO when organic co-substrates are absent (Küpper and Kroneck 2014). Halide ions are the second substrate to attach to the active site through a nucleophilic attack on the partially positive oxygen atom (Winter and Moore 2009). In order to oxidize more electronegative halides, more acidic conditions are needed because halide oxidation is pH dependent (Slebodnick et al. 1997). Vanadate ($HVO_4^{2-}/H_2VO^-_4$) at neutral pH is not catalytically effective in oxidizing bromide although species of vanadium (V) are found at neutral pH (Butler 1999). Vanadate coordinates two equivalents of peroxide at neutral pH forming oxodiperoxovanadium (V), $VO(O_2)_5^-$ without oxidizing bromide (Butler 1999). Many transition metals act as effective catalysts for oxidation of halides by hydrogen

peroxide; they thus serve as functional biomimics of the haloperoxidases (Butler 1999).

Halides bind at hydrophobic sites of some proteins such as haloalkanes dehalogenase and some amylases (Butler 1999). According to Messerschmidt and Wever (1996), the hydrophobic residues Tip-350 and Phe-397 form chloride-binding regions with His-404 in V-CPO (Butler, 1999), but the gene sequence of V-BPO (*A. nodosum*) showed differences (Butler, 1999). The study of extended X-ray absorption fine structure (EXAFS) revealed that bromide binds near to the vanadate center in the bromoperoxidase of *Ascophylum nodosum* (Littlechild et al. 2009) and the oxidized bromide attacks the peroxyvanadate center (Littlechild et al. 2009). This structural information provides a basic understanding on halide selectivity for *Corallina* bromoperoxidse and a mutant enzyme of *C. pilulifera* bromoperoxidase (Littlechild et al. 2009).

A nonenzymatic pathway allows halides to bind to organic substrates without chiral induction (Fujimori and Walsh 2007). In addition to understanding the mechanism of V-HPO activity, other important characteristics to consider include the specificity of the halide ion and the preference for vanadate as cofactor, despite the superior reactivity of molybdate (Plass 2009). V-HPO catalyzes the oxidation of halides, namely I^-, Br^-, and Cl^-, spanning a range of 0.53–1.36 V (Küpper and Kroneck 2014). In order to understand the origin of halide selectivity, the structural and biochemical aspects of the residues in the vicinity of the active site in V-CPO, V-BPO, and V-IPO were studied (Küpper and Kroneck 2014). It was shown that halide does not directly bind to vanadate as predicted, as the neighboring amino acids may act in substrate selectivity and as investigated through site-directed mutagenesis. Redox potential is important for halide selectivity and is influenced by the differences in amino acid residues at the active site and in stabilization of the peroxovanadium intermediate (Küpper and Kroneck 2014). However, there are other studies on halide selectivity along with evidence from the crystallographic information gathered for V-CPO from *C. inaequalis* and V-BPO from *A. nodosum*, that suggest that the outer sphere of the active site structure is the source of halide specificity (Plass 2009).

The subtle changes in electronic structure of the vanadate cofactor and the His404 residue (at resting state) result in protonation and create an environment of latent apical water molecules (Plass 2009). The strong hydrogen-bonding donors triggered by hydrogen peroxide (or even the halide ion) stabilize the resting state of latent water molecules. This condition also explains why the triple mutant P395D/L241V/T343A of the V-CPO of *C. inaequalis* functions at high pH conditions.

The vanadium model has bromine in different coordination spheres in comparison with the enzyme from *A. nodosum* observed through recent bromine K-edge XAS studies. This supported the observation of the absence of a bromine shell in the expected distance of ca. 2.45 Å for a direct V–Br bond in *A. nodosum* (Christmann et al. 2004). The vanadium center can activate asymmetrically bridged peroxide found in the dimer for nucleophilic attack by halides (Butler 1998). As a result the vanadium-bound peroxide in V-HPO activates hydrogen bonding (Butler 1998). The vanadium coordination appeared the same for both *A. nodosum* and *Curvularia inaequalis* (Rehder 1999). Structural studies on the peroxo enzyme predicted that peroxovanadium complexes can be active intermediates in halide oxidation by vanadate-dependent peroxidases, as well as for in vitro oxidation reactions with various organic substrates. Vanadium acts as catalyst for oxidation in the presence of oxygen or peroxides (Rehder 1999).

V-HPOs that are robust against oxidative inactivation during turnover have the potential to be suitable biocatalysts in pharmaceutical applications (Winter and Moore 2009). V-HPOs use Lewis acid-promoted mechanism to catalyze the 2-electron oxidation of a halide (Slebodnick et al. 1997). V-HPO was detected with the intense oxidation of *o*-dianisidine observed in in-gel assays when acetate was present along with halide during the staining procedure (Weinberger et al. 2007). Halogenated compounds are produced in response to oxidation of halides in acidic solution of *cis*-dioxovanadium (V) (*cis*-VO_2^+) (Butler 1998). Monohalogenated compounds are formed as a result of protonation of aryl anions (Fujimori and Walsh 2007). These anions are produced in the process of trapping of *p*-benzene intermediates by halide nucleophiles (Fujimori and Walsh 2007).

Halocarbon Production in Macroalgae

Rates of halocarbon production may vary based on species and geographical locations. Selected environmental stresses such as salinity, nutrient depletion, and desiccation influence halocarbon production as an antioxidant process associated with the defense mechanism (Leedham et al. 2013; Mata et al. 2012). In the past 30 years, many studies have been carried out to understand the biogenic processes in seaweeds from polar and temperate regions, which release volatile low molecular weight halocarbons, including the methyl halides (e.g., methyl iodide, CH_3I) and polyhalogenated compounds (e.g., bromoform, $CHBr_3$) (Baker et al. 2001; Carpenter and Liss 2000; Gschwend et al. 1985; Leedham et al. 2013). These halocarbons are released to the upper troposphere or lower stratosphere of the mid-latitudes and tropics (Quack et al. 2004), where they react with ozone, leading to its depletion and thus contributing to climate change. Furthermore, tropical coastal zones are now also recognized as strong sources of halocarbons (Phang et al. 2016; Yokouchi et al. 2005).

Lazrus et al. (1975) observed that a small concentration ~ 10^{-11} (*v*/v) of bromine contribution to the stratosphere caused approximately 0.3% of ozone reduction (cited in Wofsy et al. 1975). Biogenic reactive organic bromine is mostly comprised of bromoform which is a collective term for a range of

compounds consisting of $CHBr_2Cl$, $CHBrCl_2$, CH_2BrBL, and CH_2Br_2. Biogenic halocarbons all have a short atmospheric lifetime, of a time scale of 2–3 weeks to several months, during which all the compounds dissociate by photolysis and reactions with OH radicals, leading to temporal and spatial heterogeneity in biogenic production and atmospheric convective systems. This process will release free bromine which then reacts with ozone to form bromine oxide radicals (BrO).

The other mechanism leading to ozone depletion involves the reaction between ozone and bromine monoxide and decreased levels of nitrogen oxides. The heterogeneous reaction of inorganic bromine species on the surface of clouds and aerosols results in increases in tropospheric BrO. This eventually reduced ozone production (Salawitch 2006). Iodide (I^-) at macroalgal surfaces will react with atmospheric ozone to form iodine, which then forms particles (Küpper et al. 2008; McFiggans et al. 2004; Palmer et al. 2005). The I^- radical detoxifies both the aqueous oxidant and ozone, releasing molecular iodine. The iodide radicals also reacts with ozone to form iodine oxide which concomitantly can act as a promoter of cloud condensation nuclei (Küpper et al. 2008; Palmer et al. 2005). These eventually affect the oxidizing capacity of the air in the marine boundary layer and also form ultrafine particles which have the potential to impact on the radiative balance of the atmosphere (Chance et al. 2009; O'Dowd and Hoffmann 2006).

Due to their shorter atmospheric lifetimes, iodocarbons contribute only to tropospheric boundary layer chemistry (Saiz-Lopez et al. 2012).The emitted iodinated species (e.g., I_2, CH_3I, and diiodomethane, CH_2I_2) in the troposphere nonetheless have some important effects. In previous studies, iodine levels were reported to be in the range of < 0.01–12 pptv (Carpenter 2003) but have recently increased to 3–93 pptv (Saiz-Lopez et al. 2006; Chance et al. 2009).

Seaweeds collected from the Portuguese coast were shown to have lower HPO activities compared to those of algae from northern regions of the Atlantic Ocean (Almeida et al. 1998, 2000). This suggested that there is variation in terms of HPO activities due to environmental factors as well as across algal species. Previous studies mostly measured the ecological parameters that influenced the production of halogenated compounds. For instance, a study conducted by Laturnus et al. (2000), using the Antarctic red macroalgal species *Gymnogongrus antarcticus* Skottsberg with different parameters (temperature, light, salinity, and nutrient availability), showed that iodocompounds were highly affected after the algae were exposed to the different environmental conditions. The rate of release was higher when the algae had been adapted to the new environment for 2 months compared to short-term exposure. A 24-h incubation period (8.25 h light, 15.75 h darkness) did not influence the production of volatile halocarbons. In this incubation period, bromoform and 1-iodobutane were released continuously. Thus, the release was independent of light for short-term exposure in dark and light conditions (Laturnus 2001).

The alteration of environmental conditions induced higher rates of release of volatile halocarbons by macroalgae. For short-term changes, stress may be the reason for the observed higher release rates. However, during long-term exposure to altered conditions, stress cannot be the reason, as adaptation of macroalgae to changed conditions such as light occurs after 2–4 weeks (Orfanidis 1992).

The same idea was further supported by Laturnus et al. (2000) in their experiment of the influence of abiotic factors for organoiodine and organobromine released by polar molecules. The long-term incubation of algal biomass of 6×10^{13} g under varied factors with the assumption of 100% transfer from the ocean and globally was used for the determination of annual atmospheric input of iodine and bromine release rates in a global scale (Laturnus et al. 2000).

Biotic Interactions

The red alga *Plocamium pacificum* has been identified as the original source of polyhalogenated metabolites in sea hares, which sequester those compounds for their own chemical defense. The compounds 2,6-dibromophenol (2,6-DBP) and 2,4,6-tribromopyrrole (2,4,6-TBP) originating from red algae have also been found to be passed on to marine worms.

These compounds have fungicidal, bactericidal, ascaricidal, and molluscicidal effects, which act as deterrents against marine predators (Malmvärn et al. 2005). The halogenated products are not involved in primary metabolic processes but act as messengers of the exocrine system. This provides red seaweeds with environmental defenses (Fenical 1975). BPOs from the thallus surface will release HOBr into the surrounding water and lead to the synthesis of volatile halogenated compounds (Wever and Hemrika 2001). Seawater rich in organic matter such as fulvic and humic acids will react rapidly with HOBr. The HOBr and other brominated compounds produced act as bactericidal agents, and some of the halogenated compounds released by seaweeds possessed antimicrobial properties. The activity of HPOs can thus function as an antifeeding system, by preventing grazing by microorganisms (Wever and Hemrika 2001).

The Biogeochemical Significance of Halogenation in Seaweeds

Marine algae contribute approximately 70% of the world's bromoform (Carpenter and Liss 2000). *Laminaria digitata* is found in shallow coastal areas and emits biogenic halocarbons which has stimulated much research on iodine speciation. The dominant organic iodine species released by this kelp is CH_2I_2

(Carpenter et al. 1999, 2000). This supplies iodine nanoscale particles that function as cloud-forming nuclei (McFiggans et al. 2004). Cloud condensation nuclei (CCN) grow into large particles at supersaturation, especially when combined with up-draughts in typical marine stratocumulus clouds. The resulting particle formation may impact on local and regional radiative forcing and climate (La Barre et al. 2010).

Studies conducted at Mace Head in Western Ireland reported that high concentrations of ultrafine aerosol particles appeared rapidly during daytime and low tide in relation to tidal halogen cycling. Iodine monoxide (IO) is the most abundant coastal inorganic reactive halogen species (RHS) and, in daytime, exhibits a tidal signature consistent with photochemical formation of IO (O'Dowd et al. 1999, 2002). Lee et al. (2009) showed that macroalgal species which were exposed to the receding waterline at Roscoff, emitted molecular iodine (I_2) and were stimulated by the low tide to form iodine-mediated coastal particles. Photolysis of I_2 released a high concentration of rapidly recycled reactive iodine species, IO.

Toxic iodate can be converted into iodine by prokaryotes and is then readily incorporated in the cytoplasm and will be involved in essential catalytic functions, e.g., by coupling with essential organic molecules. Bromination of phenols followed by oxidation and polymerization, for example in *Fucus serratus*, is involved in cell adhesiveness and cell-wall strengthening (Bitton et al. 2006).

There are several halogenated metabolites, and each plays a particular role in defense mechanisms. The resulting halogenated compounds are as follows:

(i) Halogenated alkanes: In the first instance, the biosynthesis of methyl bromide and methyl iodide involves the transferase-mediated nucleophilic attack of corresponding halides at the electrophilic $CH_3{}^+S$ site of S-adenosyl methionine (SAM) but is clearly limited to monohalogenation (Amachi et al. 2006; Neilson 2003), i.e., the production of CH_3I and CH_3Br. In the second case, methylation can produce di- and polysubstituted halomethanes, including a variety of hetero-substituted forms (e.g., $CHBr_2I$ as in *Cystoseira barbata* (Milkova et al. 1997). Electrophilic reaction of I^+ and especially Br^+ with acceptors (centers of high electron density in, e.g., enols, phenolics, and phloroglucinol derivatives) can be rationalized on the basis of rearrangement of the double bond. Hence, a plausible mechanism is the successive bromination of the enols of C_2 or C_3, etc. units containing C=O groups followed by the loss of C_1 (CH_2O from CH_3CHO and CH_3CHO from $CH_3.CO.CH_3$ with concomitant formation of, e.g., CH_2Br_2 and $CHBr_3$ (Milkova et al. 1997; Neilson 2003; Nightingale et al. 1995). Thus, volatile halogenated organic compounds (VHOCs) globally predominate in brown kelp effluxes and ensure a fast disposal of the ROS detoxification products (HOI and HOBr) while conceivably regulating apoplastic iodine and bromine reserves (La Barre et al. 2010).

(ii) Tyrosine-bound halogens: In *Laminaria*, organic forms of iodine are dominated by hormone-like tyrosine derivatives, i.e., monoiodotyrosine or MIT (10–15 ppm), diiodotyrosine or DIT (20–25 ppm), and generally function as molecules involved in cell-cell communication as well as time-coordinated and dose-dependent developmental changes, in eukaryotes (Crockford 2009). Trophic transfers of thyroxin (TH) and thyroid hormone precursors are essential to the metamorphosis of larvae of marine invertebrates (Heyland and Moroz 2005) and gene regulation and signal transcription in vertebrates.

(iii) Halogenated phloroglucinols and phenols: *Eisenia arborea* (Laminariales) (Glombitza and Gerstberger 1985) releases iodophloroglucinol and bromophloroglucinol, and *Eisenia bicyclis* and *Ecklonia kurome* (Shibata et al. 2006) release monomeric bromophenols into the surrounding medium, which act as efficient deterrents against grazing predators.

(iv) Halogenated phenolics: Not many phloroglucinols have been isolated from macrophytic algae, although phlorotannins are found abundantly in brown algae, and have equivalent functions to terrestrial tannins (La Barre et al. 2010).

(v) Halogenated phlorotannins: The Fucales have been so far the best source of halogenated phlorotannins. Some examples are bromotriphlorethol in *Cystophora congesta* (Sargassaceae) (Koch and Gregson 1984) and monochlorotriphlorethol from the Laminariales *Laminaria ochroleuca* (Glombitza et al. 1977). *Carpophyllum angustifolium* (Sargassaceae) contain chlorophloroglucinol, iododiphlorethol, chlorobifuhalol, and chlorodifucol (Glombitza and Schmidt 1999). Monosubstituted eckols have been found in the Laminariales *Eisenia arborea*, along with halogenated phloroglucinols (Glombitza and Gerstberger 1985) and Colpol, a nontypical phenolic derivative from a cosmopolitan Scytosiphonales, *Colpomenia sinuosa* (Green et al. 1993). This brominated compound has a biphenyl butene structure, with strong cytotoxic activities (La Barre et al. 2010).

(vi) Halogenated fatty acids: Three chlorinated oxylipins were isolated from the Laminariales *Egregia menziesii* (Alariaceae) by Todd et al. (1993). Furthermore, six halogenated (eiseniachlorides) or iodinated (eiseniaiodides) species from a whole series of C18 oxylipins from another Alariaceae, *Eisenia bicyclis*, were isolated by Kousaka et al. (2003) and also biosynthesized from a stearidonic acid precursor. These halogenated fatty acids (Ecklonialactones A and B) act as repellents against predating abalone (Kousaka et al. 2003).

(vii) Halogenated terpenes: More than 800 chlorinated/brominated terpenes have been identified (Kladi et al. 2004). Two types of terpenes isolated were linear

nor-sequiterpenes from *Padina tetrastromatica* (Parameswaran et al. 1994) and iodinated meroterpene (terpenes with an aromatic moiety) from *Ascophyllum nodosum* (Arizumi et al. 1994).

The Biotechnological Applications of Haloperoxidases and Their Products

Haloperoxidases can be used for combating bacterial and fungal infection and act through oxidation of halides and conversion of peroxide to singlet oxygen at the surface of the target microbes (Dunford 2010). The HPO can be incorporated into a topical medicament (cream, gel, bandage, and pad), an oral dentifrice, or an injectable composition (Dunford 2010). The advantages of these enzymes for commercial applications are high resistance to azide, cyanide, and hydrogen peroxide (Suthiphongchai et al. 2008).

Marine red algae have the potential for biosynthesis of brominated cyclic sesquiterpenes. This mechanism was applied for in vitro chemoenzymatic conversion of (*E*)-(+)-nerolidol to yield the marine natural products α-snyderol, β-snyderol, and γ-snyderol (Carter-Franklin and Butler 2004). Gram-negative bacteria excrete acylated homoserine lactones (AHLs), which regulate their metabolic activity, behavior, and influence settlement success of the fouling organisms through effects on quorum sensing (Waters and Bassler 2005). AHLs even in small quantity will bind to LuxR an essential protein and activates transcription of operons encoding relevant enzymes for metabolic reactions. The red alga *D. pulchra* produces furones that regulates this quorum sensing and thereby inhibit bacterial colonization. The furones prevent binding or displacing of AHL to LuxR (Maximilien et al. 1998). These metabolites have the functional characteristic of being suitable for treating infectious diseases (Hentzer et al. 2003), and this has led to synthetic derivatives of *Delisea* furones with enhanced quorum-sensing inhibitory properties becoming available and in use for medicinal purposes (Wu et al. 2004).

V-HPOs can be used as an alternative biocide in antifouling applications, as compounds in disinfectants or detergents for bleaching purposes (Ortiz-Bermúdez et al. 2003). V-HPOs possess characteristics such as tolerance to high temperature and different organic solvents (as acetone, methanol, or ethanol). They are also able to halogenate a broad range of organic compounds that are suitable for use in the pharmaceutical industry (Littlechild 1999). This V-BPO mediates in vitro chemoenzymatic conversions of the bromonium-assisted cyclization of terpenes and ethers (Butler and Carter-Franklin 2004). Red algae (e.g., *C. officinalis*, *Laurencia pacifica*, and *Plocamium cartilagineum*) produce V-BPO that can catalyze the asymmetric bromination/cyclization reactions of the sesquiterpene nerolidol to the snyderol family of marine natural products (Crans et al. 2004; Rehder et al. 1991).

Conclusions and Future Prospects

In retrospect, it is not surprising that marine organisms evolved V-HPOs, given the halide content of the oceans and the fact that vanadium is the second most abundant transition-metal ion in seawater (Butler and Sandy 2009). In general, many studies have been carried out regarding different types of HPOs from various sources ranging from bacteria to algae and plants. Nearly all those extensive studies have focused on characterizing the enzyme. The characteristics of these enzymes and their role in halocarbon formation have implications for current global climate change. The present review addresses this climate change issue and updates information on the mechanism of halocarbon production via the HPOs, especially under the influence of environmental variability. The resulting halocarbons may contribute to catalytic destruction of the ozone layers leading to global warming. Moreover, appreciation of the role of vanadium peroxidases in pharmaceutical applications has increased significantly (Almeida et al. 2000; Sigel and Sigel 1995). Further studies on the HPOs from different algal species and different regions of the world's oceans would contribute much needed information, for management of climate change, as well as to accelerate the development of HPOs into commercial pharmaceuticals.

Funding Information This research is supported by the HICoE MOHE: IOES-2014F Grant; HICoE MOHE: IOES-2014 (Air-ocean-land Interaction); UMCoE RU Grant: RU009-2015 (Air-ocean-land Interaction) and RU009K-2015 (Knowledge Management); UMCoE RU Grant: RU012-2016 (IOES) and GC Grant (GC002A/B/-15SBS).

References

Aguilera J, Bischof K, Karsten U, Hanelt D, Wiencke C (2002) Seasonal variation in ecophysiological patterns in macroalgae from an Arctic fjord. II. Pigment accumulation and biochemical defence systems against high light stress. Mar Biol 140(6):1087–1095

Ahern TJ, Allan GG, Medcalf DG (1980) New bromoperoxidase of marine origin. Partial purification and characterization. Biochim Biophys Acta 616(2):329–339

Allen RC (1999) Method for selectively inhibiting the growth of microbes using a haloperoxidase-halide-peroxide system: Google Patents.

Almeida M, Humanes M, Melo R, Silva J, da Silva JF, Vilter H, Wever R (1998) *Saccorhiza polyschides* (Phaeophyceae; Phyllariaceae) a new source for vanadium-dependent haloperoxidases. Phytochemistry 48(2):229–239

Almeida MG, Humanes M, Melo R, Silva JA, da Silva JJ, Wever R (2000) Purification and characterisation of vanadium haloperoxidases from the brown alga *Pelvetia canaliculata*. Phytochemistry 54(1):5–11

Almeida M, Filipe S, Humanes M, Maia MF, Melo R, Severino N et al (2001) Vanadium haloperoxidases from brown algae of the Laminariaceae family. Phytochemistry 57(5):633–642

Amachi S, Kamagata Y, Kanagawa T, Muramatsu Y (2006) Bacteria mediate methylation of iodine in marine and terrestrial environments. Appl Environ Microbiol 67:2718–2722

Apel K, Hirt H (2004) Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annu Rev Plant Biol 55:373–399

Ar Gall E, Cornec L, Deslandes E (2008) Oligocarrageenans and tissue-dependent oxidative burst in *Solieria chordalis* (Rhodophyceae, Gigartinales). Phycol Res 56(1):7–11

Aravind P, Prasad MNV (2005) Modulation of cadmium-induced oxidative stress in *Ceratophyllum demersum* by zinc involves ascorbate–glutathione cycle and glutathione metabolism. Plant Physiol Biochem 43(2):107–116

Arizumi H, Hata K, Shimizu N (1994) Isolation and determination of structure of antioxidant chromanol derivative from *Ascophyllum nodosum*. Jpn Kokkai Tokyo Koho 122:160312

Baden DG, Corbett MD (1980) Bromoperoxidases from *Penicillus capitatus*, *Penicillus lamourouxii* and *Rhipocephalus phoenix*. Biochem J 187(1):205–211

Baharum H, Chu W-C, Teo S-S, Ng K-Y, Rahim RA, Ho C-L (2013) Molecular cloning, homology modeling and site-directed mutagenesis of vanadium-dependent bromoperoxidase (GcVBPO1) from *Gracilaria changii* (Rhodophyta). Phytochemistry 92:49–59

Baker JM, Sturges WT, Sugier J, Sunnenberg G, Lovett AA, Reeves CE et al (2001) Emissions of CH3Br, organochlorines, and organoiodines from temperate macroalgae. Chemosphere Global Change Sci 3(1):93–106

Bartsch I, Wiencke C, Bischof K, Buchholz CM, Buck BH, Eggert A et al (2008) The genus *Laminaria* sensu lato: recent insights and developments. Eur J Phycol 43(1):1–86

Beissner RS, Guilford WJ, Coates RM, Hager LP (1981) Synthesis of brominated heptanones and bromoform by a bromoperoxidase of marine origin. Biochemistry 20(13):3724–3731

Bernhardt P, Okino T, Winter JM, Miyanaga A, Moore BS (2011) A stereoselective vanadium-dependent chloroperoxidase in bacterial antibiotic biosynthesis. J Am Chem Soc 133(12):4268–4270

Bischof K, Rautenberger R (2012) Seaweed responses to environmental stress: reactive oxygen and antioxidative strategies. In: Wiencke C, Bischof K (eds) Seaweed biology, vol 219. Springer, Berlin, pp 109–132

Bischof K, Steinhoff FS (2012) Impacts of ozone stratospheric depletion and solar UVB radiation on seaweeds. Seaweed biology, vol 219. Springer, Heidelberg, pp 433–448

Bitton R, Ben-Yehuda M, Davidovich M, Balazs Y, Potin P, Delage L et al (2006) Structure of algal-born phenolic polymeric adhesives. Macromol Biosci 6(9):737–746

Blasiak LC, Drennan CL (2009) Structural perspective on enzymatic halogenation. Acc Chem Res 42(1):147

Borchardt S, Allain E, Michels J, Stearns G, Kelly R, McCoy W (2001) Reaction of acylated homoserine lactone bacterial signaling molecules with oxidized halogen antimicrobials. Appl Environ Microbiol 67(7):3174–3179

Bouarab K, Potin P, Correa J, Kloareg B (1999) Sulfated oligosaccharides mediate the interaction between a marine red alga and its green algal pathogenic endophyte. Plant Cell 11(9):1635–1650

Bouarab K, Adas F, Gaquerel E, Kloareg B, Salaün J-P, Potin P (2004) The innate immunity of a marine red alga involves oxylipins from both the eicosanoid and octadecanoid pathways. Plant Physiol 135(3):1838–1848

Burreson B, Moore RE, Roller P (1975) Haloforms in the essential oil of the alga *Asparagopsis taxiformis* (Rhodophyta). Tetrahedron Lett 16(7):473–476

Butler A (1998) Vanadium haloperoxidases. Curr Opin Chem Biol 2(2): 279–285

Butler A (1999) Mechanistic considerations of the vanadium haloperoxidases. Coord Chem Rev 187(1):17–35

Butler A, Carter-Franklin JN (2004) The role of vanadium bromoperoxidase in the biosynthesis of halogenated marine natural products. Nat Prod Rep 21(1):180–188

Butler A, Sandy M (2009) Mechanistic considerations of halogenating enzymes. Nature 460(7257):848–854

Butler A, Walker J (1993) Marine haloperoxidases. Chem Rev 93(5): 1937–1944

Carpenter LJ (2003) Iodine in the marine boundary layer. Chem Rev 103(12):4953–4962

Carpenter LJ, Liss PS (2000) On temperate sources of bromoform and other reactive organic bromine gases. J Geophys Res Atmos 105(D16):20539–20547

Carpenter L, Sturges W, Penkett S, Liss P, Alicke B, Hebestreit K, Platt U (1999) Short-lived alkyl iodides and bromides at Mace Head, Ireland: links to biogenic sources and halogen oxide production. J Geophys Res Atmos 104(D1):1679–1689

Carpenter L, Malin G, Liss P, Küpper F (2000) Novel biogenic iodine-containing trihalomethanes and other short-lived halocarbons in the coastal east Atlantic. Glob Biogeochem Cycles 14(4):1191–1204

Carter JN, Beatty KE, Simpson MT, Butler A (2002) Reactivity of recombinant and mutant vanadium bromoperoxidase from the red alga *Corallina officinalis*. J Inorg Biochem 91(1):59–69

Carter-Franklin JN, Butler A (2004) Vanadium bromoperoxidase-catalyzed biosynthesis of halogenated marine natural products. J Am Chem Soc 126(46):15060–15066

Chance R, Baker AR, Küpper FC, Hughes C, Kloareg B, Malin G (2009) Release and transformations of inorganic iodine by marine macroalgae. Estuar Coast Shelf Sci 82(3):406–414

Christmann U, Dau H, Haumann M, Kiss E, Liebisch P, Rehder D, et al (2004) Substrate binding to vanadate-dependent bromoperoxidase from Ascophyllum nodosum: a vanadium K-edge XAS approach. Dalton Trans 16:2534–2540

Cock JM, Sterck L, Rouzé P, Scornet D, Allen AE, Amoutzias G et al (2010) The *Ectocarpus* genome and the independent evolution of multicellularity in brown algae. Nature 465(7298):617–621

Colin C, Leblanc C, Wagner E, Delage L, Leize-Wagner E, Van Dorsselaer A et al (2003) The brown algal kelp *Laminaria digitata* features distinct bromoperoxidase and iodoperoxidase activities. J Biol Chem 278(26):23545–23552

Colin C, Leblanc C, Michel G, Wagner E, Leize-Wagner E, Van Dorsselaer A, Potin P (2005) Vanadium-dependent iodoperoxidases in *Laminaria digitata*, a novel biochemical function diverging from brown algal bromoperoxidases. JBIC J Biol Inorg Chem 10(2):156–166

Collén J, Davison I (1999a) Stress tolerance and reactive oxygen metabolism in the intertidal red seaweeds *Mastocarpus stellatus* and *Chondrus crispus*. Plant Cell Environ 22(9):1143–1151

Collén J, Davison IR (1999b) Reactive oxygen production and damage in intertidal *Fucus* spp. (Phaeophyceae). J Phycol 35(1):54–61

Collén J, Davison IR (2001) Seasonality and thermal acclimation of reactive oxygen metabolism in *Fucus vesiculosus* (Phaeophyceae). J Phycol 37(4):474–481

Collén J, Pedersén M (1996) Production, scavenging and toxicity of hydrogen peroxide in the green seaweed *Ulva rigida*. Eur J Phycol 31(3):265–271

Collén J, Del Rio MJ, García-Reina G, Pedersén M (1995) Photosynthetic production of hydrogen peroxide by *Ulva rigida* C. Ag. (Chlorophyta). Planta 196(2):225–230

Contreras L, Mella D, Moenne A, Correa JA (2009) Differential responses to copper-induced oxidative stress in the marine macroalgae *Lessonia nigrescens* and *Scytosiphon lomentaria* (Phaeophyceae). Aquat Toxicol 94(2):94–102

Cosse A, Potin P, Leblanc C (2009) Patterns of gene expression induced by oligoguluronates reveal conserved and environment-specific

molecular defense responses in the brown alga *Laminaria digitata*. New Phytol 182(1):239–250

Coupe E, Smyth M, Fosberry A, Hall R, Littlechild J (2007) The dodecameric vanadium-dependent haloperoxidase from the marine algae *Corallina officinalis*: cloning, expression, and refolding of the recombinant enzyme. Protein Expr Purif 52(2):265–272

Crans DC, Smee JJ, Gaidamauskas E, Yang L (2004) The chemistry and biochemistry of vanadium and the biological activities exerted by vanadium compounds. Chem Rev 104(2):849–902

Crépineau F, Roscoe T, Kaas R, Kloareg B, Boyen C (2000) Characterisation of complementary DNAs from the expressed sequence tag analysis of life cycle stages of *Laminaria digitata* (Phaeophyceae). Plant Mol Biol 43(4):503–513

Crockford SJ (2009) Evolutionary roots of iodine and thyroid hormones in cell–cell signaling. Integr Comp Biol 49:155–166 icp053

De Boer E, Tromp M, Plat H, Krenn G, Wever R (1986) Vanadium (V) as an essential element for haloperoxidase activity in marine brown algae: purification and characterization of a vanadium (V)-containing bromoperoxidase from *Laminaria saccharina*. Biochim Biophys Acta Protein Struct Mol Enzymol 872(1):104–115

De la Coba F, Aguilera J, Figueroa F, De Gálvez M, Herrera E (2009) Antioxidant activity of mycosporine-like amino acids isolated from three red macroalgae and one marine lichen. J Appl Phycol 21(2): 161–169

Dring MJ (2005) Stress resistance and disease resistance in seaweeds: the role of reactive oxygen metabolism. Adv Bot Res 43:175–207

Dummermuth A, Karsten U, Fisch K, König G, Wiencke C (2003) Responses of marine macroalgae to hydrogen-peroxide stress. J Exp Mar Biol Ecol 289(1):103–121

Dunford HB (2010) Peroxidases and catalases: biochemistry, biophysics, biotechnology and physiology. Wiley, Hoboken

Everett RR, Kanofsky J, Butler A (1990) Mechanistic investigations of the novel non-heme vanadium bromoperoxidases. Evidence for singlet oxygen production. J Biol Chem 265(9):4908–4914

Fenical W (1975) Halogenation in the Rhodophyta. A review. J Phycol 11(3):245–259

Fujimori DG, Walsh CT (2007) What's new in enzymatic halogenations. Curr Opin Chem Biol 11(5):553–560

Gall EA, Küpper FC, Kloareg B (2004) A survey of iodine content in Laminaria digitata. Bot Mar 47:30

Gechev TS, Van Breusegem F, Stone JM, Denev I, Laloi C (2006) Reactive oxygen species as signals that modulate plant stress responses and programmed cell death. BioEssays 28(11): 1091–1101

Glombitza K-W, Gerstberger G (1985) Phlorotannins with dibenzodioxin structural elements from the brown alga *Eisenia arborea*. Phytochemistry 24(3):543–551

Glombitza K-W, Schmidt A (1999) Nonhalogenated and halogenated phlorotannins from the brown alga *Carpophyllum angustifolium*. J Nat Prod 62(9):1238–1240

Glombitza K-W, Koch M, Eckhardt G (1977) Chlorierte phlorethole aus *Laminaria ochroleuca*. Phytochemistry 16(6):796–798

Goldberg ED (1963) The oceans as a chemical system. In: Hill MN (ed) The sea, vol 2. John Wiley & Sons, New York, pp 3–20

Green D, Kashman Y, Miroz A (1993) Colpol, a new cytotoxic C6-C4-C6 metabolite from the alga *Colpomenia sinuosa*. J Nat Prod 56(7): 1201–1202

Gschwend PM, Macfarlane JK, Newman KA (1985) Volatile halogenated organic compounds released to seawater from temperate marine macroalgae. Science 227(4690):1033–1035

Hara I, Sakurai T (1998) Isolation and characterization of vanadium bromoperoxidase from a marine macroalga, *Ecklonia stolonifera*. J Inorg Biochem 72(1):23–28

Hartung J, Brucher O, Hach D, Schulz H, Vilter H, Ruick G (2008) Bromoperoxidase activity and vanadium level of the brown alga *Ascophyllum nodosum*. Phytochemistry 69(16):2826–2830

Hentzer M, Wu H, Andersen JB, Riedel K, Rasmussen TB, Bagge N et al (2003) Attenuation of *Pseudomonas aeruginosa* virulence by quorum sensing inhibitors. EMBO J 22(15):3803–3815

Heyland A, Moroz LL (2005) Cross-kingdom hormonal signaling: an insight from thyroid hormone functions in marine larvae. J Exp Biol 208(23):4355–4361

Isupov MN, Dalby AR, Brindley AA, Izumi Y, Tanabe T, Murshudov GN, Littlechild JA (2000) Crystal structure of dodecameric vanadium-dependent bromoperoxidase from the red algae *Corallina officinalis*. J Mol Biol 299(4):1035–1049

Itoh I (1988) Substrate specificity, regiospecificity and stereospecificity of halogenation reactions catalyzed by non-heme-type bromoperoxidase of *Corallina piltllifera*. Eur J Biochem 172:484

Jannun R, Coe EL (1987) Bromoperoxidase from the marine snail, *Murex trunculus*. Comp Biochem Physiol B 88(3):917–922

Jordan P, Kloareg B, Vilter H (1991) Detection of vanadate-dependent bromoperoxidases in protoplasts from the brown algae *Laminaria digitata* and *L. saccharina*. J Plant Physiol 137(5):520–524

Kladi M, Vagias C, Roussis V (2004) Volatile halogenated metabolites from marine red algae. Phytochem Rev 3(3):337–366

Koch M, Gregson RP (1984) Brominated phlorethols and nonhalogenated phlorotannins from the brown alga *Cystophora congesta*. Phytochemistry 23(11):2633–2637

Kongkiattikajorn J, Pongdam S (2006) Vanadium haloperoxidase from the red alga *Gracilaria fisheri*. Sci Asia 32:25–30

Kongkiattikajorna J, Ruenwongsab P, Panijpanb B (2006) Chemical modification of lysine and histidine residues in Gracilaria tenuistipitata bromoperoxidase: effect on stability and activity. ScienceAsia 32(Suppl 1):37–42

Kousaka K, Ogi N, Akazawa Y, Fujieda M, Yamamoto Y, Takada Y, Kimura J (2003) Novel oxylipin metabolites from the brown alga *Eisenia bicyclis*. J Nat Prod 66(10):1318–1323

Krenn BE, Plat H, Wever R (1987) The bromoperoxidase from the red alga *Ceramium rubrum* also contains vanadium as a prosthetic group. Biochim Biophys Acta Protein Struct Mol Enzymol 912(2): 287–291

Krenn BE, Plat H, Wever R (1988) Purification and some characteristics of a non-haem bromoperoxidase from *Streptomyces aureofaciens*. Biochim Biophys Acta Protein Struct Mol Enzymol 952:255–260

Krenn BE, Tromp MG, Wever R (1989) The brown alga *Ascophyllum nodosum* contains two different vanadium bromoperoxidases. J Biol Chem 264(32):19287–19292

Küpper FC, Kroneck PM (2014) Iodine bioinorganic chemistry. Iodine Chemistry and Applications:555–589

Küpper F, Schweigert N, Ar Gall E, Legendre J-M, Vilter H, Kloareg B (1998) Iodine uptake in Laminariales involves extracellular, haloperoxidase-mediated oxidation of iodide. Planta 207:163–171

Küpper FC, Kloareg B, Guern J, Potin P (2001) Oligoguluronates elicit an oxidative burst in the brown algal kelp *Laminaria digitata*. Plant Physiol 125(1):278–291

Küpper FC, Müller DG, Peters AF, Kloareg B, Potin P (2002) Oligoalginate recognition and oxidative burst play a key role in natural and induced resistance of sporophytes of Laminariales. J Chem Ecol 28(10):2057–2081

Küpper FC, Gaquerel E, Boneberg E-M, Morath S, Salaün J-P, Potin P (2006) Early events in the perception of lipopolysaccharides in the brown alga *Laminaria digitata* include an oxidative burst and activation of fatty acid oxidation cascades. J Exp Bot 57(9):1991–1999

Küpper FC, Carpenter LJ, McFiggans GB, Palmer CJ, Waite TJ, Boneberg E-M et al (2008) Iodide accumulation provides kelp with an inorganic antioxidant impacting atmospheric chemistry. Proc Natl Acad Sci U S A 105(19):6954–6958

Küpper FC, Carpenter LJ, Leblanc C, Toyama C, Uchida Y, Maskrey BH et al (2013) In vivo speciation studies and antioxidant properties of bromine in *Laminaria digitata* reinforce the significance of iodine accumulation for kelps. J Exp Bot 64(10):2653–2664

Lazrus AL, Gandrud BW, Woodard RN, Sedlacek WA (1975) Stratospheric halogen measurements. Geophys Res Lett 2(10): 439–441

La Barre S, Potin P, Leblanc C, Delage L (2010) The halogenated metabolism of brown algae (Phaeophyta), its biological importance and its environmental significance. Mar Drugs 8(4):988–1010

Laturnus F (2001) Marine macroalgae in polar regions as natural sources for volatile organohalogens. Environ Sci Pollut Res 8(2):103–108

Laturnus F, Giese B, Wiencke C, Adams FC (2000) Low-molecular-weight organoiodine and organobromine compounds released by polar macroalgae—the influence of abiotic factors. Fresenius J Anal Chem 368(2–3):297–302

Leblanc C, Colin C, Cosse A, Delage L, La Barre S, Morin P et al (2006) Iodine transfers in the coastal marine environment: the key role of brown algae and of their vanadium-dependent haloperoxidases. Biochimie 88(11):1773–1785

Leblanc C, Vilter H, Fournier JB, Delage L, Potin P, Rebuffet E et al (2015) Vanadium haloperoxidases: from the discovery 30 years ago to X-ray crystallographic and V K-edge absorption spectroscopic studies. Coord Chem Rev 301–302:134–146

Lee JD, McFiggans G, Allan JD, Baker AR, Ball SM, Benton AK, Carpenter LJ, Commane R, Finley BD, Evans M et al (2009) Iodine-mediated coastal particle formation: an overview of the reactive halogens in the marine boundary layer (RHaMBLe) Roscoff coastal study. Atmos Chem Phys Discuss 9:26421–26489

Leedham EC, Hughes C, Keng FSL, Phang SM, Malin G, Sturges WT (2013) Emission of atmospherically significant halocarbons by naturally occurring and farmed tropical macroalgae. Biogeosciences 10(6):3615–3633

Lesser MP (2012) Oxidative stress in tropical marine ecosystems. In: Abele D, Vazquez-Medina JP, Zenteno-Savin T (eds) Oxidative stress in aquatic ecosystems, vol 1. Wiley-Blackwell, Oxford, pp 9–19

Littlechild J (1999) Haloperoxidases and their role in biotransformation reactions. Curr Opin Chem Biol 3(1):28–34

Littlechild J, Garcia-Rodriguez E (2003) Structural studies on the dodecameric vanadium bromoperoxidase from *Corallina* species. Coord Chem Rev 237(1):65–76

Littlechild J, Rodriguez EG, Isupov M (2009) Vanadium containing bromoperoxidase—insights into the enzymatic mechanism using X-ray crystallography. J Inorg Biochem 103(4):617–621

Lohrmann NL, Logan BA, Johnson AS (2004) Seasonal acclimatization of antioxidants and photosynthesis in *Chondrus crispus* and *Mastocarpus stellatus*, two co-occurring red algae with differing stress tolerances. Biol Bull 207(3):225–232

Mackey D, McFall AJ (2006) MAMPs and MIMPs: proposed classifications for inducers of innate immunity. Mol Microbiol 61(6): 1365–1371

Maharana D, Das PB, Verlecar XN, Pise NM, Gauns M (2015) Oxidative stress tolerance in intertidal red seaweed *Hypnea musciformis* (Wulfen) in relation to environmental components. Environ Sci Pollut Res Int

Malmvärn A, Marsh G, Kautsky L, Athanasiadou M, Bergman Å, Asplund L (2005) Hydroxylated and methoxylated brominated diphenyl ethers in the red algae *Ceramium tenuicorne* and blue mussels from the Baltic Sea. Environ Sci Technol 39(9):2990–2997

Manthey J, Hager L (1981) Purification and properties of bromoperoxidase from *Penicillus capitatus*. J Biol Chem 256(21):11232–11238

Mata L, Gaspar H, Santos R (2012) Carbon/nutrient balance in relation to biomass production and halogenated compound content in the red alga *Asparagopsis taxiformis* (*Bonnemaisoniaceae*) 1. J Phycol 48(1):248–253

Maurya M (2006) Structural models of vanadate-dependent haloperoxidases and their reactivity. J Chem Sci 118(6):503–511

Maximilien R, de Nys R, Holmström C, Gram L, Givskov M, Crass K et al (1998) Chemical mediation of bacterial surface colonisation by secondary metabolites from the red alga *Delisea pulchra*. Aquat Microb Ecol 15(3):233–246

McFiggans G, Coe H, Burgess R, Allan J, Cubison M, Alfarra MR et al (2004) Direct evidence for coastal iodine particles from *Laminaria* macroalgae—linkage to emissions of molecular iodine. Atmos Chem Phys 4(3):701–713

Mehrtens G, Laturnus F (1998) Halogenating activity in an arctic population of brown macroalga *Laminaria saccharina* (L.) Lamour. Oceanogr Lit Rev 2(45):351

Meister GE, Butler A (1994) Molybdenum(VI)- and tungsten(VI)-mediated biomimetic chemistry of vanadium bromoperoxidase. Inorg Chem 33(15):3269–3275

Messerschmidt A, Wever R (1996) X-ray structure of a vanadium-containing enzyme: chloroperoxidase from the fungus *Curvularia inaequalis*. Proc Natl Acad Sci 93(1):392–396

Milkova T, Talev G, Christov R, Dimitrova-Konaklieva S, Popov S (1997) Sterols and volatiles in *Cystoseira barbata* and *Cystoseira crinita* from the Black Sea. Phytochemistry 45(1):93–95

Mithöfer A, Schulze B, Boland W (2004) Biotic and heavy metal stress response in plants: evidence for common signals. FEBS Lett 566(1–3):1–5

Neidleman SL (1975) Microbial halogenation. CRC Crit Rev Microbiol 3(4):333–358

Neidleman SL, Geigert J (1986) Biohalogenation: principles, basic roles, and applications. Ellis Horwood Ltd., Chichester

Neilson AH (2003) Biological effects and biosynthesis of brominated metabolites. In: Neilson AH (ed) The handbook of environmental chemistry, vol 3. Springer, Berlin, pp 75–204

Nightingale PD, Malin G, Liss P (1995) Production of chloroform and other low molecular-weight halocarbons by some species of macroalgae. Limnol Oceanogr 40(4):680–689

O'Dowd CD, Hoffmann T (2006) Coastal new particle formation: a review of the current state-of-the-art. Environ Chem 2(4):245–255

O'Dowd C, McFiggans G, Creasey DJ, Pirjola L, Hoell C, Smith MH et al (1999) On the photochemical production of new particles in the coastal boundary layer. Geophys Res Lett 26(12):1707–1710

O'Dowd CD, Jimenez JL, Bahreini R, Flagan RC, Seinfeld JH, Hämeri K et al (2002) Marine aerosol formation from biogenic iodine emissions. Nature 417(6889):632–636

Ohshiro T, Nakano S, Takahashi Y, Suzuki M, Izumi Y (1999) Occurrence of bromoperoxidase in the marine green macro-alga, *Ulvella lens*, and emission of volatile brominated methane by the enzyme. Phytochemistry 52(7):1211–1215

Orfanidis S (1992) Light requirements for growth of six shade-acclimated Mediterranean macroalgae. Mar Biol 112(3):511–515

Orozco-Cárdenas ML, Narváez-Vásquez J, Ryan CA (2001) Hydrogen peroxide acts as a second messenger for the induction of defense genes in tomato plants in response to wounding, systemin, and methyl jasmonate. Plant Cell 13(1):179–191

Ortiz-Bermúdez P, Srebotnik E, Hammel KE (2003) Chlorination and cleavage of lignin structures by fungal chloroperoxidases. Appl Environ Microbiol 69(8):5015–5018

Palmer CJ, Anders TL, Carpenter LJ, Küpper FC, McFiggans GB (2005) Iodine and halocarbon response of to oxidative stress and links to atmospheric new particle production. Environ Chem 2(4):282

Pang AH, Garneau-Tsodikova S, Tsodikov OV (2015) Crystal structure of halogenase PltA from the pyoluteorin biosynthetic pathway. J Struct Biol 192(3):349–357

Parameswaran P, Bhat K, Das B, Kamat S, Harnos S (1994) Halogenated terpenoids from the brown alga Padina tetrastromatica (Hauck), vol 33. Council Scientific Industrial Research Publ & Info Directorate, New Delhi, pp 1006–1008

Pedersén M (1976) A brominating and hydroxylating peroxidase from the red alga *Cystoclonium purpureum*. Physiol Plant 37(1):6–11

Phang S-M, Keng FS-L, Paramjeet-Kaur MS, Lim Y-K-A, Rahman NA, Leedham EC et al (2016) Can seaweed farming in the tropics

contribute to climate change through emission of short-lived halocarbons? MJS 34(1):8–19

Plass W (2009) Vanadium haloperoxidases as supramolecular hosts: synthetic and computational models. Pure Appl Chem 81(7): 1229–1239

Plat H, Krenn BE, Wever R (1987) The bromoperoxidase from the lichen *Xanthoria parietina* is a novel vanadium enzyme. Biochem J 248(1):277–279

Potin P, Leblanc C (2006) Phenolic-based adhesives of marine brown algae. In: Smith A, Callow J (eds) Biological adhesives. Springer, Berlin, pp 105–124

Quack B, Atlas E, Petrick G, Stroud V, Schauffler S, Wallace DW (2004) Oceanic bromoform sources for the tropical atmosphere. Geophys Res Lett 31(23)

Raugei S, Carloni P (2006) Structure and function of vanadium haloperoxidases. J Phys Chem B 110(8):3747–3758

Rehder D (1999) The coordination chemistry of vanadium as related to its biological functions. Coord Chem Rev 182(1):297–322

Rehder D, Hoist H, Priebsch W, Vuter H (1991) Vanadate-dependent bromo/iodoperoxidase from ascophyllum nodosum also contains unspecific low-affinity binding sites for vanadate (V): a 51V NMR investigation, including the model peptides Phe-Glu and Gly-Tyr. J Inorg Biochem 41(3):171–185

Renirie R, Hemrika W, Wever R (2000) Peroxidase and phosphatase activity of active-site mutants of vanadium chloroperoxidase from the fungus *Curvularia inaequalis*. Implications for the catalytic mechanisms. J Biol Chem 275(16):11650–11657

Ritter A, Ubertini M, Romac S, Gaillard F, Delage L, Mann A et al (2010) Copper stress proteomics highlights local adaptation of two strains of the model brown alga *Ectocarpus siliculosus*. Proteomics 10(11): 2074–2088

Roeder V, Collén J, Rousvoal S, Corre E, Leblanc C, Boyen C (2005) Identification of stress gene transcripts in *Laminaria digitata* (Phaeophyceae) protoplast cultures by expressed sequence tag analysis. J Phycol 41(6):1227–1235

Rorrer GL, Tucker MP, Cheney DP, Maliakal S (2001) Bromoperoxidase activity in microplantlet suspension cultures of the macrophytic red alga *Ochtodes secundiramea*. Biotechnol Bioeng 74(5):389–395

Ross C, Alstyne KLV (2007) Intraspecific variation in stress-induced hydrogen peroxide scavenging by the ulvoid macroalga *Ulva lactuca*. J Phycol 43(3):466–474

Rush C, Willetts A, Davies G, Dauter Z, Watson H, Littlechild J (1995) Purification, crystallisation and preliminary X-ray analysis of the vanadium-dependent haloperoxidase from *Corallina officinalis*. FEBS Lett 359(2–3):244–246

Saenko G, Kravtsova Y, Ivanenko V, Sheludko S (1978) Concentration of iodine and bromine by plants in the seas of Japan and Okhotsk. Mar Biol 47(3):243–250

Saiz-Lopez A, Lamarque J-F, Kinnison D, Tilmes S, Ordóñez C, Orlando J et al (2012) Estimating the climate significance of halogen-driven ozone loss in the tropical marine troposphere. Atmos Chem Phys 12(9):3939–3949

Saiz-Lopez A, Shillito JA, Coe H, Plane JMC (2006) Measurements and modelling of I_2 IO, OIO, BrO and NO_3 in the mid-latitude marine boundary layer. Atmos Chem Phys 6(6):1513–1528

Salaün S, La Barre S, Dos Santos-Goncalvez M, Potin P, Haras D, Bazire A (2012) Influence of exudates of the kelp *Laminaria digitata* on biofilm formation of associated and exogenous bacterial epiphytes. Microb Ecol 64(2):359–369

Salawitch RJ (2006) Atmospheric chemistry: biogenic bromine. Nature 439(7074):275–277

Sandy M, Carter-Franklin JN, Martin JD, Butler A (2011) Vanadium bromoperoxidase from *Delisea pulchra*: enzyme-catalyzed formation of bromofuranone and attendant disruption of quorum sensing. Chem Commun 47(44):12086–12088

Shibata T, Hama Y, Miyasaki T, Ito M, Nakamura T (2006) Extracellular secretion of phenolic substances from living brown algae. J Appl Phycol 18(6):787–794

Shimonishi M, Kuwamoto S, Inoue H, Wever R, Ohshiro T, Izumi Y, Tanabe T (1998) Cloning and expression of the gene for a vanadium-dependent bromoperoxidase from a marine macro-alga, *Corallina pilulifera*. FEBS Lett 428(1):105–110

Sigel A, Sigel H (1995) Metal ions in biological systems: volume 31: vanadium and its role for life. CRC, Boca Raton

Slebodnick C, Hamstra BJ, Pecoraro VL (1997) Modeling the biological chemistry of vanadium: structural and reactivity studies elucidating biological function. In: Sadler PJ (ed) Metal sites in proteins and models, vol 89. Springer, Berlin, pp 51–108

Soedjak HS, Butler A (1990) Characterization of vanadium bromoperoxidase from *Macrocystis* and *Fucus*: reactivity of vanadium bromoperoxidase toward acyl and alkyl peroxides and bromination of amines. Biochemistry 29(34):7974–7981

Soedjak HS, Butler A (1991) Mechanism of dioxygen formation catalyzed by vanadium bromoperoxidase from *Macrocystis pyrifera* and *Fucus distichus*: steady state kinetic analysis and comparison to the mechanism of V-BrPO from *Ascophyllum nodosum*. Biochim Biophys Acta 1079(1):1–7

Strittmatter M, Grenville-Briggs LJ, Breithut L, Van West P, Gachon CM, Küpper FC (2016) Infection of the brown alga *Ectocarpus siliculosus* by the oomycete *Eurychasma dicksonii* induces oxidative stress and halogen metabolism. Plant Cell Environ 39(2):259–271

Suthiphongchai T, Boonsiri P, Panijpan B (2008) Vanadium-dependent bromoperoxidases from *Gracilaria* algae. J Appl Phycol 20(3):271–278

Tanaka N, Hasan Z, Wever R (2003) Kinetic characterization of active site mutants Ser402Ala and Phe397His of vanadium chloroperoxidase from the fungus *Curvularia inaequalis*. Inorg Chim Acta 356:288–296

Tarakhovskaya E (2014) Mechanisms of bioadhesion of macrophytic algae. Russ J Plant Physiol 61(1):19–25

Tarakhovskaya ER, Bilova TE, Maslov YI (2015) Hydrogen peroxide content and vanadium-dependent haloperoxidase activity in thalli of six species of Fucales (Phaeophyceae). Phycologia 54(4):417–424

ten Brink HB, Tuynman A, Dekker HL, Hemrika W, Izumi Y, Oshiro T, Wever R (1998) Enantio selective sulfoxidation catalyzed by vanadium haloperoxidases. Inorg Chem 37(26):6780–6784

Thannickal VJ, Fanburg BL (2000) Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol 279(6):L1005–L1028

Todd JS, Proteau PJ, Gerwick WH (1993) Egregiachlorides AC: new chlorinated oxylipins from the marine brown alga *Egregia menziesii*. Tetrahedron Lett 34(48):7689–7692

Tromp MG, Krenn BE, Wever R (1990) Some structural aspects of vanadium bromoperoxidase from *Ascophyllum nodosum*. Biochim Biophys Acta Protein Struct Mol Enzymol 1040(2):192–198

Van Pee K-H, Lingens F (1985) Purification of bromoperoxidase from *Pseudomonas aureofaciens*. J Bacteriol 161(3):1171–1175

Verhaeghe E, Fraysse A, Guerquin-Kern J-L, Wu T-D, Devès G, Mioskowski C, Potin P (2008a) Microchemical imaging of iodine distribution in the brown alga *Laminaria digitata* suggests a new mechanism for its accumulation. JBIC J Biol Inorg Chem 13(2): 257–269

Verhaeghe E, Buisson D, Zekri E, Leblanc C, Potin P, Ambroise Y (2008b) A colorimetric assay for steady-state analyses of iodo-and bromoperoxidase activities. Anal Biochem 379(1):60–65

Vilter H (1984) Peroxidases from Phaeophyceae: a vanadium (V)-dependent peroxidase from *Ascophyllum nodosum*. Phytochemistry 23(7): 1387–1390

Vilter H (1995) Vanadium and its role in life. Met Ions Biol Syst 31: 325–362

Vreeland V, Waite JH, Epstein L (1998) Minireview—Polyphenols and oxidases in substratum adhesion by marine algae and mussels. J Phycol 34(1):1–8

Walker JV, Butler A (1996) Vanadium bromoperoxidase-catalyzed oxidation of thiocyanate by hydrogen peroxide. Inorg Chim Acta 243(1):201–206

Waters CM, Bassler BL (2005) Quorum sensing: cell-to-cell communication in bacteria. Annu Rev Cell Dev Biol 21:319–346

Weinberger F, Friedlander M (2000) Endogenous and exogenous elicitors of a hypersensitive response in *Gracilaria conferta* (Rhodophyta). J Appl Phycol 12(2):139–145

Weinberger F, Richard C, Kloareg B, Kashman Y, Hoppe HG, Friedlander M (2001) Structure-activity relationships of oligoagar elicitors toward *Gracilaria conferta* (Rhodophyta). J Phycol 37(3): 418–426

Weinberger F, Leonardi P, Miravalles A, Correa JA, Lion U, Kloareg B, Potin P (2005a) Dissection of two distinct defense-related responses to agar oligosaccharides in *Gracilaria chilensis* (Rhodophyta) and *Gracilaria conferta* (Rhodophyta) 1. J Phycol 41(4):863–873

Weinberger F, Pohnert G, Berndt M-L, Bouarab K, Kloareg B, Potin P (2005b) Apoplastic oxidation of L-asparagine is involved in the control of the green algal endophyte *Acrochaete operculata* Correa & Nielsen by the red seaweed *Chondrus crispus* Stackhouse. J Exp Bot 56(415):1317–1326

Weinberger F, Coquempot B, Forner S, Morin P, Kloareg B, Potin P (2007) Different regulation of haloperoxidation during agar oligosaccharide-activated defence mechanisms in two related red algae, *Gracilaria* sp and *Gracilaria chilensis*. J Exp Bot 58(15–16):4365–4372

Wever R (2012) Structure and function of vanadium haloperoxidases. In: Michibata H (ed) Vanadium. Springer, Dordrecht, pp 95–125

Wever R, Hemrika W (2001) Vanadium haloperoxidases. Handbook of metalloproteins, pp 1417–1428

Wever R, van der Horst MA (2013) The role of vanadium haloperoxidases in the formation of volatile brominated compounds and their impact on the environment. Dalton Trans 42(33):11778–11786

Wever R, Plat H, de Boer E (1985) Isolation procedure and some properties of the bromoperoxidase from the seaweed *Ascophyllum nodosum*. Biochim Biophys Acta Protein Struct Mol Enzymol 830(2):181–186

Weyand M, Hecht H, Kiess M, Liaud M, Vilter H, Schomburg D (1999) X-ray structure determination of a vanadium-dependent haloperoxidase from *Ascophyllum nodosum* at 2.0 A resolution. J Mol Biol 293(3):595–611

Winter JM, Moore BS (2009) Exploring the chemistry and biology of vanadium-dependent haloperoxidases. J Biol Chem 284(28): 18577–18581

Wischang D, Hartung J (2012) Bromination of phenols in bromoperoxidase-catalyzed oxidations. Tetrahedron 68(46):9456–9463

Wischang D, Brücher O, Hartung J (2011) Bromoperoxidases and functional enzyme mimics as catalysts for oxidative bromination—a sustainable synthetic approach. Coord Chem Rev 255(19):2204–2217

Wischang D, Radlow M, Schulz H, Vilter H, Viehweger L, Altmeyer MO, Gaillard F (2012) Molecular cloning, structure, and reactivity of the second bromoperoxidase from *Ascophyllum nodosum*. Bioorg Chem 44:25–34

Wofsy SC, McElroy MB, Yung YL (1975) The chemistry of atmospheric bromine. Geophys Res Lett 2(6):215–218

Wu H, Song Z, Hentzer M, Andersen JB, Molin S, Givskov M, Høiby N (2004) Synthetic furanones inhibit quorum-sensing and enhance bacterial clearance in *Pseudomonas aeruginosa* lung infection in mice. J Antimicrob Chemother 53(6):1054–1061

Xu G, Wang B-G (2016) Independent evolution of six families of halogenating enzymes. PLoS One 11(5):e0154619

Yende SR, Harle UN, Chaugule BB (2014) Therapeutic potential and health benefits of Sargassum species. Pharmacogn Rev 8(15):1

Yokouchi Y, Hasebe F, Fujiwara M, Takashima H, Shiotani M, Nishi N et al (2005) Correlations and emission ratios among bromoform, dibromochloromethane, and dibromomethane in the atmosphere. J Geophys Res Atmos (1984–2012) 110(D23)

Yu H, Whittaker JW (1989) Vanadate activation of bromoperoxidase from *Corallina officinalis*. Biochem Biophys Res Commun 160(1):87–92

Zambounis A, Strittmatter M, Gachon CM (2013) Chronic stress and disease resistance in the genome model marine seaweed *Ectocarpus siliculosus*. Aquat Bot 104:147–152