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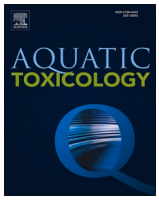

Metals and oxidative stress in aquatic decapod crustaceans: A review with special reference to shrimp and crabs

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ABSTRACT

The objective of this review is to synthetize knowledge of the relationship between metals and oxidative stress in aquatic crustaceans (mainly shrimp and crabs) to analyze antioxidant responses when organisms are exposed to metals because the direct metal binding to the active site of enzymes inactivates most of the antioxidant systems. This study reviewed over 150 works, which evidenced that: (i) antioxidant defense strategies used by aquatic decapod crustaceans vary among species; (ii) antioxidant enzymes could be induced or inhibited by metals depending on species, concentration, and exposure time; and (iii) some antioxidant enzymes, as superoxide dismutase increase their activity in low metal levels and time exposures, but their activities are inhibited with higher metal concentrations and exposure time.

1. Introduction

Aquatic ecosystems receive natural and anthropogenic loads, which increase the levels of several contaminants (Quintaneiro et al., 2015). Among these contaminants, metals are of global concern due to their persistence and toxicity in the environment, which pose high health risks to organisms, including humans (Li et al., 2014). Environmental pollution by metals began with the domestication of fire (Nriagu, 1996), which extended as some anthropogenic activities increased (mining, industry and agriculture) since the late 19th, 20th, and early 21st centuries (Tong et al., 2000; Pinto et al., 2003). Nowadays, metals are used in different and numerous anthropogenic activities around the world; moreover, these metal sources are on ascendency because of the rapid industrialization and urbanization (Wu et al., 2016). Most of the metals generated by anthropogenic sources eventually end up in aquatic environments (Li et al., 2015), which works as an entry to the food chain and become available for accumulation in biota (Páez-Osuna et al., 2017).

In the aquatic ecosystems, organisms live in persistently polluted areas, where they can be exposed to low concentration levels of metals during intermediate or long time periods; on the other hand, organisms may be abruptly exposed to high metal concentrations upon the input of a pollutant to the water (Pinto et al., 2003). Higher levels occur in estuaries, lagoons, bays because of river runoff and the adjacent concurrence of diverse anthropogenic loads (Páez-Osuna et al., 2017; Jara-Marini et al., 2020).

Duce (2010) presented an estimation of metals into the global ocean from riverine and atmospheric inputs. For copper, cadmium, zinc, lead and nickel, these dissolved-particulate inputs are 10–1500, 0.3–12, 6–3900, 2–1600, 11–1400 $\times$ 10^9 g/year, respectively. While atmospheric inputs are 7–45, 0.7–3.3, 55–170, 12–100 and 11–17 $\times$ 10^9 g/year, respectively.

Aquatic crustaceans, as other organisms, inhabit estuarine and coastal lagoon ecosystems that are recognized as areas in which their physicochemical characteristics contribute to metal retention (Duarte

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et al., 2020), these organisms uptake from sediment, water column, and preys; the main metal input is related to their feeding habits and ecological lifestyles (Livingstone, 2001). These organisms are able to accumulate metals to high body concentrations, depending on the relationship between metal uptake and excretion and the rate of diluting body growth (Rainbow, 2018).

Organisms exposed to metal sublethal concentrations have deleterious effects on biochemical, physiological, and reproductive functions that could affect long-term population survival (MacFarlane et al., 2006). In this context, cadmium exposure increased ammonia excretion and reduced oxygen consumption on shrimp *Palaemon macrodactylis* (Zhang et al., 2021). Asih et al. (2013) reported that the osmoregulatory capacity of *Macrobrachium rosenbergii* was reduced (12–47%) when exposed to copper. Wu et al. (2017) reported Pb affected *Litopenaeus vannamei* immune response, increasing its disease susceptibility. Hayati et al. (2019) reported that mercury reduces sperm motility affecting their reproductive capacity. Moreover, metals have been associated with the production of reactive oxygen species (ROS), which consequently cause oxidative stress, producing several cellular negative effects (Sabatini et al., 2009). This ROS production is due to aerobic metabolism of organisms (including crustaceans), which use oxygen as the final electron acceptor in mitochondrial electron transport chain (an essential process), but it can also generate some free radicals (Ahmed, 2005).

The enzymatic antioxidant defense system is a metabolic process that protects aerobic organisms against ROS -as a free radical-scavenging system- (Zhang et al., 2009), which leak from mitochondria into the cellular cytoplasm, causing damages to molecules (DNA, proteins, lipids) due to oxidation (Ahmed, 2005). These antioxidant enzymes – considered as the first defense line against ROS (Stohs and Bagchi, 1995) – are used as biomarkers commonly used in ecotoxicological studies to assess some sublethal effects of contaminants on aquatic/terrestrial organisms (Harayashiki et al., 2018).

Very limited number of reviews on metals and oxidative responses in aquatic organisms are available. In fact, the number of reviews of metals in crustaceans is also limited. Pinto et al. (2003) examined the evidence that links metal bioaccumulation, its cellular toxicity, and ROS production in aquatic environments, involving algae. These authors concluded that a response of algae exists in the presence of metals by induction of several antioxidants; this process includes different enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST)), as well as the synthesis of low molecular weight compounds, such as carotenoids and reduced glutathione (GSH). Mao et al. (2012) compiled the published information on metallothioneins (MTs) in mollusks and crustaceans summarizing their functions, particularly those associated to the development of the organisms. Vogt (2019) reviewed histology, ultrastructure, and structural-functional aspects of the hepatopancreas of decapod crustaceans; indicating that the R (resorptive)- and F (fibrillar)-cells are involved in metal detoxification.

Under such context, the objective of this review is to summarize and synthetize knowledge of the relationship between metals and oxidative stress in aquatic crustaceans (mainly shrimp and crabs) to analyze decapod antioxidant responses when exposed to metals. These organisms have ecological importance because they are key trophic links between lower and upper trophic levels in aquatic habitats (Rodriguez et al., 2007) due to food metal transfers from sediments to decapod crustaceans (Solé et al., 2009). Furthermore, the organisms are used in biomonitoring programs and have been extensively used in ecotoxicological tests because decapod crustaceans are considered as model to the evaluation of contamination effects (Chiodi-Boudet et al., 2015). For this review, several research papers and reviews from 1986 to 2021 were revised with some classical studies (one research paper of 1934 regarding chemical reactions during ROS production, and two more papers of 1969). SCOPUS, Web of Science, Academic Google and PubMed were used as data basis.

2. Oxidative stress

Organisms with aerobic metabolism use oxygen for several biochemical reactions, and as a result, ROS are produced in the mitochondria (Betteridge, 2000; Hamilton et al., 2015), such as superoxide radical (O_2^-), hydroxyl radical ($OH^\bullet$) and hydrogen peroxide (H_2O_2) (Fig. 1). Halliwell and Gutteridge (2001) pointed out that 1–3% of the total oxygen consumed by mammals is converted to ROS; evidently, this rate is required for aquatic decapod crustaceans.

According to Livingstone (2001), the first ROS formed during oxidative stress is O_2^- through the reactions:

$$NADPH + 2\ O_2 \Rightarrow 2\ O_2^- + NADP^+ + H^+. \quad (1)$$

This reaction is catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This superoxide radical may cause H_2O_2 dismutation via:

$$2\ H^+ + 2\ O_2^- \Rightarrow H_2O_2 + O_2; \quad (2)$$

and these ROS may react together to form $OH^\bullet$ via Haber-Weiss reaction (Haber and Weiss, 1934):

$$H_2O_2 + O_2^- \Rightarrow OH^\bullet + OH^- + O_2 \quad (3)$$

The O_2^- is not very reactive and does not have the ability to penetrate lipid membranes, so it is enclosed in the compartment where it is produced (Ahmed, 2005). Unlike O_2, H_2O_2 can cross biological membranes, which is of physiological concern (Nordberg and Arnér, 2001). Moreover, ROS are also generated by reactions involving metals (like Fe), which is known as Fenton reaction (Ercal et al., 2001).

Oxidative stress occurs when ROS generation rate is higher than their neutralization rate by antioxidant enzymes (Halliwell and Gutteridge, 2001; Singaram et al., 2013). Paital and Chainy (2010) mentioned that ROS production at the mitochondrial level occurs according to oxygen consumption and mitochondrial metabolic rate by organisms. This ROS production is higher in organs with high metabolic and detoxification functions as crustacean hepatopancreas (Pan et al., 2011). The reactive oxygen species generated are free radicals with unpaired electrons in their outer orbit; because of this characteristic, they are highly reactive (Ahmed, 2005).

This ROS production excess causes alteration of lipids (formation of malonaldehyde-like species), proteins (non-peptide carbonyl groups), and nucleic acids (8-hydroxydeoxyguanosine and other oxidized bases), affecting many metabolic/physiologic functions (Livingstone, 2001; Xu

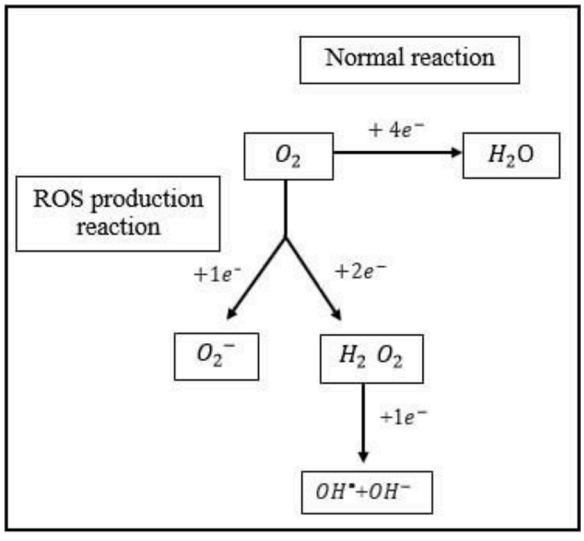

Fig. 1. Reactive oxygen species production during aerobic metabolism (Modified from Winston and Di Giulio, 1991); ROS = reactive oxygen species.

et al., 2018). Moreover, the redox state is defined as the balance of ROS production and neutralization rate by the antioxidant capacity of organisms (Paital and Chainy, 2013). Thus, a redox imbalance is critical to cellular metabolism (Ahmed, 2005).

As a defense system against ROS production, organisms (like crustaceans) have antioxidant enzymatic and non-enzymatic mechanisms. Regarding enzymatic defenses, the antioxidant enzymes to maintain the cell redox status are SOD, CAT, GPx, and GST (Quintaneiro et al., 2015). A higher enzyme activity involves higher detoxification capacity (Pinho et al., 2005; Capparelli et al., 2019), which is important to counteract the cellular damage that a ROS overproduction may cause (Parrilla-Taylor et al., 2013). Regarding tissue/organ ROS scavenge capacity, Pan et al. (2011) described that this capacity is higher in hepatopancreas than that in gills of the crab *Charybdis japonica*, because crab hepatopancreas is the organ with the highest oxidative enzyme synthesis.

Moreover, non-enzymatic responses include the formation of low molecular weight compounds, as ascorbic acid, tocopherols and GSH. Of these antioxidant compounds, GSH is the most abundant cellular thiol in organism cells and main compounds studied (Kristoff et al., 2008). Besides, MTs act not only as metal regulators but also as antioxidants (Viarengo et al., 2000). Further comparison between these antioxidant mechanisms is required.

3. Antioxidant enzymes

The antioxidant enzymes act to reduce free radical formation and they are very fast in neutralizing free radicals (Ighodaro and Akinloye, 2018). The enzymes SOD, CAT, GPx and GST are within this group and briefly described below.

3.1. Superoxide dismutase (SOD)

Environmental stress causes oxidative stress with superoxide formation (O_2^-), and SOD enzyme promotes dismutation of two O_2^- radicals to produce H_2O_2 (Paital and Chainy, 2013; Xu et al., 2018). Two types of SOD are found in cells: (1) Cu-Zn-SOD has an active center with copper (Cu) and zinc (Zn) and is found in the cytosol (Nordberg and Arnér, 2001); while (2) Mn-SOD has a manganese (Mn) ion (McCord and Fridovich, 1969; Marreiro et al., 2017) and is located within the mitochondria (Regoli and Giuliani, 2014). These ion cofactors have an important role in induced dismutation by SOD (Zhao et al., 2010). Nevertheless, the deficiency of these metals decreases cellular SOD production (Gaetke and Chow, 2003).

3.2. Catalase (CAT)

According to Paital and Chainy (2010), the consequence of SOD activity is hydrogen peroxide production, which is highly toxic to cells and generates hydroxyl radicals by Fenton reactions. To avoid this damage, H_2O_2 is converted into H_2O and O_2 by CAT enzyme (Duan et al., 2015). This enzyme is mainly present within peroxisomes (Halliwell and Gutteridge, 2015). The reaction implies two H_2O_2 molecules as acceptor and donor of hydrogen molecules, producing H_2O and O_2 ($2H_2O_2 \Rightarrow 2H_2O + O_2$) (Regoli and Giulani, 2014).

3.3. Glutathione peroxidase (GPx)

GPx is an enzyme that exerts a protective function in cells against oxidative damage by reducing hydrogen peroxide and a wide range of organic peroxides (Valko et al., 2007). As stated by Wang et al. (2012), GPx up-regulated in L. *vannamei* hepatoprancreas by cadmium (Cd) exposure, which indicates its role in protection against environmental toxicants, including metals. This Se-dependent antioxidant enzyme (Li et al., 2015) converts H_2O_2 to H_2O (Duan et al., 2015). This enzyme is present in the cytosol and mitochondria and has a high affinity by H_2O_2 compared with catalase (Valko et al., 2007).

3.4. Glutathione S-transferase (GST)

GST has an important function in detoxifying organic contaminants and endogenic compounds because this enzyme catalyzes the conjugation of the reduced form of GSH (Elumalai et al., 2002; Sun et al., 2014). Moreover, GST is important in the process related to ROS scavenging, which is used as a metal exposure biomarker (Walters et al., 2016). Their enzymatic activity is represented in the next reaction (Winston and Di Giulio, 1991):

$$2GSH + H_2O_2 \Rightarrow GSSG + ROH + H_2O \quad (4)$$

4. Environmental stress

Freire et al. (2011) pointed out that oxidative stress is an important stress response in invertebrates (i.e., crustaceans) when they are exposed to environmental stressors as temperature and salinity. Moreover, Sroda and Cossu-Leguille (2011) and Paital and Chainy (2013) reported natural seasonal variations in oxidative stress and antioxidant responses in the crustaceans *Gammarus roeseli* and *Scylla serrata*, respectively. Livingstone (2001) commented that these seasonal variations could be related to endogenous factors, such as their reproductive cycle, age, and feeding habits; while Bautista-Covarrubias et al. (2020) reported variations of oxidative stress with moon cycle in the L. *vannamei*.

4.1. Temperature

Higher temperatures stimulate all metabolic processes in living organisms (Lushchak, 2011), which increase biochemical reaction rates, and the subsequent processes may become uncoordinated, causing metabolic alterations leading to oxidative stress (Capparelli et al., 2019). These high environmental temperatures increase diffusion rate; thus, they alter cell permeability, increasing oxygen consumption and energy demand in organisms, which in turn, increase ROS production by other metabolic reactions (Lushchak, 2011; Capparelli et al., 2019).

4.2. Salinity

Salinity is a significant factor for aquatic organisms inhabiting estuarine environments, so they have developed several biochemical and physiological adaptations to cope with this stressful abiotic variable. Paital and Chainy (2010) observed that osmotic stress causes oxidative stress and the antioxidant enzyme (SOD, CAT, GPx) activities increased in the crab *Scylla serrata*. These authors pointed out that osmotic stress caused oxygen consumption increase in the crabs due to higher energy demand, which caused ROS production increase; in turn, antioxidant enzyme activity also increased. Furthermore, Liu et al. (2007) determined changes in antioxidant enzyme activity on L. *vannamei* when exposed to a hypo-osmotic environment.

4.3. Contaminants

Oxidative stress has been reported in several organisms inhabiting aquatic polluted environments. Jerome et al. (2017) described an increase in antioxidant enzyme (GPx and CAT) activities in *Callinectes amnicola*, which inhabits a coastal lagoon that receives industrial effluents. In the crab *Neohelice granulata*, GST activity was associated with mine waste (Giarratano et al., 2016); while CAT and GST activities were altered in *Liocarcinus depurator* from a metalliferous waste discharge area (Tsangaris et al., 2015). Wang et al. (2012) observed that antioxidant enzyme activities were inhibited in L. *vannamei* collected from metal-contaminated sites. Lushchak (2011) concluded that metals, and other environmental pollutants like pesticides, oil and related pollutants are oxidative stress inducers, because metals are related with (1)

interference of metal-related processes and (2) free radical productions.

Pérez et al. (2004) reported that CAT, GST and acetylcholinesterase (AChE) activities, and MTs content were altered in aquatic invertebrates from heavily polluted zones, indicating that these enzymes and MTs may be used as pollution biomarkers. This finding coincides with the study of Solé et al. (2009), who also used aquatic invertebrates to relate these biomarkers with specific-site pollution.

5. Metals and oxidative stress

Metals have several adverse effects on different levels of biological organization (Liu et al., 2014). Common mechanisms exist in metal toxicity, such as interaction with sulfhydryl groups, essential metals, and ROS generation (Wang and Fowler, 2008). Regarding oxidative damage, Livingstone (2001) indicated that in organisms exposed to metals, oxidative stress (ROS production) could occur not only by their pro-oxidant characteristics but also because of the organs/tissues damaged by the metal, which in turn, may cause indirect ROS production. According to Singaram et al. (2013), O_2^- production following metal exposure could be attributed to direct or indirect interactions with the cellular membrane. Iron (Fe), copper (Cu) and chromium (Cr) ions are considered as redox-active metals due to the ion capacity to change valence state; these metals participate in the Fenton reaction (Lushchak, 2011). Besides, Sanchez et al. (2005) pointed out that antioxidant enzymes could be induced or inhibited by metals depending on organism and concentration. Moreover, metal exposure causes a redox unbalance in decapod crustaceans affecting antioxidant enzymes (Fig. 2).

5.1. Copper

This element is considered as an essential metal, which is a cofactor in several enzymes (Martins et al., 2011) and the main component of the respiratory pigment hemocyanin used for oxygen transport in aquatic crustaceans (Capparelli et al., 2019). Nevertheless, when internal concentrations exceed the metabolic requirements and detoxification capability, copper becomes toxic to crustaceans (Rainbow, 2018). Among the deleterious copper effects in crustaceans, Lauer et al. (2012) observed a negative consequence on enzyme activity involved in glycolysis (hexokinase, phosphofructokinase and pyruvate kinase) in the Krebs cycle (citrate synthase) and mitochondrial membrane potential; while Pan et al. (2011) reported a DNA integrity effect in *Charybdis japonica* hemocytes. Lushchak (2011) commented that Cu exposure enhances the activities of primary (antioxidant enzymes) and secondary (metallothioneins) enzymes.

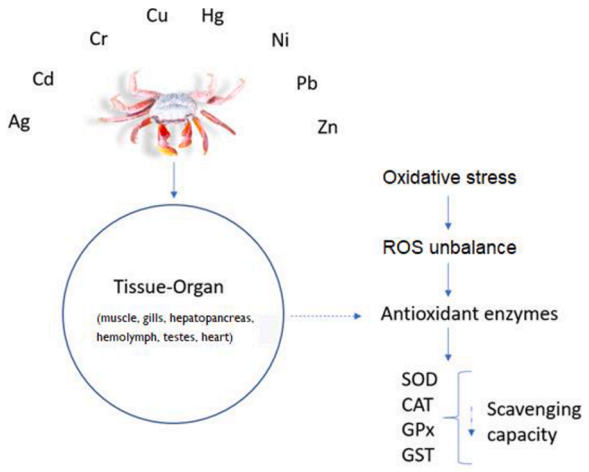

Fig. 2. Metal effects on antioxidant enzymes in decapod crustaceans; ROS = reactive oxygen species; SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GST = glutathione S-transferase.

Livingstone (2001) indicated that Cu ions excess induces ROS production, via the following reactions (Stohs and Bagchi, 1995):

$$Cu^{2+} + O_2^- \Rightarrow Cu^+ + O_2 \quad (5)$$

$$Cu^+ + H_2O_2 \Rightarrow Cu^{2+} + OH^- + OH^\bullet \quad (6)$$

This $OH^\bullet$ production is of concern because it is the most powerful oxidant that reacts with every biological molecule (Gaetke and Chow, 2003).

Capparelli et al. (2019) observed an alteration in GPx and GST activities in the mudflat fiddler crab *Minuca rapax* when exposed to Cu (Table 1). GST activities increased in the hepatopancreas, but decreased in gills because crustacean hepatopancreas is the main organ to toxicant metabolism and ROS biotransformation (redox cycle processes). These authors concluded that GST activity decreases in gills because Cu is an enzymatic cofactor of both GST and GPx enzymes. This metal may bind

Table 1
Antioxidant enzyme activities in crustaceans when exposed to Cu. ↓: decrease activity; ↑: increase activity. Copper concentration and exposure time (in days (d) and hours (h)) between parentheses.

Species	Tissue	Enzyme activity			
		SOD	CAT	GPx	GST
crab					
M. rapax[1]	gills			↓ (50 µg/L, 21 d) ↑ (500 µg/L, 21 d)	↓ (50 µg/L, 21 d)
	hepatopancreas			↓ (50 µg/L, 21 d) ↑ (250 µg/L, 21 d)	↑ (50 µg/L, 21 d)
C. sapidus[2]	hepatopancreas	↑ (3.17 mg/L, 24 h)	↑ (3.17 mg/L, 24 h)	↑(3.17 mg/L, 24 h)	
N. granulata[3]	hepatopancreas	↑ (300 µg/g food: diet, 7 d)			
E. sinensis[4]	all body (larvae)	↑ (150 µg/L, 24 h)	↑ (150 µg/L, 24 h)		↑ (150 µg/L, 12 h)
shrimp					
A. desmarestii[5]	muscle		no effect (50–200 µg/L, 48 h)	↓ (100 µg/L, 48 h)	↓ (200 µg/L, 48 h)
L. *vannamei*[6]	hemocytes	↑ (1 mg/L, 3 h)	↑ (3 mg/L, 6 h)		
L. *vannamei*[7]	hemocytes	no effect (3–18,670 µg/L, 96 h)			
P. indicus[8]	all body (larvae)	↓ (0.16 µg/L, 30 d)	↑ (0.16 µg/L, 30 d)		
prawn					
M. rosenbergii[9]	hepatopancreas	↑ (10 µg/L, 7 d)↑ (50 µg/L, 7 d)			↓ (10 µg/L, 7 d)

[1] Capparelli et al. (2019).
[2] Brouwer and Brouwer (1998).
[3] Sabatini et al. (2009).
[4] Sun et al. (2014).
[5] Quintaneiro et al. (2015).
[6] Guo et al. (2017).
[7] Bautista-Covarrubias et al. (2015).
[8] Paila and Yallapragada (2011).
[9] Li et al. (2008); SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GST = glutathione S-transferase.

to GSH and diminish the amount for GST and GPx substrates. Regarding GPx activities, a low concentration-inhibition and high concentration-stimulation was observed.

In the case of Chinese mitten crab *Eriocheir sinensis*, Sun et al. (2014) reported that copper exposure induced an increase in GST activity to improve detoxification processes. On the other hand, Quintaneiro et al. (2015) reported that the lack of effect on CAT activity in the shrimp *Atyaephyra desmarestii* could have been attributed to the increase of GPx activity; while GST activity decrease was related to Cu effects on GST structure and function and/or direct inhibition by ROS production. Li et al. (2008) reported the same conclusion on the giant freshwater prawn *M. rosenbergii* hepatopancreas. Moreover, these last authors pointed out that hepatopancreas is the organ where detoxification occurs. Guo et al. (2017) reported that SOD and CAT activities in L. *vannamei*, increased in a time and dose-dependent way when shrimp were exposed to this metal.

As final comments, copper exposure caused SOD activity increase during a three-hour – seven-day exposure time, but this SOD activity increases at high exposure time (30 days). CAT activity showed a similar pattern. However, GPx activity decreased at lower Cu concentrations and increased at higher ones in gills and hepatopancreas. Regarding GST activity, an organtropism effect was observed because GST activity decreased in gills at the same Cu level (50 μg/L) and exposure time (21 days) but increased in hepatopancreas. These results indicate that Cu affects antioxidant enzymes in different forms.

Regarding Cu levels, GST activity decreased at 10 μg/L in *M. rosenbergii* hepatopancreas at seven-day exposure time, while GPx and GST activities also decreased at 50 μg/L in gills and hepatopancreas of the crab *M. rapax*.

5.2. Cadmium

The most toxic effects of this metal are those related with the alteration of sulfhydryl protein groups and interaction of cell ligands, disrupting energy production by oxidative phosphorylation system alteration (Wu et al., 2016). Furthermore, Pan et al. (2011) observed a DNA integrity effect on *C. japonica* hemocytes. In L. *vannamei* exposed to Cd, Bautista-Covarrubias et al. (2014) reported deleterious effects in their immune response.

For oxidative stress effects, Pan and Zhang (2006) reported a time-dependent effect in SOD and CAT activities in *C. japonica* gills (Table 2), increasing their activity at 0.5 days (12 h) of exposure but decreasing significantly at 9 and 15 days of exposure. In hepatopancreas, SOD, CAT and GPx activities increased significantly during the first days of exposure, followed by a decrease but always higher than those of the controls. These authors concluded that this SOD activity decrease could have been caused by a direct Cd inhibitory effect by altering the enzyme structure; causing ROS increases, which inhibited CAT activity.

Similarly, the study of Lei et al. (2011) in the crab *Sinopotamon yantsekiense* indicated that CAT and GPx activities were first activated but then inhibited after five days of exposure, which could have been due to intracellular ROS accumulation. Regarding GPx, Cd binds to thiol groups of this enzyme decreasing their catalytic activity. Evidently, H_2O_2 accumulation occurred in the crab heart due to an increase in SOD activity and a decrease in CAT and GPx activities.

In the crab *Sinopotamon henanense*, Wang et al. (2013) reported that SOD, CAT, and GPx activities increased in gills at first Cd exposure times. However, after 24 h of Cd exposure, their activities decreased but always with higher activity than those of the control, which indicated that Cd caused an important activity decrease when exposure time increased. These authors concluded that exposure time was an important factor in antioxidant enzyme activity. In experiments with the same crab, Wang et al. (2011) reported the same Cd effects in these antioxidant enzymes, and pointed out that at low Cd concentrations, their activities are stimulated as an adaptive response. However, exposure to higher Cd levels caused impaired scavenging functions. Zhou et al. (2016) reported

Table 2
Antioxidant enzyme activities in crustaceans when exposed to Cd. ↓: decrease activity; ↑: increase activity. Cadmium concentration and exposure time (in days (d) and hours (h)) between parentheses.

Species	Tissue	Enzyme activity SOD	CAT	GPx
crab				
C. japonica[1]	gills	↑ (50 μg/L, 0.5 d) ↓ (50 μg/L, 15 d)	↑ (50 μg/L, 0.5 d) ↓ (50 μg/L, 9 d)	↑ (50 μg/L, 0.5 d) ↓ (50 μg/L, 0.5 d)
	hepatopancreas	↑ (50 μg/L, 0.5 d)	↑ (25 μg/L, 0.5 d)	↑ (25 μg/L, 0.5 d)
S. yangtsekiense[2]	gills	↓ (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)
	hepatopancreas	↓ (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)
	heart	no effect (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)	↓ (58 mg/L, 96 h)
S. yangtsekiense[3]	heart	↑ (116 mg/L, 1 d)	↑ (14 mg/L at 5 d) ↓ (14 mg/L at 7 d)	↑ (29 mg/L at 3 d) ↓ (29 mg/L at 3 d)
S. henanense[4]	gills	↑ (14.5 mg/L, 8 d)	↑ (14.5 mg/L, 8 d)	↑ (29 mg/L, 4 d)
S. henanense[5]	testes	↑ (14.5 mg/L, 7 d) ↓ (58 mg/L, 7 d)	↑ (7.25 mg/L, 7 d) ↓ (116 mg/L, 7 d)	↑ (7.25 mg/L, 7 d) ↓ (116 mg/L, 7 d)
S. henanense[6]	hemocytes	↑ (116 mg/L, 24 h) ↓ (116 mg/L, 96 h)		
S. henanense[7]	hemocytes	↑ (0.72 mg/L, 14 d)	↑ (1.4 mg/L, 7 d)	↑ (1.4 mg/L, 7 d)
S. henanense[8]	hepatopancreas	↑ (7.25 mg/L, 4 d) ↓ (14.5 mg/L, 4 d)	↑ (7.25 mg/L, 4 d) ↓ (29 mg/L, 4 d)	↓ (29 mg/L, 4 d)
shrimp				
A edulis[9]	gills	↓ (0.5 mg/L, 1 d)	↓ (5 mg/L, 3 d)	↓ (0.5 mg/L, 1 d)
	hepatopancreas	↓ (5 mg/L, 2 d)	no effect (0.5–5 mg/L, 4 d)	↓ (0.5 mg/L, 1 d)
P. macrodactylus[10]	hepatopancreas	↓ (0.07 mg/L, 4 d)	↓ (0.07 mg/L, 4 d)	no effect (0.03–0.18 mg/L, 4 d)

[1] Pan and Zhang (2006).
[2] Li et al. (2011).
[3] Lei et al. (2011).
[4] Wang et al. (2013).
[5] Wang et al. (2011).
[6] Qin et al. (2012).
[7] Zhou et al. (2016).
[8] Wu et al. (2012).
[9] Das et al. (2019).
[10] Zhang et al. (2021); SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase.

similar results in GPx activity in hemocytes of the same organism.

A time-dependent Cd concentration effect was also observed in hemocyte SOD activity of the crab *S. henanense* (Qin et al., 2012) because their activity was induced at low concentrations but decreased with prolonged exposure time. These authors commented that this SOD activity decrease could have been due to (a) O_2^-accumulation, which reduces scavenging SOD ability and (b) total hemocyte count decrease because ROS are toxic to hemocytes (Zhou et al., 2016). In the crab *Paratelphusa hydrodromaus* hemocytes, this O_2^-accumulation caused a decrease in CAT activity (Pugazhendy et al., 2015).

With regard to *S. henanense* hepatopancreas, an increase in Cd concentration caused inhibition on CAT activity and Cd ions bound to the GPx active site (Se-Cys), which altered the activity of this antioxidant enzyme (Wu et al., 2013). In *Austinogebia edulis* shrimp muscle, SOD, CAT, and GPx activities were always higher at 0.5 mg/L than those at 5.0 mg/L (Das et al., 2019), indicating that Cd excess affects SOD function, causing O_2^- accumulation in shrimp organs. Moreover, H_2O_2 and $OH^•$ production increased, inhibiting GPx activity.

To sum up, at relatively low Cd concentrations (50 - 70 μg/L), SOD, CAT and GPx activities are exposure time-dependent, because their antioxidant activities increase at low exposure time (12 h) but decrease at higher exposure time (15 days). Nevertheless, at higher Cd concentrations (> 500 μg/L) the antioxidant enzyme activities are species/organ/exposure time/ and concentration-dependent.

5.3. Mercury

Aquatic organisms (i.e., crabs, shrimps) can be exposed to environmental mercury, which is accumulated in several tissues (muscle, gills, exoskeleton, hepatopancreas), and this bioaccumulation causes deleterious effects at molecular and cellular levels (Zhao et al., 2010). According to Zhang et al. (2009), Hg forms complex compounds with nucleosides, thiol groups, and other amino acids, which alter some crustacean physiological functions. Atchison and Hare (1994) reported that organic and inorganic Hg forms have a neurotoxic effect in organisms; these forms impair nerve actin potential conduction and/or disrupt synaptic transmissions. Roos-Muñoz et al. (2019) reported damage in the nervous tissue in L. *vannamei* post-larvae and juveniles after mercury exposure. Stohs and Bagchi (1995) pointed out that Hg causes reduction in SOD, CAT and GPx activities. While Wu et al. (2016) found that during Hg exposure, oxidative stress could occur by a combination of ROS production increases and/or depletion of antioxidant biomolecules; Lund et al. (1991) indicated that Hg caused oxidative stress by triggering ROS production through the mitochondrial electron transport chain alteration. Zhang et al. (2009) reported that when the crab *C. japonica* was exposed to Hg, ROS production (O_2^- and H_2O_2) occurred. At initial exposure time, antioxidant activities increased, but at higher exposure times (15 days), they decreased (Table 3). These authors observed that the activities of these enzymes (CAT and GPx) decreased due to a direct Hg inhibitory effect on these antioxidant enzymes, and high O_2^- production inhibited CAT activity. Zhao et al. (2010) found that SOD activity decreased because Hg could displace SOD cofactors (Cu, Zn, and Mn) from the enzyme active site, which decreased its activity (Yan et al., 2007). In the shrimp L. *vannamei*, Roos-Muñoz et al. (2019) reported that time of exposure had a more important influence in SOD activity than Hg concentration to which shrimp were exposed. Table 3 shows that most of the studies reported decreasing SOD activity.

For CAT activity, Hg excess could alter mitochondria structural integrity, decreasing CAT synthesis (Zaman et al., 1994). Moreover, Singaram et al. (2013) indicated that superoxide anion production inhibited CAT activity in *Scylla serrata* when exposed to Hg. Table 3 shows dose-time-mediated CAT activity decrease.

In the case of GPx, this antioxidant enzyme contains Ser-Cys in the active site, and mercury binds to GPx cysteine (Wang and Horisberger, 1996), altering its structure and decreasing their activity (Zhao et al., 2010). At higher exposure time (40 days) and Hg concentration (100 μg/L), this enzyme was inhibited in *E. sinensis*. Elumalai et al. (2007) reported that GST increased activity in *Carcinus maenas* and *M. malcolmsonhi*, and concluded that it indicated a response to Hg-mediated oxidative stress and activation of detoxification mechanisms (Singaram et al., 2013).

Mercury effect on antioxidant enzymes is different among organs of marine crustaceans. Singaram et al. (2013) reported higher SOD, CAT, and GST activities in hepatopancreas than those of gills and muscle of

Table 3
Antioxidant enzyme activities in crustaceans when exposed to Hg. ↓: decrease activity; ↑: increase activity. Mercury concentration and exposure time (in days (d) and hours (h)) between parentheses.

Species	Tissue	Enzyme activity			
		SOD	CAT	GPx	GST
crab					
C. japonica[1]	hepatopancreas	↑ (2.5 μg/L, 0.5 d)	↑ (2.5 μg/L, 0.5 d)	↑ (2.5 μg/L, 0.5 d)	
	hemolymph	↑ (2.5 μg/L, 0.5 d)		↑ (5 μg/L, 0.5 d) ↓ (5 μg/L, 15 d)	
	gills	↑ (2.5 μg/L, 0.5 d)	↑ (5 μg/L, 0.5 d) ↓ (5 μg/L, 15 d)	↑ (2.5 μg/L, 0.5 d)	
E. sinensis[2]	hepatopancreas	↑ (10 μg/L, 40 d) ↓ (100 μg/L, 40 d)	↑ (10 μg/L, 40 d) ↓ (100 μg/L, 40 d)	↑ (10 μg/L, 40 d) ↓ (100 μg/L, 40 d)	
S. serrata[3]	hemocytes	↓ (1 μg/L, 7 d)	↓ (10 μg/L, 7 d)	↓ (1 μg/L, 14 d)	↑ (1 μg/L, 14 d)
	gills	↓ (10 μg/L, 7 d)	↓ (10 μg/L, 7 d)	↓ (10 μg/L, 7 d)	↑ (10 μg/L, 7 d)
	hepatopancreas	↓ (10 μg/L, 7 d)	↓ (1 μg/L, 7 d)	↓ (1 μg/L, 7 d)	↑ (10 μg/L, 7 d)
	muscle	↓ (10 μg/L, 7 d)	↓ (1 μg/L, 7 d)	↓ (10 μg/L, 7 d)	↑ (10 μg/L, 7 d)
C. maenas[4]	hepatopancreas				↑ (740 μg/L, 96 h)
shrimp					
P. monodon[5]	muscle		↓ (2.5 μg/g: food, 4 d)		
L. *vannamei*[6]	hemolymph	↓ (2.4 μg/L, 24 h)			
↑ (2.4 μg/L, 168 h)					
prawn					
M. malcolmsonii[7]	hepatopancreas				↑ (24 μg/L, 8 d)
	gills				↑ (24 μg/L, 8 d)

[1] Zhang et al. (2009).
[2] Zhao et al. (2010).
[3] Singaram et al. (2013).
[4] Elumalai et al. (2007).
[5] Harayashiki et al. (2018).
[6] Roos-Muñoz et al. (2019).
[7] Yamuna et al. (2012); SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GST = glutathione S-transferase.

S. serrata, but GPx was higher in gills than in hepatopancreas and muscle.

In *S. serrata*, 1 μg Hg/L caused a decrease in SOD, CAT and GPx activities but at seven days of exposure time, whereas SOD activity decrease at 2.4 μg/L at 24 h in L. *vannamei*. These Hg levels are close to water quality criteria proposed by the United States Environmental Protection Agency (EPA, 2009), which is 0.92 μg/L as CCC (continuous concentration criteria). However, in other decapods an increase in SOD, CAT and GPx activities was reported, indicating that Hg has an antioxidant enzyme-specific effect.

5.4. Other metals

5.4.1. Zinc

Zinc is an essential element required for development and several physiological processes in organisms (Elumalai et al., 2007). This element is involved in functioning of around 200 enzymes (Quintaneiro et al., 2015). However, when aquatic crustaceans are exposed to relatively higher Zn concentrations (61 μg/L), deleterious effects occur, such as decreased reproduction in cladocerans (De Schamphelaere et al., 2004), alterations in oxygen consumption, ammonium excretion, and osmoregulation in L. *vannamei* (Wu and Chen, 2004). Regarding Zn effects on antioxidant enzymes, Table 4 shows that GST caused hormesis effect (stimulation at low concentration and inhibition at high concentrations) (Calabrese and Baldwin, 2002) on *C. maenas* (Elumalai et al., 2007). In *A. desmarestii*, Quintaneiro et al. (2015) reported no effect on CAT and GST activities, while GPx activity increased. These authors commented that CAT and GPx have the same antioxidant function – convert H_2O_2 to H_2O and O_2 – and if CAT activity was inhibited due to metal exposure, GPx carried out the antioxidant activity to reduce oxidative damage.

5.4.2. Lead

Johnson (1998) found that Pb may react with important biomolecules and adversely affect several organs. Santos et al. (2014) reported an increase in oxygen consumption and ammonia excretion in *Litopenaeus schmitti*, L. *vannamei* and *Penaeus indicus* when exposed to this metal. Soto-Jiménez et al. (2011) observed growth retardation in L. *vannamei* when exposed to 20 μg/L of Pb. Moreover, Pan et al. (2011) reported DNA integrity damage in *C. japonica* hemocytes. Donaldson and Knowles (1993) reported oxidative tissue damage and altered fatty acid composition as a Pb toxicity effect.

Liu et al. (2014) found an increase of H_2O_2 in *S. henanense* when exposed to Pb and observed a reduction of CAT, GPx and GST activities, and SOD activity at high concentrations in the crab hepatopancreas (Table 4), causing oxidative stress. These authors concluded that SOD activity decrease could have been due to Pb-induced Cu deficiency which affected SOD enzyme synthesis or by direct Pb binding to SOD active sites (displacing Cu, Zn and Fe in the functional SOD group) (Li et al., 2015), resulting in enzyme inactivation. Regarding CAT and GPx, their decrease in activities was related to H_2O_2 accumulation in mitochondria and/or cytosol. Moreover, Pb displaces the selenocysteine group from the active site of GPx, causing a decrease in their catalytic function (Ursini et al., 1985; Ercal et al., 2001; Li et al., 2015). Regarding testes, Li et al. (2015) noticed antioxidant enzyme stimulation at low Pb levels, and inhibition at high levels in the same crab species, which is of ecological concern because Pb exposure could affect reproduction of this and other decapod species, affecting trophic ecology of aquatic ecosystems.

5.4.3. Nickel

Concerning nickel (Ni), Leonard et al. (2011) reported a Na and Mg homeostasis disruption in L. *vannamei*; while Blewett et al. (2015) observed an impairment of Na^+/K^+ ATPase activity in gills of *C. maenas* when exposed to Ni. This metal is considered a carcinogenic element due to direct binding to genetic material and/or ROS production due to nickel-catalyzed redox reactions (Rodríguez et al., 1990). As shown in Table 4, a decrease in CAT activity was observed by Blewett and Wood (2015) in *C. maenas* gills when exposed to Ni. These authors concluded that this enzyme decrease could be explained because Ni has a high

Table 4
Antioxidant enzyme activities in crustaceans when exposed to metals. ↓: decrease activity; ↑: increase activity. Metal concentration and exposure time (in days (d) and hours (h)) between parentheses.

Species	Tissue	Enzyme activity			
		SOD	CAT	GPx	GST
Zn					
crab					
C. maenas[1]	hepatopancreas				↑ (14.8 mg/L, 96 h)
shrimp					
A. desmarestii[2]	muscle		no effect (0.05–0.2 mg/L, 48 h)	↑ (3 mg/L, 48 h)	no effect (0.05–0.2 mg/L, 48 h)
Pb					
crab					
S. henanense[3]	hepatopancreas	↑ (9.2 mg/L, 96 h) ↓ (73.5 mg/L, 96 h)	↑ 9.2 mg/L, 96 h) ↓ (73.5 mg/L, 96 h)	↓ (36.7 mg/L, 96 h)	↓ (18.4 mg/L, 96 h)
S. henanense[4]	testes	↑ (7.3 mg/L, 5 d) ↓ (59 mg/L, 7 d)	↑ (7.3 mg/L, 5 d)	↑ (7.3 mg/L, 5 d)	
Ni					
C. maenas[5]	gills		↓ (3 mg/L, 96 h)		
Ag					
P. perlatus[6]	gills	no effect (10–100 μg/L, 7 d)	no effect (10–100 μg/L, 7 d)		no effect (10–100 μg/L, 7 d)
	hepatopancreas	no effect (10–100 μg/L, 7 d)	↓ (10 μg/L, 7 d)		no effect (10–100 μg/L, 7 d)
Cr					
B. guerini[7]	hepatopancreas	↑ (30.1 mg/L, 1 d)			
	gills	↑ 41.2 mg/L, 1 d))			
C. maenas[8]	hepatopancreas				↓ (5 mg/L, 96 h)

[1] Elumalai et al. (2007).
[2] Quintaneiro et al. (2015).
[3] Liu et al. (2014).
[4] Li et al. (2015).
[5] Blewett and Wood (2015).
[6] Walters et al. (2016).
[7] Srivedi et al. (1998).
[8] Elumalai et al. (2002); SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GST = glutathione S-transferase.

affinity by histidine residues, which are very important in CAT activity. Rodríguez et al. (1990) reported that CAT activity reduction could be due to direct binding to CAT causing denaturation (structure distortion) of the enzyme.

5.4.4. Silver

Grosell et al. (2002) reported physiological changes in the crustacean *Cambarus diogenes* when exposed to waterborne silver (Ag). Bianchini et al. (2005) measured lower Na^{+}-K^{+} ATPase activity in gills of the shrimp *Penaeus duorarum* and found that a lower Na^{+} uptake by gills causes osmoregulatory alterations, affecting ion balance. Walters et al. (2016) reported a SOD and CAT activity decrease in gills and hepatopancreas, respectively, in the crab *Potamanautes perlatus* when exposed to silver-nanoparticles (Table 4). The increase in GST and SOD activities in the hepatopancreas indicated the oxidative stress of Ag. Evidently, there are different physiological and metabolic responses of antioxidant enzymes by crab organs.

5.4.5. Chromium

This element has been reported both as an essential and non-essential metal with beneficial effects on glucose metabolism (Lushchak, 2011). Cr^{6+} is the most toxic chemical species because this hexavalent form has a higher ability than Cr^{3+} to penetrate the cell membrane (Mertz, 1969). Lee et al. (2000) reported a reduced hatching rate in grass shrimp *Palaemonetes pugio*; while Doughtie and Rao (1984) reported histopathological damages in hepatopancreas, antennal glands, and gills of the same shrimp when exposed to this metal. Stohs and Bagchi (1995) and Lushchak (2011) reported that chromium (Cr) exposure generates hydroxyl radicals by the next reactions:

$$Cr^{6+} + O_2^{-} \Rightarrow Cr^{5+} + O_2 \quad (7)$$

$$Cr^{5+} + H_2O_2 \Rightarrow Cr^{6+} + OH^{-} + OH^{\bullet} \quad (8)$$

In the crab *Barytelphusa guerini*, Srivedi et al. (1998) observed a SOD activity increase in gills and hepatopancreas due to Cr^{3+} and Cr^{6+} exposure (Table 4). These authors interpreted that this antioxidant enzyme increased its activity to cope with ROS production. Whereas GST activity decreased in *C. maenas* hepatopancreas, indicating an alteration in the detoxification process of endogenic compounds (Elumalai et al., 2002).

With respect to these metals (Zn, Pb, Ni, Ag and Cr) Zn caused no effect on CAT and GST activities at relatively low concentrations (0.05–0.2 mg/L) during 48 h exposure time, but at higher Zn concentrations (> 3 mg/L) GPx and GST activities increased. Regarding Pb, SOD, CAT and GPx activities increased at 7.3 mg/L; while Ni and Cr caused a decrease in CAT and GST activity at 3 and 5 mg/L, respectively. Nevertheless, a concentration of 10 μg/L of Ag is enough to reduce CAT activity. Finally, for Ag, Ni and Cr, more studies are required for a better elucidation of the effect of these metals on antioxidant enzymes.

6. Toxic mechanisms

Regarding oxidative stress, the metals included in this review are classified in two sections: (1) redox-active as Fe, Cu, and Cr; and (2) non-redox-active, as Cd, Hg, Pb, Ni, Ag and Zn. For redox-active metals, as previously commented, these elements generate ROS by reactions involving metals (M) (like Fe), which is known as Fenton reaction (Torreilles and Guérin, 1990; Stohs and Bagchi, 1995; Ercal et al., 2001):

$$M^{(n)} + O_2^{-} \Rightarrow M^{(n-1)} + O_2 \quad (9)$$

$$M^{(n-1)} + H_2O_2 \Rightarrow M^{(n)} + OH^{-} + OH^{\bullet} \quad (10)$$

This $OH^{\bullet}$ production is of significant biological/ecological concern, because this free radical is the most potent oxidant (Winston and Di Giulio, 1991).

For non-redox-active metals, Wätjen and Beyersmann (2004) and Rani et al., (2014) observed an indirect Cd mechanism for ROS production because this metal replaces Cu, Zn and Fe ions in several cytoplasmic organelles and metalloproteins; this unbound free ions (mainly Fe) participate in ROS production via the Fenton reaction (Chang et al., 2009). Moreover, ROS are generated when Cd affect the mitochondria and alters the cellular respiratory process (Li et al., 2011). Ercal et al. (2001) reported that Cd induces oxidative stress due to (1) lipid peroxidation enhancement; (2) antioxidant enzyme (SOD and CAT) activity reduction; and (3) GSH level disturbance.

According to Ercal et al. (2001) and Lushchak (2011), the Hg relationship with oxidative stress is through GSH, which is considered the first line of defense against Hg. When organisms are exposed to Hg, this metal complexes with GSH, reducing their role in scavenging ROS activity. Besides, Hg may displace Fe and Cu ions from proteins (as Cd), and these elements are redox-active metals (Fenton reaction-mediate ROS production).

Ballatori (2002) also reported that Pb toxicity occurs by replacing divalent cations (Zn, Fe) by the mimicry of Ca. Furthermore, Ercal et al. (2001) pointed out that Pb causes a CAT and GPx inhibition due to binding to these enzymes. Furthermore, Stohs and Bagchi (1995) pointed out that Ni induces oxidative damage by displacing Fe from the cofactor binding sites of cellular proteins, which increases Fe flux into Fenton reactions, generating hydroxyl radicals (Tamzin and Wood, 2015). For Ag, Walters et al. (2016) associated oxidative stress to Ag interaction with SOD and CAT thiol groups causing inactivation.

7. Oxidative stress effects

Lipid peroxidation (LPO) is considered the main consequence of oxidative damage (Halliwell and Gutteridge, 2001). ROS have a high affinity to bind polyunsaturated fatty acids causing LPO, which is considered as a good biomarker of cellular membrane damage by ROS (Torreilles and Guérin, 1990; Das et al., 2019). Stohs and Bagchi (1995) pointed out that metals as Cd, Cu, Cr, Fe, Hg, Ni, and Pb causes oxidative tissue damage as LPO; and integrity and permeability disturbances of cell membranes have been reported as cytotoxic damages by LPO (Svendsen et al., 2004), which alters cellular vital functions. In this context, Singaram et al. (2013) reported lesser membrane stability in *S. serrata* hemocytes when exposed to 10 μg/L of Hg, which affect their phagocytic capacity and reduce crab immune response and other cellular functions. Similarly, Singaram et al. (2013) reported higher LPO in hemocytes, gills, and hepatopancreas of *S. serrata* at 14 days of exposure at 1–10 μg/L Hg for seven days.

Malonaldehyde (MDA) – a biomarker of lipid peroxidation – is a highly reactive pro-oxidant (Livingstone, 2001), which is an important LPO product, and its quantity is related to cell damage (Li et al., 2015). In this context, Wang et al. (2011) and Li et al. (2016) reported high MDA levels in the crab *S. henanense* testes and sperm, respectively, when the crab was exposed to Pb (58.8 mg/L). Liu et al. (2014) and Li et al. (2015) also observed an increase in MDA production when exposed to Pb in the hepatopancreas and testes of *S. henanense*, respectively; they concluded that this MDA production was a consequence of antioxidant defense decrease. When exposed to Cd, this metal caused an increased level in MDA and protein carbonyl in hepatopancreas, gills, and heart of *Sinopotamon yangtsekiense* (Li et al., 2011). After this metal exposure, MDA reacts with amino acids causing a cross-linking within and between proteins, which alters crustacean cellular physiology (Wu et al., 2013).

Brouwer and Brouwer (1998) and Quintaneiro et al. (2015) reported an increase in LPO levels in crab *Callinectes sapidus* and shrimp *A. desmarestii* when exposed to 3.17 mg/L of Cu and 0.5 mg/L of Zn, respectively. While Srivedi et al. (1998) reported that MDA levels increased in crab *Barytelphusa guerini* hepatopancreas after 15 days exposed to 20.1 mg/L of Cr. Sabatini et al. (2009) reported a time-dependent MDA and carbonyl increase in the crab *Neohelice granalata* fed with 300 μg of Cu/g food, indicating that antioxidant defenses

were overwhelmed. This carbonyl production is the result of ROS damage to proteins, which causes structural alteration and functional loss (Hamilton et al., 2015). Oxidative damage could be a consequence of disease conditions (Livingstone, 2001). Zhang et al. (2009) observed significant damage to DNA in the hemocytes of the crab *C. japonica* when exposed to 5 μg/L of Hg. These authors concluded that DNA strand break is one type of oxidative damage in organisms.

According to Singaram et al. (2013), O_2^-production could cause higher infection susceptibility in *S. serrata* when exposed to Hg. Moreover, Guo et al. (2017) observed a direct relationship between ROS production and hemocyte apoptosis, which affected the immune response of L. *vannamei* when exposed to Cu. Brouwer and Brouwer (1998) reported protein oxidation in *C. sapidus* when exposed to 3.17 mg/L of Cu. Oxidation of iron-sulfur ligands by O_2^- is a common effect that inactivates enzymes (Stadtman, 1986). Furthermore, Wang et al. (2011) and Wang et al. (2013) observed a high H_2O_2 production in *S. henanense* testes and gills when exposed to 14.5 and 29 mg/L of Cd, respectively.

Blewett and Wood (2015) observed protein oxidation in *C. maenas* exposed to 3 mg/L of Ni, which is a result of the ROS effect on proteins, causing carbonyl formation. Li et al. (2011, 2016) reported carbonyl group formation in *S. henanense*, which was related to ROS production during Cd (29 mg/L) and Pb (59 mg/L) exposure, respectively. The formation of these groups could have been produced by amino acids oxidation (e.g., Lys, Arg, Pro and Thr) because $OH^{\bullet}$ reacts with these amino acids and produces carbonyl, indicating that normal protein metabolism was altered (Lushchak, 2011).

The oxidative damage by Pb exposure (at 59 mg/L) has been related to histological alterations in *S. henanense* testes, sperm decrease, and disorder in cell germs distribution (Li et al., 2015). Li et al. (2016) reported DNA damage in crab sperm of the same crustacean when exposed to 29.4 mg/L of Pb, which was attributed to oxidative stress. Moreover, Lewis and Ford (2012) pointed out that crab sperm has a high quantity of polyunsaturated fatty acids, and ROS have a high affinity to these fatty acids. Lei et al. (2011) found that excessive ROS alters mitochondrial membrane permeability and affects the respiratory chain in *S. yangtsekiense* when exposed to Cd. Wang et al. (2013) observed in *S. henanense* H_2O_2 increase when exposed to 14.5 mg/L of Cd, and concluded that this radical activates the cellular apoptotic response.

8. Conclusions

The metals with higher studies regarding effects on antioxidant enzyme activities on marine decapods are Cu and Cd (27 and 27%, respectively), and the antioxidant enzymes with more studies are SOD and CAT (32 and 28%, respectively). To our knowledge, this review demonstrates that no studies on effects of cadmium-GST, Zn-SOD, Cr-CAT and Ni-GPx have been available or performed. The decapod with the highest number of studies is *S. henanense* (21%); the tissues/organs used are hepatopancreas, gills, hemocytes, muscle, heart and testes; while hepatopancreas is the organ with the most studies carried out of each metal.

Considering that a more accessible speciation modeling is now available, in the near future studies of metal toxicity in crustaceans should be carried out taking into account metal speciation and their combination or mixture. Antioxidant enzymes are induced or inhibited by metals depending on decapod species and metal concentration, but the information revised in this review indicates that exposure times is another important factor in the inhibition/stimulation of antioxidant enzymes in decapod crustaceans. For example, at relatively low Cd concentrations (< 70 μg/L), SOD, CAT and GPx activities are exposure time-dependent at low exposure time (12 h), but these antioxidant activities decrease at higher exposure time (15 days). Nevertheless, at higher Cd concentrations (> 500 μg/L) antioxidant enzyme activities are species/organ/exposure time/ and concentration-dependent. Evidently, metal exposure causes ROS accumulation that overcomes the scavenging capacity of antioxidant enzymes. These results suggest that antioxidant defense strategies used by aquatic crustacean decapods vary widely among species. Mercury was the most toxic metal because a low level (1 μg/L) affects antioxidant enzymes. This fact is of ecological concern because this concentration is very close to EPA (EPA, 2009) guidelines (0.9 μg/L as continuous concentration criteria). Moreover, metal mixture effects on antioxidant enzymes must be carried out in aquatic decapod crustaceans.

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