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CRITICAL REVIEW

Emerging trends in environmental and industrial applications of marine carbonic anhydrase: a review

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Abstract

Biocatalytic conversion of greenhouse gases such as carbon dioxide into commercial products is one of the promising key approaches to solve the problem of climate change. Microbial enzymes, including carbonic anhydrase, NAD-dependent formate dehydrogenase, ribulose bisphosphate carboxylase, and methane monooxygenase, have been exploited to convert atmospheric gases into industrial products. Carbonic anhydrases are Zn^{2+}-dependent metalloenzymes that catalyze the reversible conversion of CO_2 into bicarbonate. They are widespread in bacteria, algae, plants, and higher organisms. In higher organisms, they regulate the physiological pH and contribute to CO_2 transport in the blood. In plants, algae, and photosynthetic bacteria carbonic anhydrases are involved in photosynthesis. Converting CO_2 into bicarbonate by carbonic anhydrases can solidify gaseous CO2, thereby reducing global warming due to the burning of fossil fuels. This review discusses the three-dimensional structures of carbonic anhydrases, their physiological role in marine life, their catalytic mechanism, the types of inhibitors, and their medicine and industry applications.

Keywords Carbonic anhydrase · Structural aspects · Pharmacological and monitoring application · Marine organisms

Introduction

Oceans are among the richest sources of bioactive molecules used in industrial and medical applications [1–11]. In addition to pharmaceutical applications, these bioactive molecules are used in the food and cosmetics industries [12, 13]. The demand for biomaterials from marine sources has increased considerably because of their unique properties compared to compounds from the terrestrial origin [14–17]. Over the past decades, more than 16,000 marine organisms have been identified and studied as sources of various critical biological materials, such as proteins, peptides, glycoproteins, polysaccharides, and lipids [18, 19]. In particular, marine enzymes, among which carbonic anhydrases, were discovered using traditional and metagenomics screening approaches [17].

In the nineteenth century, the various enzymes were reported for the medical purposes including pancreatic enzymes, collagenase, glutaminase, and asparaginase which were frequently used for the treatment of gastrointestinal disorders [20], skin wounds [21], and leukemia [22]. Hyaluronidase has been used to treat heart attacks [23], and lysozyme has been reported to produce antibiotic drugs [24–26]. Furthermore, bacterial β-lactamase was used to inactivate β-lactam antibiotics by hydrolyzing the β-lactam ring structure [27, 28]. Various foods rich in therapeutic enzymes also contribute to body health and disease resistance [29, 30]. In the twentieth century, crude proteolytic enzymes were used to treat gastrointestinal disorders,

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which was a turning point for the use of enzymes in the treatment of infections, cancer, and many other diseases [31]. Mostly, enzymes having medicinal values were isolated from fungi, yeasts, bacteria, and algae [32]. For example, agarase was extracted from seaweeds and used in the food and medical industries as an emulsifying, gelation, and stabilizing agent [14, 33]. Enzymes, including α-amylase [34], lipases [35], esterases [36–38], chitinases [39], laccases [40, 41], glycine oxidase [42], glutamine synthetases [43–52], and serine hydroxyl methyltransferases [53], which were stable and retained their activity at critically higher temperatures and pHs, were widely used in the paper, textile, food, and detergent industries [33, 53–68]. Another enzyme, pullulanase, isolated from marine bacteria, including *Archaebacterium* and *Fervidobacterium pullulanolyticum*, was widely used in the starch industry, as this enzyme can withstand higher temperatures (90 °C) [33]. The enzyme cyclomaltodextrin glucanotransferase (Cgtase) isolated from a deep sea-dwelling *Bacillus subtilis* was reported for cyclodextrin production [33]. Alginate lyase extracted from microorganisms *Bacillus* sp., *Alteromonas* sp., and *Photobacterium* sp. was widely used to convert brown algae biomass to methane [33]. The α-galactosidase reported from marine organisms, including photobacteria *Alteromonas* sp., sponges, red algae *Polysiphonia* sp., mussel *Crenomytilus grayanus*, and scallop *Patinopecten yessoensis* hydrolyzes the sugar in living organisms [33].

Carbonic anhydrases (CAs; EC 4. 2. 1.1) are widespread enzymes in bacteria, archaea, and eukaryotes [69]. They are only catalytically active when one metal ion bound in the active site cavity [70]. Generally, the metal ion is bound in a tetrahedral geometry, coordinated by three amino acid residues and a water molecule/hydroxide ion (Fig. 1). So far, eight evolutionarily independent CA families are known (α-, β-, γ- δ-, ζ-, η-, θ-, and ι-CAs) [71, 72] (Fig. 1). Various members of these CA classes have been crystallized and structurally characterized [73]. The CA families do not show significant sequence homology, and their three-dimensional structures are also different [74]. However, they all contain a catalytically essential Zn^{2+} ion in their active site, thus offering good examples of convergent evolution [74]. However, in ζ-CAs, Cd^{+2} can replace Zn^{+2} [75], and, in γ-CAs under anaerobic conditions, Fe^{2+} is present [76] (Fig. 1). Moreover, Co^{2+} is another ion that can substitute the zinc in many α-CAs without a significant loss of catalytic activity [74, 75]. The θ-CAs appear dissimilar to α- and δ-CAs, but are similar to β- and ζ-CAs, using cysteine, histidine, and sometimes aspartate for Zn coordination [75]. The ι-CAs from the marine diatom *Thalassiosira pseudonana* have recently been reported as a new subclass of CAs, which unusually prefers Mn^{2+} over Zn^{2+} as a cofactor [77].

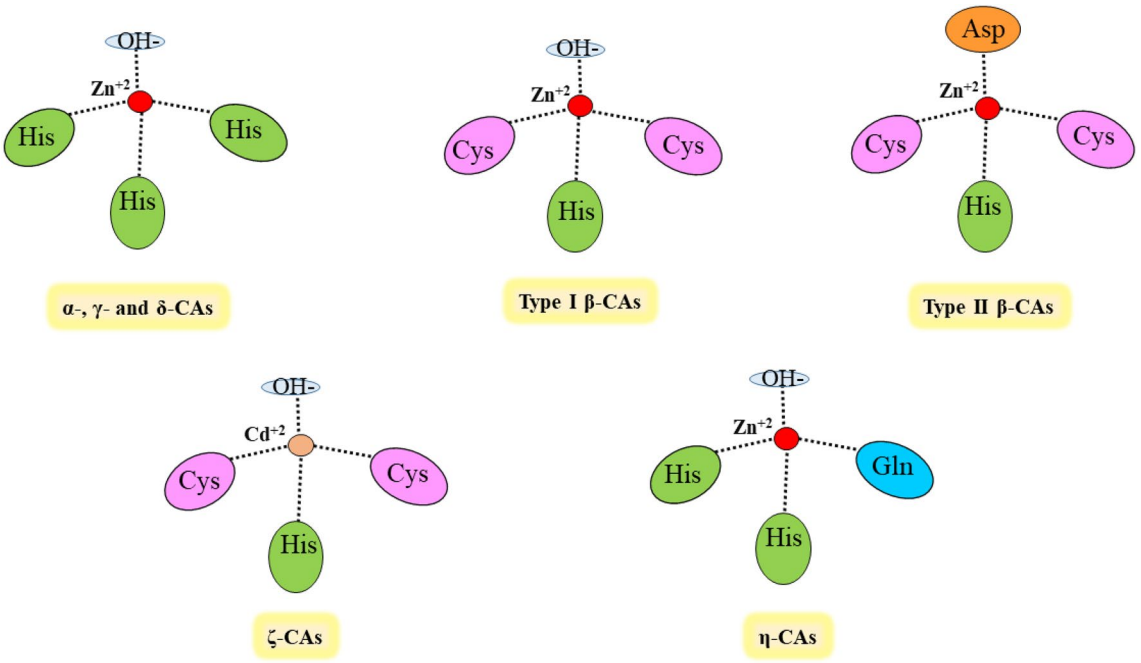

Fig. 1 Schematic structure of CAs: α-, γ- and δ-CAs, the coordinating residues are from the same monomer in the α- and δ-classes, whereas in γ-CAs, the third His is from an adjacent monomer; Type I β-CAs with opened active site; Type II β-CAs with closed active site (An aspartate residues as the fourth zinc ligand); ζ-CAs with Cd^{2+} bound within the active site; η-CAs with different pattern of the metal ion coordination than other CAs, with two histidine and one glutamine residue in addition to the water molecule/hydroxide ion binding the Zn^{2+}

The metal ion stabilizes a hydroxide ion in the active site, which, through physiological pH, forms a hydrophilic reaction in the hydroxide ion. At the active site of metalloenzymes, not only the metal ion but also the amino acid residues modulate the solvent reactivity [78–81]. The active site of CA is in the gap near the center of the cone with a depth of 15 Å. It contains the hydrophobic binders and on the other side with hydrophilic residues containing Glu-106 and Thr-199 [78, 82]. The zinc ion lies deep inside the gap. The second construct is the active site of the enzyme, the beta sheets, and the three histidine residues ligating the zinc ion, are located in the central part of the platelet [83, 84]. Zn^{2+} is coordinated by three residues, His-49 Nε1, His-96 Nδ2, His-119 nitrogen, and a water molecule deep in the active site. His-94 Nδ2 forms a hydrogen bond with the oxygen atom of Glu-92, His-119 Nε1 with Gln-117 Oε1, and His-96 Nδ2 with carbonyl oxygen group of Asp-224 [78, 82, 85]. A water molecule/hydroxide ion completes the quad pole structure of the zinc ion. The active site of the enzyme consists of hydrophobic ligands. In the absence of substrate, the substrate-binding site is filled with a network of water molecules in direct contact with the carbonic anhydrase. This water molecule is replaced by carbon dioxide [78, 82, 86].

Carbonic anhydrase is an effective model for biophysical studies of ligand–protein interactions. High-resolution crystal structures of the various isoenzymes of CAs have been reported, allowing protein engineering by site-directed mutagenesis for enhanced stability and catalytic activity for medical and industrial applications [87, 88]. CAs high-catalytic efficiency, relative stability, and simple process of purification and expression have become them as an exciting candidate for use in various applications such as biosensors, artificial lungs, CO_2 sequestration, etc. (Fig. 2). In the marine environment, CA is involved in biomineralization. The CA enzyme has recently drawn attention for its role in sequestration/capture of CO_2 to mitigate global warming effects by reducing CO_2 released into the atmosphere [89–92]. Microbes can form calcium carbonate by reacting with CO_2, thus helping in converting CO_2 into value-added products [89–91, 93]. Furthermore, CAs are widely studied to treat various diseases such as cancer, obesity, and glaucoma.

An overview of previous studies showed the importance of CAs as activators and inhibitors for treating various disorders [94–100] with a specific focus on α-CAs from terrestrial sources. In this work, we provide a comprehensive review of CAs extracted from marine organisms, their physiological roles, locations, and recent advances in CAs for medical and environmental purposes and their inhibitors' applications. This study may provide new insights into CAs from marine sources for future industrial and medical applications.

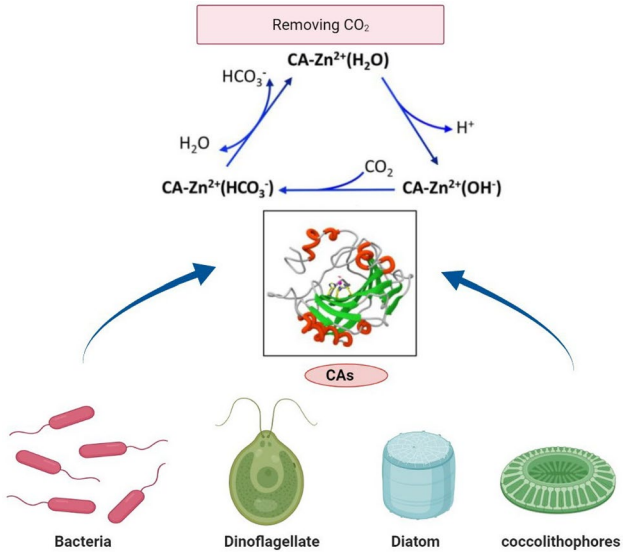

Fig. 2 Schematic representation of CAs extracted from the different marine organisms, their activations to capture CO2 and applications in various fields

Types of carbonic anhydrase in marine organisms, their structure, position in cells, physiological roles, and inhibitors

Carbonic anhydrase α

Alpha-carbonic anhydrase is found in vertebrates, bacteria, algae, and the cytoplasm of green plants. The presence of Zn^{2+} in the active site is essential for its catalytic action. The carbonic anhydrase α are typically monomeric. However, some α-CAs from humans and bacteria have been reported to be homodimers [69]. α-CAs have a zinc catalyst located on the three remaining parts of His [101]. X-ray crystallography data show that the zinc ion is at a depth 15-degree below the enzyme's active site (Fig. 1). Histidine clusters play an important role in the transferring proton between the active site and the environment in some isozymes of this family [78, 82, 85].

Mechanism of action of carbonic anhydrases have been described in the following reaction (1)

$$CO_2 + H_2O \rightleftarrows HCO_3^- + H^+ \quad (2)$$

As shown in Fig. 3, the enzyme's active form occurs when zinc metal binds to the hydroxide ion (Stage 1). This hydrophilic OH^- attacks the CO_2 at the hydrophobic site inside the active site (Stage 2). These reactions form the Zn^{2+} bicarbonate complex (Stage 3). The bicarbonate ion is released into the solution by a water molecule resulting in the enzyme's acidic form (Stage 4). The water molecule is coordinated with the zinc ion, which is catalytically inactive (Fig. 3). The

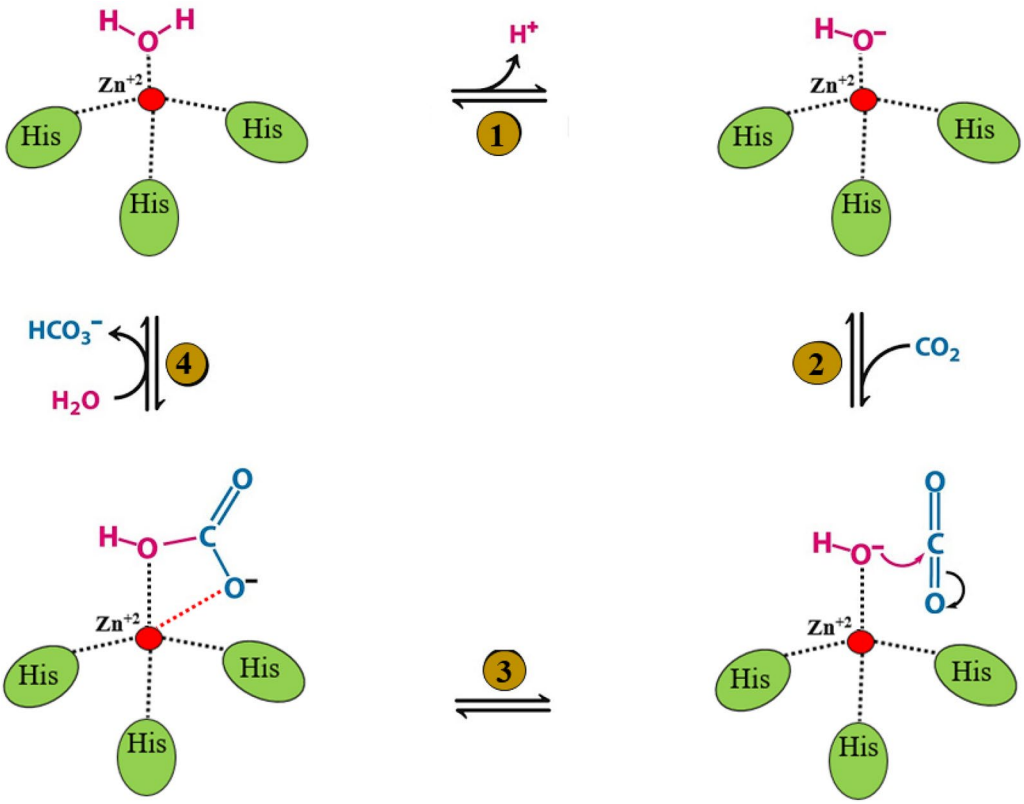

Fig. 3 Catalytic (for the physiological reaction) mechanism of α-CAs: In step 1, proton shuttle residues play a crucial role in the proton transfer processes. Step 2: The substrate CO_2 as bound in hydrophobic pocket is observed near to the Zn^{2+} ion. Stage 3: The orientation of bound CO_2 in this favorable position will result for the nucleophilic attack by the zinc hydroxide species of the CAs, and transformation CO_2 into bicarbonate coordinated to the Zn^{2+} ion. Stage 4: With an incoming water molecule, liberating the bicarbonate into solution will make because the rather labile binding of bicarbonate to zinc and the acidic species of the CAs, with water as the fourth zinc ligand will formed. Generation of the nucleophilically active species of the CAs (with hydroxide bound to zinc, stage 1, achieved through a proton transfer reaction from the zinc-coordinated water to the buffer), is the rate-determining step of the entire process

proton transfer from the active site to the medium must be carried out to achieve the enzyme's active form. This may be the residue of His-64 (Fig. 3) or clusters of histidine at the active site of the proton shuttle in isozymes (I, II, IV, VI, VII, IX, XII, XIV) and buffer in the medium (BH^+) [82, 102, 103].

This process may take the form of reactions 2 and 3 [82, 104, 105].

$$E - Zn^{2+} - OH^- \overset{CO_2}{\leftrightarrows} E - Zn^{2+} - HCO_3^- \overset{H_2O}{\leftrightarrows} E - Zn^{2+} - OH_2 + HCO_3^- \quad (2)$$

$$E - Zn^{2+} - OH_2 \rightleftarrows E - Zn^{2+} - OH^- + H^+ \quad (3)$$

Carbonic anhydrase α is present in vertebrates, especially mammals. So far, 16 different isozymes have been identified and characterized in these organisms with other catalytic activity. Such isozymes demonstrate different sensitivities to inhibitors such as sulfonamides. Table 1 shows a variety of isoenzymes α-CAs have been extracted from marine organisms including, diatoms, coccolithophore, alga, calcareous sponges, corals, tubeworms, euryhaline crabs, oysters, mussels, teleost fishes, and sea lamprey, up to now (Table 1).

The location of α-CAs in marine organisms can vary regarding functional roles for the organism (Table 1). In diatoms and alga, α-CAs were typically located in the chloroplast stroma, periplasmic space, cytosol, and mitochondria (Table 1). The physiological roles of α-CAs in primary marine organisms are mainly carbon concentrating mechanisms, photosynthesis, and global biogeochemical carbon cycling (Table 1). These marine α-CAs are mostly inhibited by sulfonamides [106] (Table 1). In the sclerocytes of calcareous sponges and ectoderm, endoderm, scleroblasts, and desmocytes of corals, α-Cas are involved in calcite formation, pH regulation, and inorganic carbon delivery (Table, 1). The inhibitors reported for these organisms are sodium hypochlorite (NaOCl) and Diamox [107, 108] (Table 1). In crustacea and Mollusca, α-CAs are located in gill epithelial cells, muscles, mantle, hepatopancreas, and hemocytes

Table 1 Structural diversity of marine carbonic anhydrases, their location, and functions

Class	Species	Molecular mass (kDa)	Families of CAs	Location (intracellular, out cellular)	Physiological functions	Inhibitors	References
Diatom	*Phaeodactylum tricornutum*		Two β-CA and five α- and two γ-CA genes,	The central part of the pyrenoid structure in the chloroplast	Carbon concentrating mechanisms/Photosynthesis		[136]
Diatom	*P. tricornutum*	28, 25, 24, 23.5	Two internal CA isoforms Two external CA isoforms	1. Periplasmic space and on the cell membrane 2. High CO_2-grown cells	CO2 concentrating mechanism		[137]
Diatom	*P. tricornutum*		θ-CA	Thylakoid lumen	Growth and photosynthesis		[138]
Diatom	*Thalassiosira pseudonana*		Three α-, five γ-, four δ-, and one ζ-CA	Stroma and periplasm	Carbon concentrating mechanisms/ Photosynthesis		[136]
Diatom	*T. pseudonana*		1. TpδCA1 2. TpδCA3 and TpγCA2 3. TpδCA2, TpγCA1, TpγCA3, and TpγCA 4	1. Periplasmic space or the frustule 2. Periplastidal compartment and the cytosol 3. Mitochondria	CO_2 concentrating mechanism		[72]
Diatom	*T. pseudonana*		iota-CA	Chloroplast	CO_2 concentrating mechanisms, global biogeochemical carbon cycling	Sulfonamides	[77]
Diatom	*Thalassiosira weissflogii*	69	CDCA1(ζ class)	-	Trace-metal geochemical cycling		[139]
Green algae	*Chlamydomonas reinhardtii*		θ-CA	Thylakoid membrane spanning the pyrenoid	CO_2 concentrating mechanisms/photosynthesis	Acetazolamide	[140]
Green algae	*C. reinhardtii*		Three α-CAs and five β-CAs	1. Chloroplast stroma 2. Chloroplast thylakoid lumen	CO_2 concentrating mechanism	Sulfonamides	[106]
Green algae	*C. reinhardtii*		CAH7 and CAH8 (β-type CAs)	Periplasmic space	Inorganic carbon acquisition		[141]
Coccolithophorid algae	*Emiliania huxleyi*	δ-EhCA1 (77.3) γ-EhCA2 (24.9)	(γ-EhCA2) (δ-EhCA1)		Incorporate dissolved inorganic carbon (DIC) into both calcite and photosynthetic products		[142]
Unicellular protozoan parasite	*Plasmodium falciparum*		η-CA			Sulfamide, sulfamic acid, phenylboronic acid, and phenylarsonic acid	[133]

Table 1 (continued)

Class	Species	Molecular mass (kDa)	Families of CAs	Location (intracellular, out cellular)	Physiological functions	Inhibitors	References
Calcareous sponges	*Sycon ciliatum* and *Leucosolenia complicate*		Two α-CAs (one intracellular and one extracellular)	Sclerocytes	Calcite spicule formation		[143]
Calcareous sponge	*Sycon raphanus*		Putative CAs	Sclerocytes	The catabolism of amorphous calcium carbonate (ACC)	Sodium hypochlorite (NaOCl)	[108]
Coral	*Stylophora pistillata*	35.2	STPCA-2	The oral endoderm and the aboral tissue	pH regulation and/or inorganic carbon delivery to symbiont and calcification		[144]
Coral	*S. pistillata*		STPCA (α-CA)	Calicoblastic ectoderm	Responsible for the precipitation of the skeleton		[145]
Gorgonian	*Leptogorgia virgulata*			1. The sclero-blasts and axial epithelium (the membranes of the spicule-forming vacuole) 2. Microvilli and plasma membranes of the desmocytes	The regulation of HCO3 and calcification	Diamox	[107]
Sea anemone	*Aiptasia pulchella*			Endodermal cells, on or near the vacuolar membranes surrounding the zooxanthellae	Increasing Photosynthetic rate with dissolved inorganic carbon (DIC)	Acetazolamide	[146]
Vent tubeworm	*Riftia pachyptila*		CARp (Similar to cytosolic isoforms in vertebrates)	Cytosolic and membrane-bound CA isoform	The optimization of CO_2 transport and conversion		[147]
Euryhaline crab	*Chasmagnathus granulata*			Cytosolic and microsomal fractions of gills	Ion transport process	Sulfonamide acetazolamide	[110]
Euryhaline crabs			The cytosolic form	Membrane-bound of gill epithelial cells	CO_2 excretion, osmoregulation and ion transport	Acetazolamide	[109]
White shrimp	*Litopenaeus vannamei*			Gills and epidermal tissue	Supplying counter-ions for $Na+$ and $Cl-$ uptake during molting		[148]
Mussel	*Mytilus galloprovincialis*	28		Digestive gland	Sensitivity to in vivo cadmium exposure		[149]

Table 1 (continued)

Class	Species	Molecular mass (kDa)	Families of CAs	Location (intracellular, out cellular)	Physiological functions	Inhibitors	References
Mussel	*M. galloprovincialis*		MgNACR (α-CAs)	Mantle	Regulating mussel shell production		[150]
Pacific Oyster	*Crassostrea gigas*		CgCAII-1 (a Cytosolic α-CA)	Muscle, mantle, hepatopancreas, gill, and hemocytes	Inhibited by acetazolamide (AZ) Respond to ocean acidification and participate in acid–base regulation		[151]
Pathogenic nematode	*Caenorhabditis elegans*		CAH-4b alpha (α-CAs)		Survival in pH conditions ranging from pH 3 to 10	Complex benzenesulfonamide compounds	[152]
Green sea urchin	*Lytechinus variegatus*			Epithelium, free odontoblasts, row odontoblasts and their membranes surrounding the calcareous parts, and Extracellular areas	Facilitating the movement of CO_2 through the membrane and/or extracellular spaces to promote calcification		[153]
Seastar	*Asterias forbesi*			The tissues containing the ossicles, and the non-calcifying tube feet	Facilitating the ongoing maturation process of newly formed ossicles		[154]
14 teleost, 2 agnathans, and 1 shark				Gill pavement cells and chloride cells	Acid–base regulation and NaCl regulation	Ouabain, Acetazolamide	[111]
Acorn worms	*Saccoglossus bromophenolosus* and *Ptychodera-flavagalapagos* (Hemichordata)			Epidermal structures of sclerocytes	Secreting biominerals including small $CaCO_3$ aragonitic elements		[155]
Sea lamprey	*Petromyzon marinus*		A cytosolic carbonic anhydrase (ca19)	Highest in the gill of ammocoetes and decrease during metamorphosis	CO_2 transport, acid–base, and ion regulation and metabolic processes		[156]

(Table 1). They play leading roles in osmoregulation, ion transport, acid–base regulation, and regulating shell production (Table 1).

Sulfonamide, acetazolamide is inhibitor was reported for these organisms [109, 110] (Table 1). In evolutionarily higher marine organisms, such as hemichordate and lamprey, α-CAs are located in sclerocytes, gill pavement cells, and chloride cells responsible for secreting $CaCO_3$ aragonitic elements, acid–base ion ad regulation, and metabolic processes (Table 1). Ouabain and acetazolamide were reported as inhibitors for fishes [111] (Table 1).

In the context of inhibitors acting on α-CA, the researchers examined the inhibitory properties of pyrazole compounds (1–8, 9a, b) by IR and NMR. These derivatives were identified as effective CA inhibitors and also for the enzymes acetylcholinesterase (AChE) [112]. Due to the inhibitory ability, these compounds can be used in the pharmaceutical industry to treat diseases such as glaucoma, leukemia, epilepsy, and Alzheimer's disease, etc. [113]. Studies have shown that bromophenol are potent inhibitors of CAs [114]. Bis-thiomethylcyclohexanone (3a–3j) is a member of the hydrolase family that plays an important role in acetylcholine's neurotransmission. In general, these compounds have effective inhibitory properties for CA, hCA I, hCA II, and these are potent anti-Alzheimer's drugs [115].

Rosmarinic acid and 3–4-dihydroxyphenolytic acid are present predominantly in plant species belong to *Boraginaceae* and *Lamiaceae* family. These compounds showed an inhibitory effect against the CAs [116]. The nitrile inhibitor of the latest benzotropon derivatives has been studied on human carbonic anhydride anisoenzymes II (hCA I and hCA II). It has been established that these functional benzotropic-myelothyrin analogs perform inhibition of CA isoenzymes in the micromolar range. Capsaicin, the main ingredient of bell peppers, is commonly used in sauces, pickles, food additives, and medical goods, responsible for their spicy flavor. The effect of capsaicin's against cytosolic hCA I isoenzymes, and hCA II isoenzymes were studied. Capsaicin blocks all Cas at a low concentration in the micromolar range [117].

Carbonic anhydrase β

Carbonic anhydrase β is a highly reactive enzyme in organisms, including protozoans, arthropods, nematodes, bacteria, fungi, algae, and plants [118–122]. These enzymes have also been found in several human pathogens, such as fungi, yeasts, and bacteria. Inhibition of β-CAs through a variety of inhibitors may help in the treatment of diseases caused by these factors. Reactive β-carbonic anhydrases are present with α variants in other families. The monomeric, oligomeric, and trimeric forms of carbonic anhydrases are categorized as α, β, and γ. The crystalline structure of the dimeric, tetrameric, and octameric β-carbonic anhydrases has not been reported up to date [123–125].

The active site of the β-CAs possesses a zinc atom coordinated by one histidine group, one water molecule, and two cysteine residues [125, 126] (Fig. 1). β-Carbonic anhydrases have a highly conserved amino acid pair consisting of aspartate and asparagine groups, which appear to be necessary for the enzyme's catalytic mechanism. High-mutation residues significantly reduce the catalytic activity of the enzyme. Aspartate forms a hydrogen bond to the water molecule attached to the zinc atom and activates it for the nucleophilic attack of the CO_2 molecule [125, 126]. As Table 1 presents, β-CAs were extracted from the pyrenoid structure of the chloroplast in diatoms, and chloroplast thylakoid lumen and periplasmic space alga, along with other CAs, and are involved in carbon concentrating mechanisms and photosynthesis similar to α-CAs (Table 1). Sulfonamides were reported as the main inhibitors β-CAs [106].

Carbonic anhydrase γ

Gamma class of CAs is the most ancient form of CA, which is mostly present in archaea bacteria and exists as a trimer. Such carbonic anhydrases take advantage of the presence of Fe^{2+} for their catalytic activity, but when the enzymes are attached to Zn^{2+}, Co^{2+} metals, they still have catalytic activity [78, 81]. γ-CAs is an active biocatalyst and is considered as a critical modifier in various biochemical reactions. Subunit histidine in each monomer will determine the metal ions between the monomers [127]. Recently the crystalline structure of a γ-CA has been reported [27]. This trimeric molecule has an entirely different fold to that of α-carbonic anhydrases [128, 129]. There are seven circular left β spiral screws in each subunit with three short strings per screw. Zinc ions are bound to histidine 81, histidine 122, and histidine 117 subunits bound to the neighboring subunit. The disordered tetrahedral coordination is completed by a water molecule [130, 131]. In marine organisms, γ-CAs were found in stroma and pyrenoid of the chloroplast, periplasm, and mitochondria in diatoms and coccolithophorid algae (Table 1).

Carbonic anhydrase δ

To date, the delta class of CA has only been found in marine diatom *T. weissflogii*. Its active site is similar to α-, γ-CAs, coordinating the Zn^{2+} with three histidine residues and a water molecule/hydroxide ion (Fig. 1). δ-CAs in marine organisms were found in the stroma, periplasm of diatoms, coccolithophorid algae, and carbon concentrating mechanisms (Table 1).

Carbonic anhydrase ζ

This CA, named ζ-CA, was reported in chemolithotrophic bacteria, marine diatoms, and coccoliths. In the ζ-CAs, the metal ion coordination is similar to β-CAs, except that the metal ion may be Cd^{2+}or Zn^{2+}, which metal ions are attached to one histidine and two cysteines (X, X + 52, X + 62, where X = 263 on CDCA1) [127, 132], as shown in Fig. 1.ζ-CA were extracted from stroma and periplasm of diatoms *Thalassiosira pseudonana* and *T. weissflogii*, where they play functional roles in trace-metal geochemical cycling, carbon concentrating mechanisms and photosynthesis (Table 1).

Carbonic anhydrase η

This carbonic anhydrase class was recently discovered in the protozoan parasite *Plasmodium falciparum* [133] (Table 1). Besides, in the catalytic cycle, the water molecule and the hydroxide ion act as a nucleus. This property is unique to other families of carbonic anhydrase [134, 135]. A η-CA has three histidines for Zn coordination and is phylogenetically related to α-CA [133]. Sulfamide, sulfamic acid, phenylboronic acid, and phenylarsonic acid are the main inhibitors η-CAs [133] (Table 1).

Carbonic anhydrase θ

The θ class of CA has been recently reported in diatom *Phaeodactylum tricornutum* and green algae *Chlamydomonas reinhardtii* (Table 1). Structurally, θ-CAs are similar to β-CAs in the overall fold, zinc-binding motif, and especially putative active site architecture [140]. The functional roles of θ-CAs are identical to other CAs in CO_2 concentrating mechanisms and photosynthesis for the organism (Table 1) [138]. Acetazolamide has been reported as an inhibitor of θ-CAs [140].

Carbonic anhydrase ι

ι-CA was recently reported from the chloroplast of the marine diatom *T. pseudonana* as a new widespread subclass of carbonic anhydrase [77]. ι-CA unusually prefers Mn^{2+} to Zn^{2+} as a cofactor and plays an essential role in CO_2 concentrating mechanisms and global biogeochemical carbon cycling (Table 1).

Carbonic anhydrase inhibitors

CAs is classically inhibited by compounds with a sulfonamide-based zinc (ZBG) bonding group (SO_2NH_2) or their derivatives (sulfamates and sulfamides). Sulfonamides bind in a quad geometry, as direct interaction with catalytic site containing zinc, so that CA activity is restricted by the displacement with zinc ions and binding to water/hydroxide ions (Fig. 4). Several aromatic and heterocyclic sulfonamides are active and potent inhibitors of CAs. These inhibitors bind through the sulfonamide groups nitrogen atom to metal ions as R-SO_2N-OH- or R-SO_2NH-anions [157] (Fig. 4).

Currently, several sulfonamide-based CA inhibitors are clinically used to treat various diseases. However, the design of special isoforms of inhibitors have been developed which is particularly complexed with the active site of the isoform CAs. Since the CA inhibitors act systematically and connect non-specifically, they causes side effects and disease [70, 158–160]. Therefore, the development of specific inhibitors can result lower side effects [161–163]. In the sequence method, a compound and a ZBG with a high compound affinity are used [164]. Recently, the tail method has been used in the production of specific isoform inhibitors designed by SLC-0111, a proprietary CA IX-specific inhibitor, and these isoforms have also been tested in clinical trials for the treatment of breast cancer (Table 2) [165].

In studying the metal center characteristics and the relationship between structure and function of CAs, carbonic anhydrase inhibitors (CAIs), including sulfonamide drugs,

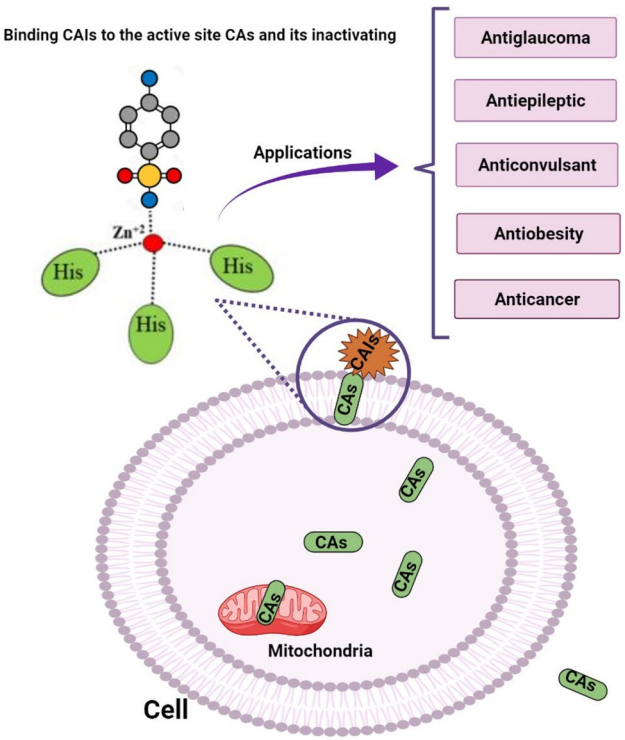

Fig. 4 Schematic representation of binding CAIs to CAs, inactivating of CAs, and its application in the field of medicine (*CAs* carbonic anhydrases, *CAIs* carbonic anhydrases inhibitors)

Table 2 Inhibitors of CAs developed for selective targeting

Inhibitor	CA inhibited	Application(s)	Reference(s)
3,4-Dihydroxyphenyl)(2,3,4-trihydroxyphenyl)methanone	hCA I and hCA II	Antiglaucoma	[196]
NCX250	CA, EC 4.2.1.1	Blood supply to the optic nerve (increasing ocular hemodynamics, decreasing the inflammatory processes and ocular apoptosis)	[197]
Dithiocarbamates	hCA I, II, IX, and XII	Adequate intraocular pressure lowering activity of CAs (antiglaucoma) and cancer	[198]
Dithiocarbamates (DTCs)	hCA II	Excellent intraocular pressure (IOP) lowering properties in an animal model of glaucoma	[99]
Dithiocarbamates and the xanthates	α- and β-CAs	Potent antiglaucoma activity in animal models of the disease	[100]
A Class of 4-Sulfamoylphenyl-ω-aminoalkyl Ethers	hCA II	Effective IOP lowering properties in an animal model of glaucoma	[199]
Coumarins	CA II	Antiepileptic	[200]
Branched aliphatic carboxylic acids and 4-aminobenzenesulfonamide	1. Type of 13, 16, and 17 potent inhibitors of CAs VII and XIV 2. Compounds 9, 14, and 19 inhibited CA II 3. 10 and 12 inhibited all isoforms	Anticonvulsant	[201]
Hesperidin	HCA I and II	Antiglaucoma	[98]
Topiramate and zonisamide	Mitochondrial isoforms CA VA and VB	Reducing lipogenesis and mitochondrial oxidative stress associated with many obesity comorbidities	[69]
Sulfonamide analogs	Mitochondrial carbonic anhydrase (CA) isozymes (CA VA and CA VB)	Shifting metabolism and glucogenesis flux to treat obesity and diabetes	[202]
Pyrazolo[4,3-e][1,2,4] triazine sulfonamides	CA IX and XII,	Cytotoxic effects on breast cancer cell line ex-vivo	[203]
A set of benzenesulfonamide(BSA) derivatives			
SLC-0111 a sulfonamide	CA IX/XII	Completed a successful Phase I clinical trial for the treatment of advanced, solid metastatic tumors	[204]
	CA IX	A potential antitumor effect	[205]

organic and inorganic anions, are beneficial. Sulfonamides are an important class of biologically active compounds inhibiting the CAs to prevent pathological and physiological abnormalities.

The sulfonamide inhibitors of CAs are used as diuretics, anticoagulants, anti-obesity, and anticancer therapies. Several new sulfonamides were synthesized using the raw materials imides and tosyl chloride. N-acylsulfonamides are used effectively to remove CAs isozymes such as human cytosolic I, and II (hCA I, II), and these compounds are potent inhibitors of CAs [166]. The researchers studied the inhibitory effects of urea and sulfamide, tetrauline scaffolds on human CAs (hCA I and hCA II). They found that these compounds have high inhibitory power against CA [167].

It was also reported inhibitory effects of heavy metals on CAs. In study, the inhibitory effect of different heavy metal ions, including Fe^{2+}, Pb^{2+}, Co^{2+}, Ag^{+} and Cu^{2+} on the function of CAs from Black Sea fish *Salmo labrax*, was studied, and a 50% decrease in CA activity was reported [168]. In a study, heavy metal ions including Fe^{2+}, Cu^{2+}, Co^{2+}, Pb^{2+}, Hg^{2+}, and As^{3+}, as well as certain excretory toxins including tiram, clofentzin, propinib, deltamethrin, azoxystrobin, and thiophanate from *Trachurus trachurus* showed a special inhibitory effect on the CA [169].

Eugenol is a phenolic compound that inhibits carbonic anhydrase. In clinical trials, the researchers have studied the effective concentration profile of phenolic inhibitors on the hCA1, hCA II, and AChEiso enzymes. Eugenol inhibitors blocking the active site of carbonic anhydrase (CAI) are used to treat diuretics, antifungals, antiepileptics, and gastric ulcers [170]. Pyrazolesulfamids and sulfamides-containing carbamide play a significant role in curing

diabetes [171]. In addition to inhibiting α-glycosidase, AChE, and BChE, these inhibitors also inhibit the enzyme carbonic anhydrase [172, 173].

The inhibitory effect of trichloroacetone on human CAs (hCA I and hCA II) has already been reported. Trichloroacetone may have promising therapeutic potential for glaucoma, leukemia, and epilepsy treatment [174]. Pyridine and its aminopyridine derivatives are used in the manufacture of drugs, dyes, and detoxifying compounds. The researches on the crystal structure, properties, and inhibitory effects of these compounds showed their effective inhibitory effects on CA [175]. The inhibitory effects of enzymes including acetylcholinesterase (AChE) and CA reported in recent studies can be a promising strategy to produce drugs against epilepsy, Alzheimer's disease, and obesity. CAs play an important role in catalyzing the balance of CO_2 and bicarbonates [176]. Bromophenol derivatives are selective cytosolic inhibitors of isoforms I and II (hCA I and II) of CA and acetylcholinesterase (AChE). CA inhibitors are used to treat many disorders such as Alzheimer's disease, Parkinson's disease, and ataxia [177]. Moreover, they include antibacterial, antidiabetic, anticancer, and antimicrobial properties [177].

CA inhibitors are used as an alternative medicine to treat many diseases such as heart failure and epilepsy [178, 179]. Various compounds such as (E)-4-(3-bromo-4,5-dihydroxyphenyl) but-3-en-2-one (1), (E)-4-(2-bromo-4,5-dihydroxyphenyl) but-3-en-2-one (2), and (E)-4-(2,3-dibromo-4,5-dihydroxyphenyl) but-3-en-2-one (3) are known as natural bromophenols. These new compounds, are the potent inhibitors of the carbonic anhydrase enzymes I and II (hCA I and II). 4-Phenylbutene derivatives are used as carbonic anhydrase inhibitors to produce drugs for the treatment of glaucoma, autism, gastric ulcers, neurological disorders and osteoporosis [180, 181].

Almost CA inhibitors have been approved by the FDA and have clinical usage. The most efficient CA inhibitors that have been well-known for their pharmaceutical properties are acetazolamide, Ethoxylamide, Sulphim, Diclofenamide, Dorzolamide, Brinzolamide, Insulam, Topiramate, Zonisamide, Sulpyride, Comat, EMATE, Celecoxib, Darodoxib, and Saccharinetc. These inhibitors are located near the activation site of CAs, disrupting the zinc-bound water interactions and blocking enzyme activity (Fig. 4). Long-term use of these inhibitory drugs can affect other enzymes in body tissues and lead to side effects such as kidney and liver damage [86, 182]. However, these inhibitors are used to treat many diseases and develop antibiotics, diuretics, anticancer drugs, anti-obesity, antiglaucoma, and antiepileptic drugs (Table 2) (Fig. 4). The challenges faced by presently available CAIs are indiscriminate inhibition of CA isoforms other than the target one, which will result in undesired side effects [74]. Nowadays, CAIs are designed in such a way that they target isozyme-selective compounds and show fewer side effects [74].

Various efforts have been made to develop inhibitors such as (3,4-dihydroxyphenyl)(2,3,4-trihydroxyphenyl)methanone, NCX250, Dithiocarbamates, 4-Sulfamoylphenyl-ω-aminoalkyl ethers, hesperidin that can inhibit selectively α-Cas to reduce the side effects of CAIs, and widely used as antiglaucoma agent (Table 2) (Fig. 4). Inhibitors including branched aliphatic carboxylic acids and 4-aminobenzenesulfonamide inhibits CAs VII and XIV and have anticonvulsant effects (Table 2) (Fig. 4). The inhibition of mitochondrial isoforms CA VA and VB have been reported from topiramate, zonisamide and sulfonamide analogs which play essential role in reducing lipogenesis and shifting metabolisms to treat obesity and T1DM and T2DM (Table 2) (Fig. 4). Finally, CA IX and XII that are highly expressed in cancer cells can be selectively inhibited by Pyrazolo[4,3-e][1,2,4]triazine sulfonamides and benzenesulfonamide (BSA) derivatives (Fig. 4) (Table 2). These inhibitors may serve as promising drug targets for various diseases. Polyamines are polycyclic and aliphatic molecules that initially act as activators of CAs. However, measuring the activity of several polyamines, such as spermin, spermidine, and their derivatives, indicated the inhibitory properties on CAs [183].

Carboxylic acid derivatives are inhibitors that block the cavity entry of the active site of CAs and inhibit them. [184, 185]. Coumarins are produced as secondary metabolites in many plant species. Natural coumarins have attracted the attention of many scientists because of their wide range of biological activities, including anti-HIV [186], anticancer [187, 188], antimicrobial [189], anticoagulant [190], antioxidant [191], and anti-inflammatory [192]. Natural coumarin 6-(1S-hydroxy-3-methylbutyl) -7-methoxy-2H-chroman-2-one is an enzyme inhibitor of CAs [193]. This inhibitor acting on CAs is widely used in medical science to treat diseases [194, 195].

Use of marine carbonic anhydrase as innovative approach for medical requirements

Carbonic anhydrase showed high potential in medical developments. A study of carbonic anhydrase extracted from sea sponges *Subereamollis* and *Pseudoceratina* sp., were pharmacologically performed. It showed particular potential for the treatment of many diseases, including cancer tumors [206, 207]. Marine carbonic anhydrase CA IV and type II inhibitors, such as dorzolamide in the eye, can treat glaucoma through decreasing secretion of fluid and intraocular pressure [199].

Many marine organisms, including deep-water bacteria, volcanic-bacteria, and marine animals such as

sponges, algae, marine plants, and other marine organisms, having CAs showed high potential for pharmaceutical application [208, 209]. Furthermore, various studies showed that marine carbonic anhydrase can be applied to manufacture artificial lungs to treat respiratory failure. Moreover, CAs have different medical usages, including SazCA extracted from a thermophilic hydrogen-oxidizing, which has been used to treat analgesic overdose and blood substitutes for the optimization CO_2 removal rates (Table 3) (Fig. 2). Carbonic anhydrides extracted from marine organisms are also notable in the pharmaceutical industry. Another potential medical application reported for CAs is artificial blood production [210, 211].

Marine carbonic anhydrase: novel and potential enzyme for environmental monitoring and industry

Pollution has become a significant concern for the environment. Many toxic compounds are released into the environment continuously, most of which originate from industrial and agricultural activities [221, 222]. Structure and function of CAs have created their recent advances perspectives in environmental monitoring and health. Carbonic anhydrase as the first zinc metalloenzyme [223] is ideal for measuring the ion concentration because to zinc affinity. Various mutants of CAII with altered zinc affinities, were developed to measure zinc concentrations over wide dynamic range [2]. The determination of metal ions including Cu^{2+} and Zn^{2+} in natural waters are of interest environmentally. Availability

Table 3 Types of CAs extracted from different marine organisms and high potential usage for environmental monitoring and capturing CO_2

	CAs used	Application(s)	Reference(s)
Thermophilic bacterium *Sulfurihydrogenibium yellowstonense*	SspCA	Post combustion carbon dioxide capture	[212]
S. yellowstonense	SspCA	Biosensors checking the toxic effects of zinc on marine life	[213]
S. azorense	SazCA	Measuring sulfanilamide pharmaceutical residues in biological and environmental samples	[213]
Marine prokaryotes	–	Detecting leaks of CO_2 from storage areas	[214]
	HCA II	Quantify trace amounts of zinc in sea and wastewater	[215]
	HCA II	Efficient and selective extraction of carbon dioxide (CO_2) at low to medium concentration by CA-based reactor	[216]
	Bovine carbonic anhydrase II	Employing in CO_2-responsive cationic hydrogels in antidote delivery to treat analgesic overdose	[97]
-	Bovine CA	Used in blood substitutes for the optimization CO_2 removal rates	[96]
Marine Diatom *Thalassiosira weissflogii*	CDCA1 (δ-CAs)	CDCA1-based biosensors for the detection of Cd^{2+} trace amounts in the marine environment	[217]
T. weissflogii	CDCA1 (δ-CAs)	A useful tool for the design of bioreactor systems for carbon dioxide capture and its conversion into water-soluble ions	[217]
Desulfovibrio vulgaris	Highly thermostable β–CA	Highly efficient carbon capture from flue gas	[218]
Polyextremophilic bacterium *A. pallidus*	Thermo-alkali-stable γ–CA (ApCA)	Biomineralization	[219]
	Highly thermostable CAs	Potential for the formation of bioconcrete	[94]
	CAs	Developing small artificial lungs	[94]
	HCA II	Checking the toxic effects of zinc on marine life	[95]
Diatoms, dinoflagellates, and coccolithophores	δ-CAs	Potential biosensors able to detect Zn and Co	[220]
Diatoms, dinoflagellates, and coccolithophores	δ-CAs	Potential to capture and sequester carbon dioxide in bioreactors	[220]

Cu^{2+} and Zn^{2+} is essential to control the growth of primary producers, thus other organisms in higher trophic levels in the food chain, however, their increased levels are toxic and alarming to many life forms [3].

A biosensor can be defined as a compact analytical instrument or a continuous biological unit with a transducer related biosensor part [224, 225]. Many biosensors were used in clinical analysis, health monitoring, veterinary applications, agriculture, processing, industrial monitoring, and environmental pollution control [225, 226]. In recent years, research interest has been increased towards designing fluorescence-based biosensors to determine free metals in solution [220]. Sensors based CAII determining Cu^{2+} is based on copper binding to the His3 metal site [227]. A variety of copper concentrations can be measured through the CAII variants with altered copper affinity. Unique advantages including the high sensitivity and selectivity of CA-based fluorescence sensors for zinc and copper have created them potential ideal tools to determining free metal ions in the complex matrix of seawater [228]. CA-based sensors can provide continuous readout of metal ion concentration in situ, in real time without any processing or separation steps [229]. The fluorescent-labeled CAII sensor can determine the metal ion concentration remotely in situ at some depth [230]. CA-based sensors were used to check the toxic effects of zinc on marine life [231], as well as to measure sulfanilamide pharmaceutical residues in biological and environmental samples [231].

hHCA II has a high affinity towards zinc and has been used for the detection of minute amounts of zinc in waste and seawater for concerns over toxicity to fishes, invertebrates and plants (Table 3) (Fig. 2). However, because of the relative abundance of this element in the environment, trace amounts of other metal ions may be challenged through CA-based biosensors [220]. Now, HCA II variants obtained by site-directed mutagenesis have resulted in the high sensitivity, selectivity and affinity for detecting various heavy metals such as Cu^{2+}, Co^{2+}, Cd^{2+}, and Ni^{2+} [220]. δ-CAs extracted from diatoms, dinoflagellates, and coccolithophores have shown the high potential to detect Zn^{2+}, $Co^{2+}$and Cd^{2+}in environment (Table 3). Finally, it is expected many potential application of CA-based sensors in future for environmental monitoring of metal ions because of their high sensitivity, selectivity, power and flexibility.

On the other hand, CAs can be referred to as a multifunctional and multitasking superfamily because of their ability to capture carbon dioxide creating them as exciting candidates to be used in environmental and industrial applications [232–234]. Global warming created by increasing of atmospheric CO_2 levels is being major concern in worldwide. The usage of CO_2 capture strategies can be an innovative approach to solve this continuous increase of global temperature [233]. CO_2 of the atmosphere produced by the anthropogenic activities can be easily captured through the use of "robust" CAs [234] (Fig. 2). The biomimetic strategy was introduced as an eco-friendly strategy to CO_2 capture allowing CO_2 conversion to water-soluble ions for purposes such as $CaCO_3$ mineralization [232]. Usage of CAs for biomimetic $CaCO_3$ mineralization is one of promising approaches among the various carbon capture and storage (CCS) technologies [235]. CAs are known as zinc ion relating biocatalyst for reversible hydration of CO_2 [207, 236, 237] and precipitation to calcium carbonate [238, 239]. CAs that are overexpressed in a variety of microalgae are a promising way to effectively capture excess CO_2 for biomitigation [240] (Fig. 2). Thus, CCS based on CAs have advantages including no secondary pollution, environmentally friendly, fast process of mineralization without additional energy consumption [241].

It is essential providing the high stable CAs on the extreme and harsh environment for carbon fixation. Recombinant *E. coli* are beneficial and efficient choice for increasing the production and improving characteristics of carbonic anhydrase [242, 243]. The various CAs from thermophilic bacteria were reported including CA from *Sulfurihydrogenibium* with the ability to incubation at 90–100 °C [244–246], *Hahella chejuensis* KCTC 2396, *Dunaliella* sp. [247] and *Lactobacillus delbrueckii* CGMCC 8137 [248], EX-H1 *Persephonella marina* [249] with thermostability at 50, 55, 60, and 100 °C, respectively, showing effective development for CO_2 sequestration. Moreover, the ability of CAs to withstand in harsh conditions can show the stability of alkaline CAs such as CA from *Pseudomonas fragi* with stability at pH range 7.0–8.5 [250], CahB1 of *Microcoleus chthonoplastes* at alkaline pH near 9 [251], β-CA and γ-CA from the *Bacillus sp*. SS105 with stability at pH 8.0 [252]. The using bovine CA has been reported as one of successful approach for effectively facilitates CO_2 capture [253]. Carbon capture and storage (CCS) process using CAs has been widely reported. However, the use of CAs in free form for this purpose can be expensive because its loss reusable and non-recyclable from the reaction environment [232]. Immobilization of CAs was introduced as one of effective and economical approaches to solve the whole process of CCS [254, 255]. Up to now, various strategies for immobilization of CAs have been reported including adsorption, covalent bonding, encapsulation and entrapment [232].

A limited number of industrial processes using CA for capturing CO_2 have been known to date. A pilot-scale CO_2 capture plant at Center in Wilsonville, AL, the USA by Codexis Inc. was installed in which carbonic anhydrase enzyme from *D. vulgaris* was used, and the CO_2 absorption rate was improved 25-fold as compared to non-enzymatic reaction [256]. In areas such as mines, shipyards, or underground tunnels, and spacecraft or submarines, where airflow is low, there is a little buffering capacity to absorb. In another

study, a novel enzyme-based reactor was used to capture CO_2 from a mixed gas stream, and this system efficiently captures CO_2 over the range of 400 ppm to 100,000 ppm [257]. Therefore, the use of enzymes in the industries is precious. CAs from thermophilic bacteria and diatoms, dinoflagellates, and coccolithophores have been reported as suitable tools to capture and sequester CO_2 in bioreactors (Table 3) (Fig. 2). It was also reported the microorganisms living in extreme environments were employed as natural CA-based biosensors to detect leaks of CO_2 from storage areas [258] (Table 3). Marine CAs from marine algae in the production of biofuels are of interest to researchers. Adding this enzyme to the algae culture medium, *Dunaliella, Chlorella,* and *Spirulina* had increased biofuel production, which is economically valuable [259–261]. CA enzyme contains many lysine residues that increase CA stability and facilitates the covalent CA immobilization. One of the benefits of inactivation of CAs is increasing its strength and improving the possibility of its repeated use, which reduces the costs of its purification and production in the industry [262]. The bacterial α-CA immobilization from *Neisseria gonorrhoeae* and *Clostridium thermocellum* has also been investigated, which was satisfactory [263].

Conclusion

Currently, the world's population is rising, and people need to be supplied with various food and medicine methods. Increasing microorganisms' knowledge and advancing biotechnology research, the use of microorganisms and enzymes derived from them, and other microbial metabolites are considered a strategy for food and pharmaceuticals, development, increasing efficiency, and improving production processes. Our finding showed, to date, the high diversity of CAs extracted from marine organisms, but a limited number of CAs have been applied for practical application. The recent advancement in medical and industrial areas have commonly focused on human or covine isoform II of CAs. Further research is essential that characterizes individual marine CAs with unique properties, leading to further advancement in the biotechnology and medical areas. Moreover, there are still vast resources for marine CAs yet to be explored. Future researches are required to explore CAs originated marine organisms with improved chemical characteristics and thermal stability for the decreasing costs of production for CCS. CAs from Marine organisms are promising candidate for carbon capture because of unique properties such as active at high temperatures and long-lived. CAs-based biosensors have been indicated high potential to determine free Zn^{2+} and Cu^{2+} concentrations in seawater. It is expected the development biosensors based CAs-originated marine organisms to measure the readily exchangeable concentration of other metal ions in cells and in seawater. With regarding the ongoing progress, developments concerning the use of marine CAs can be expected for medical, industrial purposes and environmental monitoring in the near future.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals by any of the authors.

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