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Review

Insights on Cadmium Removal by Bioremediation: The Case of Haloarchaea

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Abstract: Although heavy metals are naturally found in the environment as components of the earth's crust, environmental pollution by these toxic elements has increased since the industrial revolution. Some of them can be considered essential, since they play regulatory roles in different biological processes; but the role of other heavy metals in living tissues is not clear, and once ingested they can accumulate in the organism for long periods of time causing adverse health effects. To mitigate this problem, different methods have been used to remove heavy metals from water and soil, such as chelation-based processes. However, techniques like bioremediation are leaving these conventional methodologies in the background for being more effective and eco-friendlier. Recently, different research lines have been promoted, in which several organisms have been used for bioremediation approaches. Within this context, the extremophilic microorganisms represent one of the best tools for the treatment of contaminated sites due to the biochemical and molecular properties they show. Furthermore, since it is estimated that 5% of industrial effluents are saline and hypersaline, halophilic microorganisms have been suggested as good candidates for bioremediation and treatment of this kind of samples. These microorganisms, and specifically the haloarchaea group, are of interest to design strategies aiming the removal of polluting compounds due to the efficiency of their metabolism under extreme conditions and their significant tolerance to highly toxic compounds such as heavy metals, bromate, nitrite, chlorate, or perchlorate ions. However, there are still few trials that have proven the bioremediation of environments contaminated with heavy metals using these microorganisms. This review analyses scientific literature focused on metabolic capabilities of haloarchaea that may allow these microbes to tolerate and eliminate heavy metals from the media, paying special attention to cadmium. Thus, this work will shed light on potential uses of haloarchaea in bioremediation of soils and waters negatively affected by heavy metals, and more specifically by cadmium.

Keywords: haloarchaea; heavy metals; bioremediation; cadmium; environmental pollution

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1. Introduction

Environmental pollution by heavy metals is becoming globally an urgent problem. This can occur through natural processes [1] or anthropogenic activities related to industrial processes, generation of domestic waste, or the application of phosphate fertilizers [2–4].

Heavy metals are a group of chemical elements showing high density (greater than 4 g/cm^3), and an atomic weight above 20, among which are aluminum (Al), copper (Cu) or cadmium (Cd). Naturally, they are distributed in the environment at low concentrations to not cause toxicity, but enough to supply the different life forms with essential nutrients [5], because some of them are involved in several biological functions [6,7].

Based on the role that heavy metals play in biological systems; they are classified as essential or non-essential. Some of them like zinc (Zn) are essential elements acting as cofactors of several enzymes thus playing important roles in several metabolic processes [3].

Others, such as cadmium (Cd), are non-essential heavy metals, since not only biological roles in living tissues have not been described for them, but also, they could become carcinogenic and teratogenic [8,9].

Heavy metals accumulation in the environment is increasing dramatically threatening human health, and environmental homeostasis and passing through water or food ingestion to the body tissues of living organisms, being transmitted to higher trophic levels. This bioaccumulation can cause oxidative stress in living beings due to the formation of free radicals (generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) capable of disturb cellular antioxidant defenses) [1,10], cause cell damage/death [11,12], or even replacing essential metals in pigments or enzymes, disrupting their function [13]. Toxicological processes due to heavy metals can also occur in soil microorganisms thus affecting the abundance and diversity of microbial populations as well as their metabolic activities [14,15].

During the last two decades, some absorbents such as polysaccharides, nanoparticles or hydrogels have been developed for heavy metals removal and several studies have demonstrated the removal of heavy metals in water using living organisms [16–18]. Despite these advances, some limitations have been related to economic viability, process efficiency or environmental friendliness have been found in the biodegradability of these pollutants in the environment [19]. More recently, bioremediation-based approaches are proposed as economical, feasible and environmentally friendly biotechnological process, able to remove pollutants from the environment. Bioremediation implies the use of organisms to treat contaminated sites/samples and several microbes have focused the attention of the scientific community worldwide due to metabolic capabilities to remove toxic compounds for most of the living beings.

As examples of potential uses of microbes in bioremediation-based processes different groups of extremophiles (Archaea and Bacteria) like methanogens, thermoacidophiles or halophiles have been proposed as good candidates to carry out bioremediation, due to their metabolic capabilities under extreme conditions (including the presence of toxic compounds) [20,21]. The most extremophilic phenotypes described so far belong to Archaea domain [22], which are more widespread than initially thought [23]. This wide distribution is due, among other factors, to their membrane and cell wall architecture (that allow them to tolerate extreme environments), their ability to adjust gene expression to respond to these conditions [22,24] or molecular adaptations to high osmotic affecting protein composition, synthesis of specific membrane transporters or metabolites to deals with extreme environmental parameters [23–28]. One of the best characterized archaeal groups is the one commonly named "haloarchaea", constituted by microbes requiring moderate or high salt concentrations. Within this microbial group, *Haloarcula* and *Haloferax* genera are the best described at the time of writing this work [29]. Thus, it has been described that *H. mediterranei* is able to tolerate and metabolize high concentrations of compounds that seems toxic to most living beings, such as aromatic compounds, nitrogenous compounds like nitrate and nitrite or oxychlorides like (per) chlorate [30,31]. Consequently, this microorganism has been considered as a biological tool to treat wastewater and contaminated soils [30,31].

To highlight the last finding about the potential uses of haloarchaea in bioremediation of soils and waters negatively affected by heavy metals, this review deeply analyses scientific literature focused on metabolic capabilities of haloarchaea that may allow these microbes to tolerate and eliminate heavy metals from the media, paying special attention to cadmium. The main conclusions from this work will shed light on bioremediation at large scale using haloarchaea.

2. Materials and Methods

2.1. Search Strategy and Information Processing to Carry out Bibliometric Analysis

To know the impact of the use of haloarchaea in bioremediation of wastewater/soils containing heavy metals, and specifically cadmium, a bibliometric analysis was performed using the keywords related to the topic. For this proposal, three bibliographic scientific-technical content databases were used: PubMed (https://www.ncbi.nlm.nih.gov/pubmed/; Accessed on 31 January 2021) as a free search engine, Web of Science (https://www.webofknowledge.com/; Accessed on 31 January 2021) and Scopus (https://www.scopus.com/; Accessed on 31 January 2021) as subscription-based tools. The reason justifying the used of these databases is that they were the databases retrieving the highest number of documents in the preliminary search carried out. The keywords used in the search were "archaea", "haloarchaea", "halophilic archaea", "bioremediation", "heavy metals", "cadmium", "industrial waste", "wastewater", "salty water" and "contaminated water". Furthermore, to analyze the impact of cadmium in bioremediation using haloarchaea, a search combining the keywords "bioremediation and cadmium", "bioremediation and haloarchaea or halophilic archaea" and "cadmium and haloarchaea or halophilic archaea" was performed. The Boolean system was used to retrieve the information form databases [32]. The search of the documents based on the use of the keywords was made according to the fields "article title", "abstract" and "keywords". Once the results were obtained, different filters were applied such as publication date, country, institution, or affiliation of the authors.

The search was performed considering a period of 30 years from 1990 to 2020. All the information retrieved was collected in different Excel files and independently analyzed by the authors. Then, an integrated Excel database was obtained to make the global analysis and to obtain different graphics showing the main results.

2.2. Search Strategy and Information Processing to Carry out Bibliographic Analysis

The compilation of bibliographic information was carried out using scientific-technical content databases Scopus, Web of Science, PubMed and ScienceDirect. To conduct the compilation, an individual search of the 10 main keywords was firstly made. Subsequently, to get a more optimized search, different combinations of these 10 keywords were made using the connector "AND" to identify only those articles that included both terms. Finally, 35 combinations were used: "Archaea and Bioremediation", "Archaea and Heavy metals", "Archaea and Cadmium", "Archaea and Industrial waste", "Archaea and Wastewater", "Archaea and Salty water", "Archaea and Contaminated water", "Haloarchaea and Bioremediation", "Haloarchaea and Heavy metals", "Haloarchaea and Cadmium", "Haloarchaea and Industrial waste", "Haloarchaea and Wastewater", "Haloarchaea and Salty water", "Haloarchaea and Contaminated water", "Halophilic archaea and bioremediation", "Halophilic archaea and Heavy metals", "Halophilic archaea and Cadmium", "Halophilic archaea and Industrial waste", "Halophilic archaea and Wastewater", "Halophilic archaea and Salty water", "Halophilic archaea and Contaminated water", "Bioremediation and Heavy metals", "Bioremediation and cadmium", "Bioremediation and Industrial waste", "Bioremediation and Wastewater", "Bioremediation and Salty water", "Bioremediation and Contaminated water", "Heavy metals and Industrial waste", "Heavy metals and Wastewater", "Heavy metals and Salty water", "Heavy metals and contaminated water", "Cadmium and Industrial waste", "Cadmium and Wastewater", "Cadmium and Salty water" and "Cadmium and contaminated water". In spite that the keywords search was made according to the fields "article title", "abstract" and "keywords", a massive number of results was obtained in some cases. To restrict the selection, only those documents that dealt with the format "article", "review" and "news" were included. For those searches in which the number of publications retrieved was still high, only recent reviews (published between 2009 and 2019; it was detected that not all papers reported in 2020 were indexed in databases at the time of writing this work).

3. Results and Discussion

3.1. Bibliometric Review

3.1.1. Study of the Number of Publications According to Their Distribution by Country

The search of documents conducted as described in materials and methods section reported a total of 667,894 publications from PubMed, 748,331 from Scopus, and 961,063 from Web of Science. The filter "country" is not available in PubMed database, consequently, the study of the number of publications according to their distribution by country was made using the results obtained from Web of Science and Scopus databases (Figure 1). The countries reporting the highest number of publications are China, the United States and India, accounting 183,589, 158,323 and 68,599 publications, respectively.

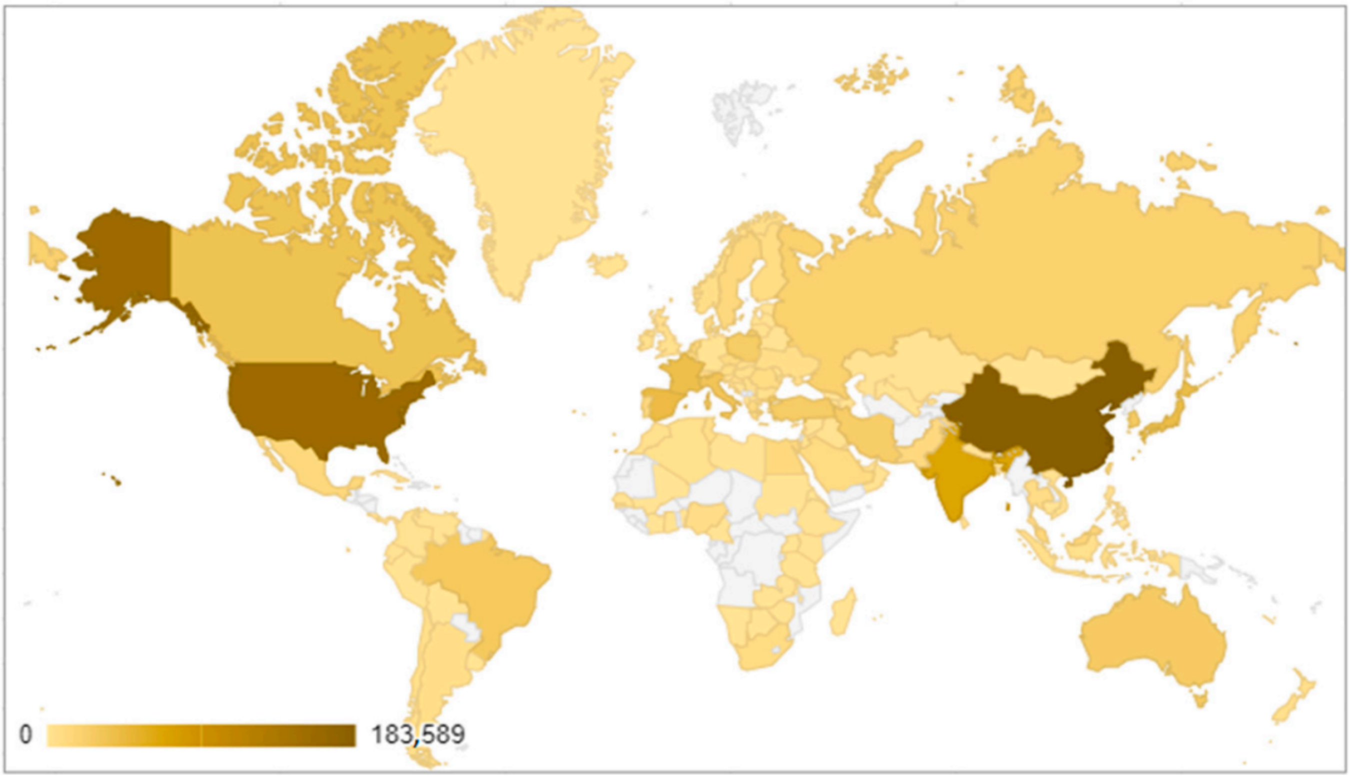

Figure 1. Global map representing the total number of publications represented by countries (sum of the results retrieved by using the 10 main keywords). The greater or lesser intensity of color coincides with the higher or lower number of publications, respectively. Most of the research studies involved collaborations within institutions and countries, consequently the results represented in Figure 1 exceed the number of total publications obtained in the search of publications by keywords. Those countries that have not shown any results in the search appear without coloring. Figure obtained using Excel.

3.1.2. Number of Publications Focused on Bioremediation of Cadmium Contaminated Samples/Sites

The search carried out using the keywords "bioremediation", "cadmium" and "haloarchaea" (considering the terms "haloarchaea" and "halophilic archaea" have been as synonyms) revealed that the term "haloarchaea" firstly appeared in the databases in 1993, and the number of publications over time has increased significantly, being 5 times higher nowadays compared to the beginning of the period analyzed. However, when the identification of the documents was made by combining the keywords over time ("cadmium and bioremediation", "cadmium and halophilic archaea or haloarchaea" and "bioremediation and halophilic archaea or haloarchaea"), a considerable decrease in the total number of articles published is observed for the same period analyzed. These results indicate that the number of studies carried out in which bioremediation processes have been used to eliminate cadmium is relevant, but also reinforce the idea that studies in which haloarchaea are related to bioremediation, and specifically, to cadmium are still scarce.

The use of haloarchaea as organisms for bioremediation is quite innovative proposal. The first publication on this topic dates from 1993 and was conducted with *Haloferax volcanii* as model organism involving cadmium as contaminant [33]. The second publication appears in 2007 and summarized the ability of some species of the *Haloferax* genus to metabolize aromatic compounds and polycyclic aromatic hydrocarbons (PAH), which lead to the possibility of using them as bioremediation tools in hypersaline environments contaminated with aromatic compounds [34]. From that date, few more publications have been reported about the relevance of haloarchaea and other halophilic microbes in global biogeochemical cycles and bioremediation processes [20,31,35–38]. Figure 2 display the number of publications retrieved using the same key words in the top 10 countries: United States, India and China are the dominant countries in terms of bioremediation research and connecting bioremediation to cadmium (Figure 2a,b). However, looking at the countries that have carried out bioremediation studies using haloarchaea, Spain and Kuwait appear as dominants (Figure 2c), with the University of Alicante (Spain) and the University of Kuwait (Kuwait) as the main institutions developing these research lines.

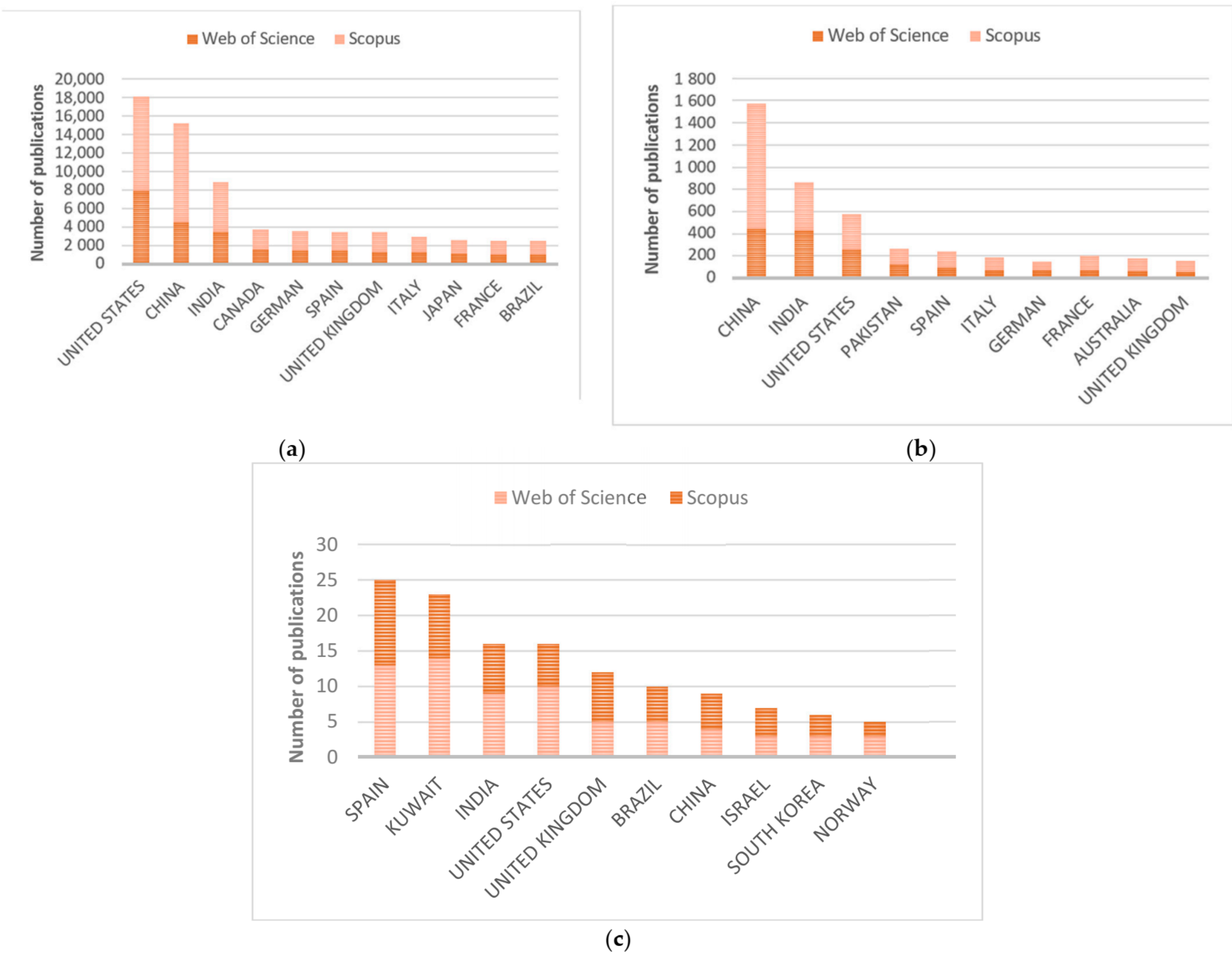

Figure 2. Top countries contributing to studies related to (**a**) “Bioremediation”; (**b**) “Bioremediation and cadmium”; (**c**) “Bioremediation and haloarchaea or halophilic archaea”. Results from PubMed database are not shown because this database does not allow the results classification by country.

Countries such as China or India are included within the 17 countries with the highest global pollution index (Pollution Index by Country, 2020; https://www.numbeo.com/pollution/rankings_by_country.jsp; Accessed on 31 January 2021). In China, authorities confirmed serious contamination risks in 2014, claiming that approximately 16% of soils, and 34.9% of brownfields exceed national standards of heavy metal contamination [39]. In India, the shortage of drinking water is exacerbated by groundwater contamination due to wastes from nearby industries [40]. This may explain why these countries are the top three with the highest number of publications about bioremediation processes for the removal of metals like cadmium.

3.1.3. Publications Related to the Use of Haloarchaea in Bioremediation. The Case of *Haloferax mediterranei*

Several organisms have been used in the different bioremediation studies, but extremophiles represent one of the best tools for bioremediation of contaminated sites due to their biochemical and molecular properties [41]. Considering that the 5% of industrial effluents are saline and hypersaline, halophilic microorganisms have been proposed as good model organisms for the treatment and bioremediation of this kind of environments [31,37,42,43].

The growing interest in haloarchaea in connection with bioremediation during the last decades is significant in some countries; as examples Spain and Kuwait collect the largest number of publications related to the topic. The fact that Kuwait appears as the second country with the highest number of studies about bioremediation using haloarchaea may be firstly surprising, because it is not included in the top 10 countries with the largest number of publications concerning bioremediation (Figure 2). However, several areas of Kuwait are characterized by hypersaline environments in which halophilic microbes with potential uses bioremediation studies predominate [41]. The same reason could be associated to Spain, where the salinity of soils is, along with drought, one of the main factors affecting the Mediterranean [44,45].

Most of the haloarchaeal species are grouped into two main families: *Halobacteriaceae* and *Haloferacacaeae* [46]. The species *H. mediterranei*, is probably the better described up to know. This species belongs to the *Haloferacacaeae* family and was first isolated in 1980 in Alicante, Spain [47]. Between 1980 and 2012, the number of publications involving *H. mediterranei* is low, but since 2013, there is an increase in interest about this haloarchaea mainly due to topics such as CRISPR-Cas technology and other biotechnological applications [48,49]. Spain, and specifically the University of Alicante, leads the list of institutions with publications focused on *H. mediterranei*, followed by the Institute of Microbiology of the Chinese Academy of Sciences, in China and the Technical University of Darmstadt, in Germany.

3.2. Bibliographic Review

3.2.1. Bioremediation: Possible Solution to Contamination of Soils and Water by Heavy Metals

The term "bioremediation" was officially coined in the early 1980s and refers to protocols, methods, and strategies (usually based on biotechnology) in which metabolic capacities of different organisms are used to degrade pollutants, which are harmful to organisms or transform them into less toxic compounds through natural degradation processes [35]. Based on the nature of the procedures designed, bioremediation techniques can be classified into: Intrinsic in situ; Engineered in situ [41], which can follow two approaches: "biostimulation" and "bioaugmentation" [50,51]; and Ex situ techniques [52].

Several laboratory tests have demonstrated the ability of certain microorganisms in the biodegradation and biosorption of toxic compounds, however, these tests have been carried out under stable physicochemical conditions (pH, concentration of the contaminant, presence of other solids, etc.), which cannot be guaranteed on an industrial scale or in environmental conditions [53]. For this reason, bioremediation techniques are still controversial.

Once the bioremediation process has been carried out (in the lab or in real environments), the biomass used must be removed from the medium/sample/ecosystem treated. This is another important concern regarding to bioremediation-based techniques. The use of microbial cultures in immobilizing matrix is gaining interest in bioremediation processes, since it seems to be one of the best techniques to physically separate cell cultures from the treated media [54]. Related to this issue, several works demonstrated that the elimination percentages of heavy metals are higher when the microbial cultures used for bioremediation are used as immobilized cells in matrixes like sodium alginate matrix [54,55], showing the advantages that immobilized biomass offers, such as high biomass loading in the process, better reusability, and even improving the removal capacity of the compounds of interest due to the increased protection and resistance of cells against toxicity of the media [54,55]. In summary, although scientific literature on bioremediation is abundant, more efforts must be paid in the next future to optimize bioremediation-based processes for the removal of heavy metals involving cellular immobilization.

3.2.2. Description of the Main Molecular Mechanisms Sustaining Heavy Metals Resistance in Microorganisms

Some microbes show natural resistance to heavy metals due to specific molecular mechanisms. The accurate characterization of these mechanisms could be a great progress in environmental biotechnology and microbial ecology, opening new ways for bioremediation. So far, several conventional methods such as chemical precipitation, ion exchange or membranes filtration have been used for the elimination of these pollutants [56], but these treatments involve high economic cost, and in those situations in which the metal concentration is low, they are not entirely effective [57]. It is for this reason that the interest in knowing the bacterial/archaeal resistance to heavy metals and the mechanisms involved on it has increased in recent decades [58]. Recent publications from bacteria have described genes coding for proteins involved in metal resistance mechanisms. Those genes have been identified not only in bacterial chromosomes, but also in mobile elements such as plasmids and transposons [58]. This is of great importance since plasmids hosting genes for metal resistance can be transmitted to other cells horizontally, thus contributing to the adaptation of microbial communities to contaminated environments [59,60]. From a biochemical point of view, the molecular mechanisms sustaining heavy metals resistance can be divided into two groups: (i) mechanisms based on intra and extracellular metal binding processes (according to the energy requirements can be distinguished between biosorption or bioaccumulation processes) [61] or (ii) mechanisms based on the active efflux of heavy metals (P-type ATPases; RND transporters family; cation diffusion facilitators (CDF)). These are the most widespread processes since they ensure cellular ion homeostasis as well as cell survival [58]. In 2003, Nies complied the genomes of 64 prokaryotic organisms belonging to the Bacteria and Archaea domains with the aim of identifying the distribution of heavy metal exporting proteins families. Regarding to archaea, the study revealed that four types of P-type ATPases, one type of CDF proteins and any RND proteins could be identified in halophilic archaea genomes [62]. All the mentioned molecular mechanisms are following described:

Biosorption

Biosorption technology has been widely studied in recent years as part of bioremediation processes for the removal of metals such as zinc, lead, nickel, or cadmium, due to its high yield, profitability, and ecological nature [56]. Biosorption is used for the passive uptake of metals present in the sample (mainly in water treatments) using live or dead biomass through mechanisms like adsorption and ion exchange. The process requires a solid phase (biomass) which will absorb the metal ions present in the liquid phase (water contaminated with heavy metals) [63]. Once the process has finished, the biomass is easily removable from the system and it could be even used for the isolation of metabolites of interest from a biotechnological point of view. Consequently, it is a profitable bioremediation mechanism [58]. Biosorption could be carried out using only one microbial species, microbial consortia or even combining microorganisms and macromolecules serving as sorbents.

In 2015 Rajesh et al. carried out a study using the halophilic bacterium *Halomonas* BVR1 immobilized in a chitosan matrix to explore the absorption capacity for heavy metals. This strain was used due to its halotolerance thus offering a distinctive advantage over other bacterial strains in the bioremediation of heavy metals from affluent samples. In addition, previous works revealed that it was able to tolerate levels of up to 400 mg/L of lead, and 250 mg/L of cadmium [64,65]. Chitosan is a biodegradable polymer which consist of β-2-amino-2-deoxy-D-glucopyranose, and in this work it was interlinked with glutaraldehyde with the aim of improving stability and physical and mechanical resistance. The fact of using this polymeric matrix confers advantages such as having a controlled particle size, ensuring biomass regeneration, and favoring the interaction with metal ions thanks to the hydroxyl and free amino groups [65]. The results of the study showed that chitosan adsorption capacity was 17.54 mg/g for lead and 13.84 mg/g for cadmium, while *Halomonas* BVR1 adsorption capacity was 24.15 mg/g for lead and 23.88 mg/g for cadmium. This characterization was performed using optical imaging techniques, scanning electron microscopy (SEM), infrared spectroscopy (FT-IR) and X-ray energy dispersion spectrometry (EDAX). From these results it was concluded that the combination of *Halomonas* BVR1 and chitosan was able to effectively absorb lead and cadmium from aqueous solutions [65].

Another study carried out by Showalter et al. demonstrated the adsorption capacity of cadmium by the halophilic archaea *Halobacterium noricense*. Cadmium concentrations between 10 and 20 ppm were tested. Thanks to X-ray absorption spectroscopy (XAS), it was observed that cadmium was attached to the archaea surface through a hydrogen sulfide bond. Although the amount of cadmium adsorbed on the cell surface is unknown, it was possible to determine that adsorption occurs at specific sites on the cellular surface [66].

Bioaccumulation

Bioaccumulation is a metabolism dependent process in which metal ions can pass into the cell through cell membrane diffusion, but the entrance mainly occurs thanks to a specific transport for the internalization of these metals (generally an H^+-ATPase system) [58]. Once the heavy metals have been uptaken, they are sequestered by intracellular compounds [61]. Metallothioneins (MTs) can be mentioned as example of intracellular compounds allowing the sequestration of cadmium inside the cells. These are metal-binding proteins of low molecular weight and cysteine rich, whose expression is induced by various physiological and toxicological stimuli. They were first discovered by Margoshes and Vallee in 1957 from horse kidney cells, and subsequently they have been found throughout the animal kingdom, higher plants, and in many prokaryotes and eukaryotic microorganisms [67].

A study carried out by Olafson et al. in 1979 demonstrated the role of these proteins in the cadmium tolerance of the cyanobacteria *Synechococcus* sp. Polarographic analysis determined that those cells grown for one month in the presence of $2.5{\cdot}10^{-2}$ mM $CdCl_2$ produced approximately 50 ng metallothionein/mg wet cells (whilst the analysis of control cells grown in the absence of $CdCl_2$ revealed that they did not produce metallothioneins) [68]. Recently, it has been described that *smt* operon codes for metallothioneins. This operon consists of the *smtA* gene, coding for the metallothionein protein; the *smtB* gene, that controls the expression of the *smtA* gene; and the operator-promoter region between both genes [69].

Das and co-workers carried out another study in 2014 testing the ability of the haloarchaea *Haloferax* BBK2 to accumulate cadmium. The growth of this strain was monitored in culture media with different concentrations of NaCl (5–30%) and Cd (0.5–1 mM). The cells were able to accumulate up to 21.08% of the cadmium initially added to the cultures (0.5 mM Cd). The authors verified that cadmium was accumulated intracellularly forming nanoparticles in which cadmium interacts interaction with biomolecules such as proteins, lipids, and carbohydrates being polysaccharides the most important biomolecules for intracellular cadmium adsorption in haloarchaea [60].

P-Type ATPases

They constitute a super family of transport proteins that require energy from the hydrolysis of ATP, and inorganic cations as substrates. They sustain the uptake of the substrates from the outside of the cell as well as the transport of substrates from the periplasm to the cytoplasm. Besides, some of these proteins are involved in substrate export from cytoplasm to periplasm [62]. Therefore, they play a main role in the homeostasis of cellular cations and consequently, some of them are involved in heavy metals removal from the inner cell through their active efflux [58].

In Gram-positive bacteria, CadA proteins are the most studied P-type ATPases. These proteins oversee the transport of cadmium ions towards the outside of the cell. Usually, those ions are previously introduced into the cell by metal ion transporters (MIT) [70]. Some studies carried out at the end of last century demonstrated that the presence of these ions induces the transcription of the CadCA plasmid, which encodes the CadA protein (P-type ATPase) [71].

In the case of archaea, several P-type ATPases involved not only in the transport of ions like sodium, potassium, calcium, but also in the uptake of copper have been described [72–74]. To the best of our knowledge, P-type ATPases from haloarchaea involved in the uptake of cadmium of other heavy metals like zinc have not been described at the time of writing this work.

RND Transporters Family

Resistance-Nodulation-Division transporters constitute a family of proteins widespread in organisms ranging from Archaea to Eukaryotes and perform diverse functions [75]. They are well-known as the major drug efflux pumps of Gram-negative bacteria; others are involved in the transport of heavy metals and hydrophobic and hydrophilic compounds; they could be related to nodulation factors or protein excretion processes [58]. RND proteins are expressed together with MFPs (membrane fusion proteins), also described as periplasmic export or adapter proteins. Along with these two families of proteins, a third one named OMF (external membrane factors) cooperates in the transport of heavy metals [76]. Thus, different kind of protein complexes capable of exporting substrates (including heavy metals) outside the cell from the cytoplasm has been described in Bacteria [58]. As an example, the CzcABC system found in *Cupriavidus metallidurans* CH34 has been described as a RND transporter involved in metal resistance [77]. Although studies about this type of transporters have not been reported from halophilic archaea up to now, few studies about them from thermophiles have been published [78].

Cation Diffusion Facilitators (CDF)

CDF proteins constitute a family of transporters widespread in the three domains of life, although they are more abundant in eukaryotes [62]. Members this family are integral membrane divalent cation transporters that transport metal ions out of the cytoplasm either into the extracellular space or into internal compartments such as the vacuole. The spectrum of cations known to be transported by proteins of the CDF family include Zn, Fe, Co, Cd, and Mn. These proteins are capable of transporting ions using a chemiosmotic, potential, pH, or potassium concentration gradient. Initially they were identified as a group of Zn and Co transporter proteins, but it has also been shown that they can interact with other divalent cations such as Cd [79]. The Czc protein for instance, belonging to this family, was firstly identified in *C. metallidurans* CH34. Initially it was described as a regulator of the expression of CzcABC operon, but it was demonstrated that in the absence of this operon, the cells were also capable of reducing the metals concentration in the cell cytoplasm. The presence of metals inside the cell induces the expression of *czc* genes, which encode these proteins [58]. Biochemical details about these transporters are far from known in archaea at the time of writing this work.

3.2.3. Environmental Contamination by Cadmium. Adverse Effects on Human and Animal Health

Global production of cadmium has increased in recent years because of its applications in electroplating, synthesis of pigments to create dyes or paints, and the manufacture of electronic components like television screens or batteries [80]. Moreover, it can be obtained as a product of industries related to metal processing and mining [60]. Cadmium is a heavy metal belonging to the transition metals of the periodic table, which has an atomic number of 48, an atomic mass of 112.40 g/mol and a relative density of 8.65 g/cm^3 at 20 °C. It is not found in free state naturally, but associated with other metals such as zinc, lead, or copper; or elements such as oxygen, chlorine or sulfur forming minerals and rocks [81,82]. It can pass into the atmosphere through volcanic activity, and into the soil and continental waters through the decomposition of the rocks that contain it. However, anthropogenic activity is the main contribution of this element to the environment through the generation of industrial waste from mining, paint pigments, waste incineration or its use as a fungicide in some agricultural treatments [82]. It is estimated that around 30,000 tons of this heavy metal are annually released into the environment, with some 13,000 tons coming from anthropogenic activities [83].

Through these human activities, cadmium reaches agricultural soils (during fertilization processes) and aquatic systems like rivers or lakes when they are irrigated with contaminated water from industrial parks, mine waste or landfill filtrations without previous treatments [84]. In fact, cadmium is highly soluble in water and soil thus, favoring its entry into the food chain by ingesting water or food that contains it.

One of the largest cadmium-associated disasters took place in Toyama (Japan) due to the excessive production of cadmium at industrial level. This caused the pollution of waters used for irrigating rice paddies because of the proximity to these industries and caused the Itai-Itai disease due to the ingestion of high concentrations of cadmium through rice [85]. Living beings could be exposed to environmental cadmium mainly due to two ways:

- Oral route: through contaminated food or water. The United States Environmental Protection Agency (EPA) has established a reference dose as a limit value for daily cadmium consumption to avoid adverse health effects: concentration in water up to 0.5 µg/L, and in feeding up to 1 µg/kg (ATSDR, 1999) (available at https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf, accessed on 16 February 2020). In some Europe and North America countries the intake of this metal can be up to 40 µg per day through the diet [86].
- Respiratory route: it occurs when people are exposed to several industrial activities, reaching inhalation values of up to 50 µg/L [87].

When cadmium is absorbed by the organism, it is transported in the blood to the liver and kidney (main targets), where it accumulates for up to 30 years, producing irreversible damages [87]. Some common health side effects of cadmium exposure in human beings and other animals are nephropathies [88] and alteration in the renal metabolism of vitamin D [89], kidney and prostate cancer [90] and reduction of antioxidant defense, since it inhibits the activity of several antioxidant enzymes (such as superoxide dismutase and catalase or promotes DNA damage [88,90].

3.2.4. Cadmium Removal in the Presence of Other Heavy Metals: Synergistic and Antagonistic Effects

Considering that cadmium is usually associated to other heavy metals, cadmium bioremediation approaches should be designed tacking into account synergistic and antagonistic effects between them. This issue is not usually considered when carrying out experiments about cadmium bioremediation, which is one of the main shortcomings of the studies on bioremediation of heavy metals. Despite the wide variety of studies about the ability of bacteria and archaea to tolerate cadmium, there are less research studies aiming its removal from environments contaminated with several heavy metals at the same time. Therefore, it is necessary to study conditions in which more than one toxic metallic species are present and even different microorganisms could be involved, to carry out bioremediation studies that are closer to real conditions [91].

Most of the studies monitoring cadmium removal from the medium in the presence of other heavy metals focus on biosorption as a bioremediation tools and use bacteria as sorbent biomass [91,92]. The carboxylic, carbonyl, phosphate, sulphate, amino, amide and hydroxyl groups are those most frequently joining the biomaterial and the metal ions of the system [91]. The analysis of all documents identified in the bibliometric analysis have revealed the following factors as the most important to promote metal adsorption to biomass if cadmium joins other heavy metals:

- pH of the media: at low pH values, the functional groups located in the cell wall are fully protonated, so the metal ions adsorption does not take place. If pH value increases, these groups become deprotonate, and the metal binding sites would be free to join heavy metals [92].
- Hydrated ion radius: it is the amount of water surrounding the ions, and this depends on each element. Compounds with a lower hydration radius will present a higher biomass adsorption affinity than those with a higher hydration radius. In the study conducted by Sulaymon and co-workers, the removal efficiency of Pb, Cr and Cd metals found in synthetic wastewater was tested using a heterogeneous culture containing protozoa, yeast, and anaerobic bacteria [93]. In this study, the element with the highest adsorption capacity was Pb, followed by Cr, and finally Cd (Pb > Cr > Cd). This order correlated with the values of the hydration radius showed by each element (Pb for instance shows the smaller hydration radius (4.01 Å) and the highest adsorption capacity to biomass) [93].
- Metal electronegativity: this is the ability of an atom to attract the electrons belonging to another atom. As the electronegativity of the atom increases, the ionic form can be easily adsorbed by the sorbent [93]. Thus, the preference for Pb adsorption is also enhanced by its high electronegativity (2.33). Cadmium, however, is the one with the lowest biosorption capacity, coinciding with its low electronegativity (1.69); Cr for instance has an intermediate electronegativity value (1.66) [93].
- Solute solubility: solubility of heavy metals in water is in general low thus negatively affecting biosorption increases. If several heavy metals are in a solution, biosorption of Cd is lower than biosorption of other heavy metals like Pb (examples of solubility values: Pb (52 g/mL), Cr (81 g/mL) and Cd (136 g/mL)). Consequently, this factor has a negative impact on bioremediation of cadmium when it is joining other heavy metals [93].
- Ionic radii and molecular weight: compounds characterized by higher ionic radii and higher the molecular weight shows greater biosorption [94]. Studies like the one conducted by Moreira using the macroalgae *Fucus vesiculosus* demonstrated greater adsorption capacity for Pb followed by cadmium and Ni, respectively. This order coincides with the ionic radii values of each element: the ionic radii value for Pb, Cd and Ni are 119 p.m.; Cd, 95 p.m. and 60 p.m., respectively [94].

Comparing all the results reported in the literature, it is possible to emphasize that the removal/bioremediation of cadmium works better if cadmium is the only heavy metal present in the sample to be treated. The presence of other heavy metals alters or even avoid cadmium removal by biosorption, which is highly influenced in the presence of other metals showing lower electronegativity, ionic radii, molecular weight, and positive charges than cadmium, as well as greater hydration radii and solubility. [92,94,95].

3.2.5. Haloarchaea as Model Organisms for Bioremediation of Heavy Metals Contaminated Sites: The Case of Cadmium

During the last two decades, several works have revealed that archaea can be of high interest for biotechnological purposes including bioremediation. Archaea domain were first characterized as a group of single celled prokaryotic microorganisms requiring extreme environmental parameters to be alive: temperatures (thermophiles), low or high pH (acidophiles, alkalophiles), high salinity (halophiles), or strict anoxia. The ability of those species to grow under a wide range of extreme conditions equally to their mechanisms supporting genetic plasticity make them good candidates for bioremediation [96]. Acidophiles and thermophiles are probable the most used archaeal microbes in processes related to heavy metals removal and mining [76,97–99].

Currently, scientific community is focusing efforts on the optimization of bioremediation approaches in high salt environments, which are mostly influenced by the discharge of industrial effluents [100,101]. Considering that conventional microbiological processes are not capable of being executed at high salt concentrations, microbial bioremediation of hypersaline samples/ecosystems requires halophiles [102,103]. The study of haloarchaea in bioremediation has gained significant traction in recent years. Among halophiles, haloarchaea belonging to *Halobacteriaceae* and *Haloferacaceae* families have been successfully tested for biotechnological applications throughout the last decade [48,104]. Regarding to bioremediation by haloarchaea, biochemical reactions related to nitrogen cycle, heavy metals redox reactions and hydrocarbons or aromatic compounds degradation have been described as efficient pathways to develop bioremediation techniques [23,35,37]. Table 1 summarize some of the most recent works described metabolic capabilities of haloarchaea with potential uses in bioremediation.

Table 1. Examples of haloarchaea species showing metabolic capabilities to deal with toxic compounds.

Metabolic Capacity	Haloraceal Species	Poluant	Concentration	Degradation/ Resistance	Coexisting Compounds	Condition	References
Mineralization of aliphatic alkane. Aromatic hydrocarbon/ Hydrocarbon degradation	*Halorientalis hydrocarbonoclasticus* IM1011 *Halorientalis* sp.	Hexadecane	5 g/L	Degradation 57%	Eicosane, Duodecane	3.6 M NaCl; 37 °C; 7/18 days 3.6 M NaCl; 37 °C; 24 days	[105,106]
p-Hydroxybenzoic acid degradation	*Haloferax* sp. *Haladaptatus* sp.	p-hydroxybenzoic acid	0.4 mM	Degradation 50%	Naphthalene, Anthracene, Phenanthrene, Pyrene and Benzo[a]anthracene Naphthalene, Benzoic acid, and o-Phthalate	20% NaCl, 40 °C, 7 days 10% salt medium; 37 °C; 7–14 days	[102,107]
Removal of nitrogenous compounds (nitrate and nitrite)	*Haloferax mediterranei* R4	Nitrite Nitrate	40 mM 50 mM	Degradation 75% 60%	Na, Ca, Mg, Chlorides, Sulphates	25% (*w/v*) mixture of inorganic salts; 42 °C	[35,37]
Uranium biomineral-ization	*Halobacterium noricense* DSM 15987	U (VI)	30 µM 85 µM	U (IV) carbonate compound formation	-	Modified DSM372 medium; 30 °C; dark conditions; 5 min–360 h	[108,109]

Table 1. *Cont.*

Metabolic Capacity	Haloraceal Species	Poluant	Concentration	Degradation/ Resistance	Coexisting Compounds	Condition	References
Curium and europium complexation	*Halobacterium noricense DSM 15987*	Eu (III) Cm (III)	30 µM 300 nM	Complexation with Eu(III) and Cm(III) by phosphate species and carboxylic groups, respectively	-	DSM372 medium; 30 °C; dark conditions	[110]
Decolorization of azo dyes	*Halogeometricum* sp. strain A *Haloferax* sp. strain B	Remazol black B (di-azo dye) and Acid blue 161 (mono-azo dye)	50 mg/L	Degradation 70% Acid blue 161,95% Remazol black B 68% Acid blue 161, 91% Remazol black B	-	MGM broth with 3 M NaCl; 40 °C; 7 days	[111]
Acetamide and formamide degradation	*Halorubrum lacusprofundi*						[112]
Heavy metals resistance	*Haloferax strain* BBK2	Cd	0.5 mM 1 mM	Accumulation 21.08% 15.19%	-	Complex (NTYE) or minimal media (NGSM); 5–30% NaCl; 37 °C; 10 days	[60]

Table 1. *Cont.*

Metabolic Capacity	Haloraceal Species	Poluant	Concentration	Degradation/ Resistance	Coexisting Compounds	Condition	References
Heavy metals resistance	*Haloferax* sp. *Halobacterium* *Halococcus*	$HgCl_2$	0–300 ppm	Resistance 100 and 200 ppm 200 ppm 100 ppm	-	Solid mineral medium; 0–4 M NaCl; 40 °C for *Haloferax* and 45 °C for *Halobacterium* and *Halococcus*; dark conditions; 10 days	[113–118]
Synthesis of nanoparticles involving metals (silver)	*Haloferax* sp.	$AgNO_3$	0.5 mM	Intracellular silver nanoparticles formation	-	SW broth medium; 40 °C; 3–7 days	[114]

More recent studies on haloarchaeal isolates belonging to *Haloferax*, *Halococcus*, *Halorubrum*, and *Haloarcula* genera revealed a similar resistance pattern as previously reported by Nieto, with *Haloferax* BBK2 and *Halococcus* BK6 strains showing the highest tolerance (MIC 0.5 mM) to Cd^{2+} and Zn^{2+}. However, maximum Cd^{2+} and Zn^{2+} concentrations supporting growth (4 and 2 mM, respectively) were only observed on complex NTYE agar medium [117,118]. In the case of. *Haloferax* sp. st. BBK2, the growth was affected by 0.5 mM concentrations of cadmium, but cells were resistant to cadmium toxicity up to 4 mM accumulating cadmium intracellularly. Intracellular accumulation of cadmium, probably as CdS nanoparticles, may be part of the Cd-resistance strategy in *Haloferax* BBK2 [60]. An important feature observed during the growth of haloarchaea in the presence of metal was related to cellular pigmentation (the highest the cadmium concentration the lower intensity of pigmentation), so the carotenogenesis in haloarchaea is clearly affect by the presence of heavy metals [118]. To the best of our knowledge the study caried out on cadmium resistance in *Haloferax* strain BBK2 in the only one conducted up to now into detail.

Heavy metal resistance elements such as *ars* operons were detected in halophilic Archaea. As an example, the operon arsADRC and *arsR2M* on the pNRC100 plasmid and the chromosomal *arsB* gene ensure As-resistance in *Halobacterium* sp. NRC-1 [119,120]. However, little is known on their distribution in halophilic archaea [121].

Simultaneous presence of different types of pollutants often complicates bioremediation as previously mentioned. However, the presence of specific compounds could contribute to enhance the tolerance of several species to heavy metals. A recent study has investigated the effect of heavy metal concomitating with hydrocarbon degradation in hypersaline systems [96,122]. In this study, the growth of strains of both Archaea (a strain of *Haloferax elongans* and a *Halobacterium salinarum*) and Bacteria (a strain each of *Arhodomonas*, *Marinobacter*, and *Halomonas*) was inhibited in the presence of high levels of Hg, Pb, Cu, Cd, and As and the inhibition was even more sensitive to these metals in the presence of crude oil [55]. Overall, the archaeal strains had less tolerance for heavy metals than three halophilic/halotolerant Bacteria tested, though the bacterial genus *Kocuria* had similar levels of sensitivity to heavy metal toxicity [122]. The addition of $Fe_2(SO4)_3$ and proline to halophilic microbial populations in salty environments (mainly soils) enhanced the tolerance of several species (including bacteria and archaea) to heavy metals, and consequently their potential for oil and heavy metals biodegradation. Thus, in *Haloferax elongans* for instance, FeIII amendment lessened the toxicity of Hg, Pb, Cu, and Cd, while for the *Halobacterium salinarum*, FeIII amendment lessened the toxicity of Cu, Cd, and As and proline lessened the toxicity limit of cadmium [122]. In the case of *Halobacterium salinarum*, the rate of crude oil consumption was tested under heavy metal stress with and without FeIII or proline amendment. The crude oil degradation rate increased significantly under Hg or Pb stresses with FeIII or proline amendment, while the enhancement of oil consumption rates in Cu, Cd, and As-stressed cultures were more nuanced [122]. The results are useful in designing bioremediation technologies for oil spilled in hypersaline areas.

Other studies focused on soil microbial ecology has analyzed the effect of salinity in cadmium toxicity. Wang and coworkers have examined the response of soil archaeal communities to saline stress in different types of Cd-contaminated soils from the North China Plain. Increased soil salinity by addition of 0.5% sodium salts increased available cadmium concentration, resulting in saline stress. This stress decreased archaeal abundance and diversity and changed major soil archaeal taxa (taxa in the archaeal phyla *Thaumarchaeota* and *Euryarchaeota* were enriched) [123,124]. Other studies have described changes on nitrogen pathways (like nitrification, denitrification, and ammonia oxidation) developed by microorganisms in freshwater sediments and soils due to saline stress and the presence of Cd alone or in combination to other heavy metals. The main conclusions from these studies state that the abundance and richness of archaeal communities, mainly ammonia oxidizing archaea (AOA) considerably varied with time. Even though, the abundance of AOA is in general higher in the presence of cadmium compared to soils without cadmium, indicating that cadmium addition has a profound effect on the balance of N mineralization and may further impact the plant productivity and water quality of constructed wetlands [122].

4. Conclusions

Bioremediation in general, and particularly cadmium bioremediation, has focused the attention of global scientific community as stated by the bibliometric analysis here displayed. The countries contributing significantly to the research on this topic are those showing the highest pollution index at the time of writing this work (United States, India, and China). Bioremediation using haloarchaea is gaining importance in recent years, especially in countries characterized by having large geographical hypersaline environments, such as Spain and Kuwait. Among the heavy metal resistance mechanisms based on the active metal efflux, only P-type ATPases and CDF proteins have been described in haloarchaea to date. Other heavy metals resistance mechanisms based on the intra and extracellular metal sequestration like biosorption are far from known in haloarchaea. In addition, although the application of bacterial cultures immobilized in biopolymer matrix is efficient to remove heavy metals, this approach has not been investigated in haloarchaea. Cadmium removal from aqueous environments and soils using biosorption methods is hindered in presence of metals such as Pb, Cr, Cu and Ni. Other aspects like salinity also affect microbial capability of cadmium removal. Considering the unique metabolic capabilities of haloarchaea and their high saline requirements, they could be considered as good model organisms for bioremediation of heavy metals in samples and environments affects by salinity and pollution. Research of this topic is still scare, and more efforts must be done in the next future to use haloarchaeal for bioremediation at large scale.

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