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Review article



Microalgae potential to protect from heavy metals-induced carcinogenicity

Hadjira Hamai-Amara [a], Haissam Abou-Saleh [a], Mohammad A. Al-Ghouti [a], Sergio Crovella [a], Imen Saadaoui [b,*], Lama Soubra [a,*]

[a] Biological and Environmental Sciences Department, College of Arts and Sciences, Qatar University, Doha, Qatar
[b] Biotechnology Program, Center of Sustainable Development, College of Arts and Sciences, Qatar University, Doha, Qatar

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ABSTRACT

Toxic elements are present naturally in the environment; however, during the last century, their level has been continuously rising in the air, water, and soil due to anthropogenic activities, including urban runoff, pesticides and fertilizers, industrial effluents, and vehicle emissions. Once released in the environment, they are extremely stable, and therefore humans can get in contact with them through different routes of exposure. In addition, because of their toxicities, they are increasingly threatening human health. Exposure to toxic elements such as heavy metals (HMs) might contribute to the onset of disorders through their ability to generate reactive oxygen species (ROS), which are involved in cell macromolecule injuries. Moreover, several heavy metals (arsenic (As), cadmium (Cd), nickel (Ni), chromium (Cr), and beryllium (Be)) are classified by the International Agency for Research on Cancer as group one carcinogens and can induce different types of cancer through various and heterogeneous mechanisms. Therefore, a better understanding of heavy metals etiopathogenesis in cancer development and the identification of new bioactive products to prevent heavy metal carcinogenicity is warranted. Microalgae, known for their wide range of biological activities, could possess a promising metalloprotective effect against heavy metal-induced carcinogenicity. This protective effect is mainly attributed to their antioxidant and anti-cancer capacities as well as their heavy metal chelating potential. This review discusses the mechanisms implicated in heavy metal carcinogenicity. In addition, a deep understanding of microalgae's mitigating roles and strategies against heavy metal carcinogenicity are reviewed.

1. Introduction

During the last century, the earth's environment has become more threatened by pollution caused by natural and anthropogenic activities. Heavy metals, known for their high atomic weight and density [1], are the most critical environmental pollutants. This is due to their potential toxicity and high environmental stability which cause several adverse effects on human health [2].

Heavy metals can promote the onset of numerous disorders by different mechanisms, mainly oxidative stress through free radicals, injuring cell macromolecules such as DNA, proteins, and lipids [3,4]. Furthermore, HMs' carcinogenic potential is considered among the most serious impacts of their acute and chronic toxicity [5,6]. Several studies have emphasized the relationship between heavy metals exposure and certain types of cancer [7–9]. Moreover, a correlation between exposure to HMs and cancer-related mortality was proposed, including gastric, kidney, colon, nasopharyngeal, and lung cancer [10]. For instance, atmospheric pollution has been related to a 45 % raised lung cancer risk, promoting 36 % of death [11].

The most conventional process to detoxify the body from HMs is the administration of chelators [12], considering that this removal and inactivation of HMs can prevent cellular damaging effects and reduce cancer prevalence. Previously, extensive research on chemical chelating agents was conducted. However, they cannot be applied to humans because of their side effects and elevated doses required to be effective [13]. Consequently, some studies were performed to evaluate the promising effects of human-tolerable bioactive compounds extracted from natural sources, while new appropriate strategies are still considered necessary. In the last decade, the investigation of effective bioproducts and their derivatives obtained from fresh or marine water resources has been reported due to their biochemical diversity [14,15]. Microalgae have attracted much attention as a potential renewable, sustainable, and economical source of natural compounds such as polysaccharides, pigments, phenolics, and vitamins [16]. Furthermore,

* Corresponding authors.
E-mail addresses: imen.saadaoui@qu.edu.qa (I. Saadaoui), lama.soubra@qu.edu.qa (L. Soubra).

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they appear to be remarkably appropriate and widespread in medical applications and also as a bioremediation agent to remove HMs from contaminated soil and wastewater [12,17,18].

Based on their dominant bioactive compound, the microalgae are able to exhibit a wide range of biological activities such as antimicrobial, antiviral, antioxidant, anti-inflammation, and anticancer [19–21]. For instance, carotenoids, such as β-carotene and astaxanthin, are known to have strong antioxidant and anti-inflammatory properties. Similarly, phycobiliproteins like phycocyanin and phycoerythrin have been revealed to have a significant antiproliferative activity against several cancer cell lines [23,24]. Moreover, microalgae are considered as a rich source of omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids have numerous health benefits, including anti-inflammatory and cardiovascular effects [25,26]. Additionally, the sulfated polysaccharides and exopolysaccharides compounds produced by microalgae have been recognized for their antiviral, antioxidant, and immunomodulatory properties and widely investigated in the development of drugs and functional foods [26,27].

However, the protective effect of microalgae on heavy metal-induced carcinogenicity has not been fully described, and a deeper understanding in that area is needed. Therefore, this article provides a clear picture of the carcinogenic potential of some heavy metals and how microalgae might be effective to protect from this carcinogenicity.

This review aims to describe the main sources and routes of exposure to heavy metals. Moreover, different carcinogenic mechanisms of heavy metals are discussed. Finally, the role of microalgae in the prevention of heavy metal-induced carcinogenicity is also discussed.

2. Heavy metals from the environment to humans: sources and exposure routes

In addition to releases from natural sources of HMs (volcanic, erosion, bacterial, and spring waters) [28,29], a variety of anthropogenic activities, including industrial, agricultural, domestic, and medical applications, have resulted in increased levels of HMs in the environment [30]. HMs are released and distributed in the air, then, transported through the soil, and water and may reach human beings via various routes of exposure.

These include inhalation through the respiratory system [31]; dermal contact through the skin [32], or ingestion via the digestive tract [4]. Fig. 1 illustrates the natural and antropogenic sources of HMs as well as their different exposure pathways to the human body.

Based on a human health risk analysis, it seems that oral ingestion may be the main route of exposure [33]. The ingested HMs undergo acidification in the presence of stomach secretions, which induce their oxidation and result in the formation of metal ions such as Zinc ion (Zn^{2+}), Arsenic ions (As^{2+}, As^{3+}), Lead ion (Pb^{2+}), and Cadmium ion (Cd^{2+}). These ions can easily build strong and stable bonds with the main thiol functionalities of various proteins and enzymes which lead to the alteration of normal cell functioning and damage [5]. Hence, the normal physiological function of several organs and tissues becomes altered, the brain, liver, kidney, lung, blood, and skin are the most affected [3]. Many adverse health effects could emerge from acute and chronic exposures to HMs. Acute HMs poisoning can induce various clinical symptoms such as headaches, appetite loss, abdominal pain, vomiting, nausea, skin rashes, diarrhea, fatigue, hallucinations, lung and

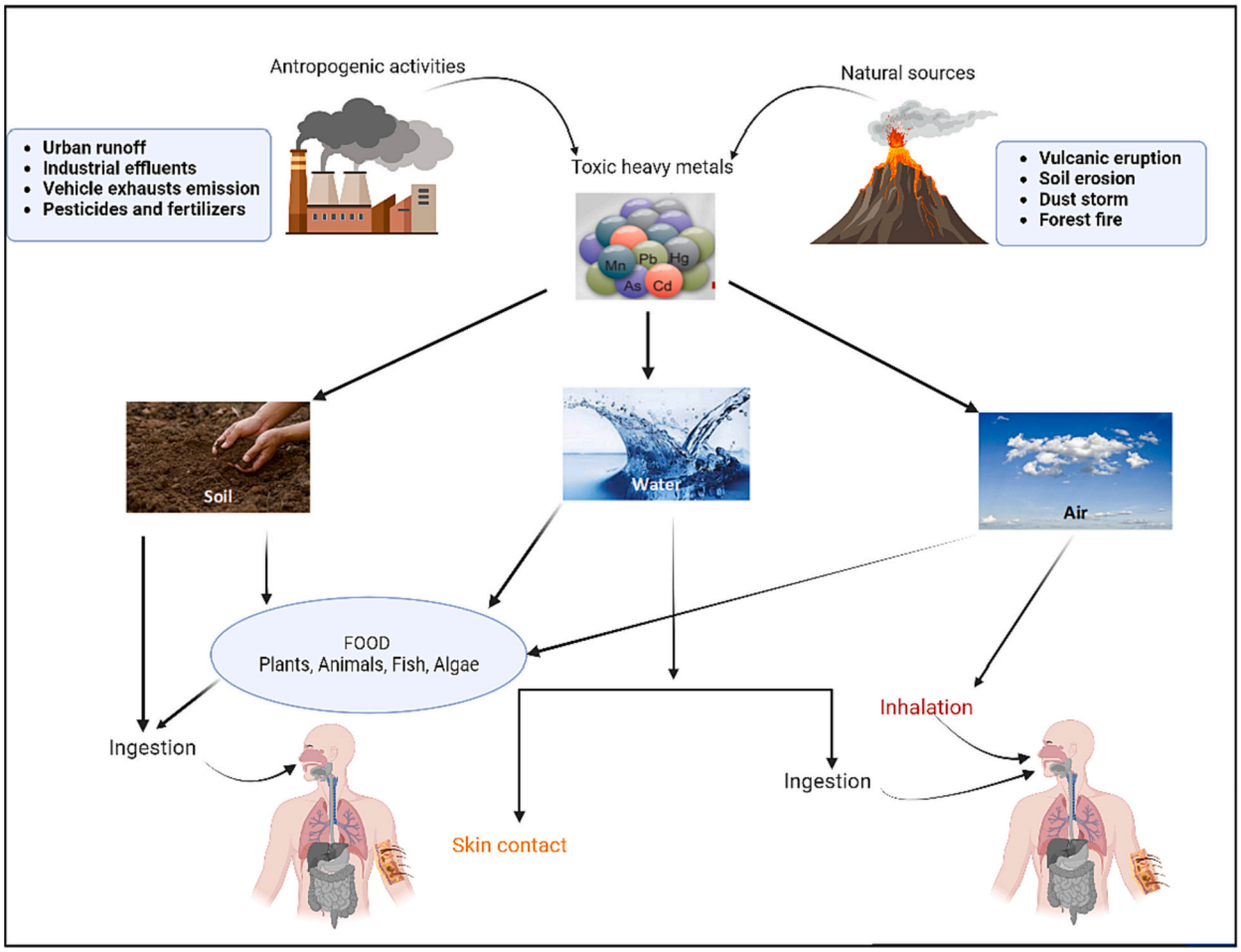


Fig. 1. Sources of heavy metals and their exposure pathways to the human body.

blood vessel damage, and many other symptoms depending on the metal element [34]. In addition, long-term or chronic exposure to HMs would adversely affect various body systems such as muscular, cardiovascular, and nervous systems, as well as induce carcinogenesis at various sites in the body [35]. As a result, the safety of food in terms of human health preservation from ingested HMs became a crucial need, mainly with the persistent rise in food demand.

3. Cancer risk related to heavy metals exposure

The International Agency for Research on Cancer has classified several HMs (As, Cd, Ni, Cr, and Be) as group one carcinogens [36,37], which means that there is sufficient evidence of HMs' carcinogenicity in exposed humans [38]. Using molecular pathway analysis, Kim et al., [36] showed a rise in cancer risk induced by above listed HMs through different mechanisms. In a recent study conducted in the groundwater surrounding a contaminated landfill, Aendo et al., [39] indicated that the cancer risk from oral consumption and the lifetime carcinogenic risk of Ni, Cr, and Cd in that area exceeded the carcinogenic risk limit in both children and adults, concluding that an environmental monitoring program including soil and groundwater surveillance must focus on decreasing health risks. Furthermore, according to Kopp et al., [40], in their "in vitro" study conducted on liver and colon cell lines (HepG2 and LS-174 T) to evaluate the impact of several HMs present in the human diet, they found that some metalloids could induce DNA damage and interact with cell signaling. Also, they suggested that Pb ions were implicated in a rise in cell proliferation in both cell models. Moreover, Aendo et al., [41] have suggested that duck eggs and meat from Thailand might be the cause of improved cancer risk in humans due to the contamination by some heavy metals (Lead (Pb), Cadmium (Cd), Cobalt (Co), and Chromium (Cr)). In another study, both positive and negative impacts of HMs present in consumed rice were revealed, suggesting a link between an increased rate of Co and a raised risk of colon cancer, but the high selenium (Se) concentrations may instead reduce this risk [33].

Many studies have illustrated the interrelationship between risk exposure and the source (natural or occupational) of HMs [42–44]. For instance, a raised risk of cancer disease has been shown in individuals working in industrial regions where heavy metals are manipulated [45]. A significant association between occupational exposure and a high risk of colorectal cancer was highlighted in a case-control study performed in Algerian Eastern [46].

Similarly, an elevated rate of lung cancer was seen resulting from some environmental contamination by HMs and showed a higher incidence of lung cancer with a higher level of Cd in urine [9]. Additionally, Cd was linked with a wide variety of cancers, including stomach, colon, lung, liver, kidney, bladder, breast, prostate, and nasopharyngeal cancers according to cell model studies through the establishment of a gene or genome expression profiling [47,48].

A recent study [49] highlighted the spatial incidence rate pattern of colon cancer and its link to the amount of heavy metals present in the Iranian rice. Besides, Chu et al., [8] provided considerable evidence of the association between $PM_{2.5}$ exposure and a high incidence of colorectal cancer. According to Men et al., [50], Cd, Cr, and As were significantly higher in the urines of breast cancer patients compared to the control group ($P < 0.05$), however, the Mercury (Hg) and Pb levels showed a non-significant difference. Also, they identified small molecule metabolites (amino acids and nucleotides) alterations in the urine of the patients, concluding that those metabolites are involved in breast cancer development. Similarly, using the inductively coupled plasma mass spectrometry technique, Lim et al., [51] evaluated the association between several HMs and prostate cancer risk and demonstrated that the patient's serum concentrations of As and Zn correlated positively with the prostate cancer risk, highlighting the increased risk in the case of combined exposure. In addition, a correlation between exposure to HMs and cancer-related mortality was determined, including gastric, kidney, colon, nasopharyngeal, and lung cancers [10]. Table 1 summarizes the main heavy metal exposure routes and their carcinogenic effects and mechanisms according to the IARC evaluation.

4. Molecular mechanisms of heavy metal-induced carcinogenesis

Heavy metals can induce carcinogenesis through various mechanisms, mainly (i) generating ROS by binding to additional sites designated to other elements, which promote oxidative stress; (ii) triggering biochemical events leading to DNA damage and repair disruption; (iii) inducing protein damage and enzymatic alteration; (iv) activating hypoxia signaling; (v) dysregulating the transcription factors and signaling pathways (vii) promoting epigenetics alterations and (viii) dysregulating epitranscriptome. The different mechanisms by which heavy metals are implicated in the induction of carcinogenesis are summarized in Fig. 2.

4.1. Reactive oxygen species and oxidative stress

The role of ROS seems to be an essential and common process induced by exposure of cells to heavy metals [69,70]. It is recognized that ROS are potentially carcinogenic and related to tumorigenesis and cancer progression [28]. Once they are present in the cell, ROS act as suppressors of the defense system, such as a variety of antioxidant elements with distinct roles, inducing cell injuries and subsequent disorders, including tumor formation [71]. All ROS such as ($O_2^{\cdot-}$,·OH, and H_2O_2) are produced by mostly all carcinogenic metals [5]. In Fig. 3, the mechanisms by which several carcinogenic heavy metals generate ROS and promote carcinogenesis are presented.

An experimental study revealed that oxygen molecules are utilized to generate $O_2^{\cdot-}$ radicals and H_2O_2 during Cr (VI) reduction activity. As a result, cell exposure to Cr(VI) could generate a whole range of ROS [5]. Another study demonstrated the inhibition of ROS effects by the antioxidant enzymes (CAT and SOD) which are recognized to decrease the arsenic-induced cell transformation efficiently [72,73]. Moreover, methylated arsenic has been shown to play the role of a metabolic product and participate in ROS generation in the liver and spleen [5]. Also, in an "in vivo" study, ROS generation has been demonstrated to induce bladder cancer in rats exposed to methylated As [36]. Moreover, the mice's exposure to lead revealed its capability to induce ROS production, which triggers the alteration of specific gene sequences [64].

Ni has similarly been revealed to produce free radicals, contributing to the carcinogenic process [74]. While its carcinogenic mechanism is still unclear, some studies suggest that Ni contamination could generate oxidative stress through antioxidant enzyme reductions [75]. On the contrary, ROS production is decreased in transformed cells, demonstrating certain malignant characteristics, mainly the resistance to apoptosis and fast proliferation [73]. Therefore, via the reduction of oxidative stress in malignantly transformed cells, the tumorigenesis process is promoted and maintained by the simultaneous activation of NF-E2–related factor 2 (Nrf2) [76].

Nrf2 is a crucial molecule in metal-induced carcinogenesis because it has two opposite roles. In the earlier exposure stage, Nrf2 uses its antioxidant protection properties to reduce the elevated ROS level and consequently decline cell transformation. In the later stage, stimulated Nrf2 directs the lowered ROS to achieve the required conditions for apoptosis resistance via its oncogenic role by upregulating the proto-oncogene Bcl-2 [77,78].

4.2. DNA damage and disruption of its repair

DNA damage and changes in its reparation process are the most important and implicated carcinogenic process caused by HMs exposure [44,79]. According to Pizzino et al., [80], constant exposure to HMs (large range at low doses) was correlated with a rise in oxidative DNA

Table 1
Heavy metals exposure routes, their corresponding cancer risks and carcinogenesis- induced mechanisms.

HMs	Carcino-genic category	Main exposure route	Cancer type	Carcinogenic mechanisms
As	Group1	Ingestion	Lung cancer Skin cancer Breast cancer [38,50]	-ROS generation [5]. -Hypoxia response induction and VEGF level increase [52]. -Alteration of AP-1 and NF-kB, transcription factors [2]. -miR-182-5p suppression inducing HIF-1 expression [53].
Cr(VI)	Group1	Ingestion/ inhalation	Lung cancer Nasal cancer Breast cancer [38,50,54]	-ROS generation [5]. -DNASingle Strand Breaking [55] -Activation of MAP kinase family elements [56]. -Epigenetic modification through p16 gene methylation [57].
Ni	Group1	Ingestion/ Inhalation	Lung cancer Nasal cancer [38]	-Single (SSB)- and double (DSB)-Strand Breaking [36]. -Hypoxia-like state [58] -p53's alteration inducing cell cycle arrests [59]. -Epigenetic modifications through DNA methylation [60]. -Dysregulation of miRNA inducing gene expression alterations [61].
Pb	Group2B	Inhalation/ ingestion	Lung cancer Bladder cancer Kidney cancer [62,63]	Direct DNA damage and inhibition of DNA repair [64].
Cd	Group1	Ingestion	Lung cancer Prostate cancer Breast cancer [38,50,63]	-Chromosomal aberrations [65] -Histone demethylase inhibitor [66] -Alteration of AP-1, NF-kB, and p53 transcription factors [2]. -Epigenetics changes through histone modification [67].
Hg	Group2B	Ingestion	Lung cancer Pancreatic cancer Colorectal cancer [38,68]	-ROS production by thioredoxin reductase and glutathione peroxidase inhibition [68].

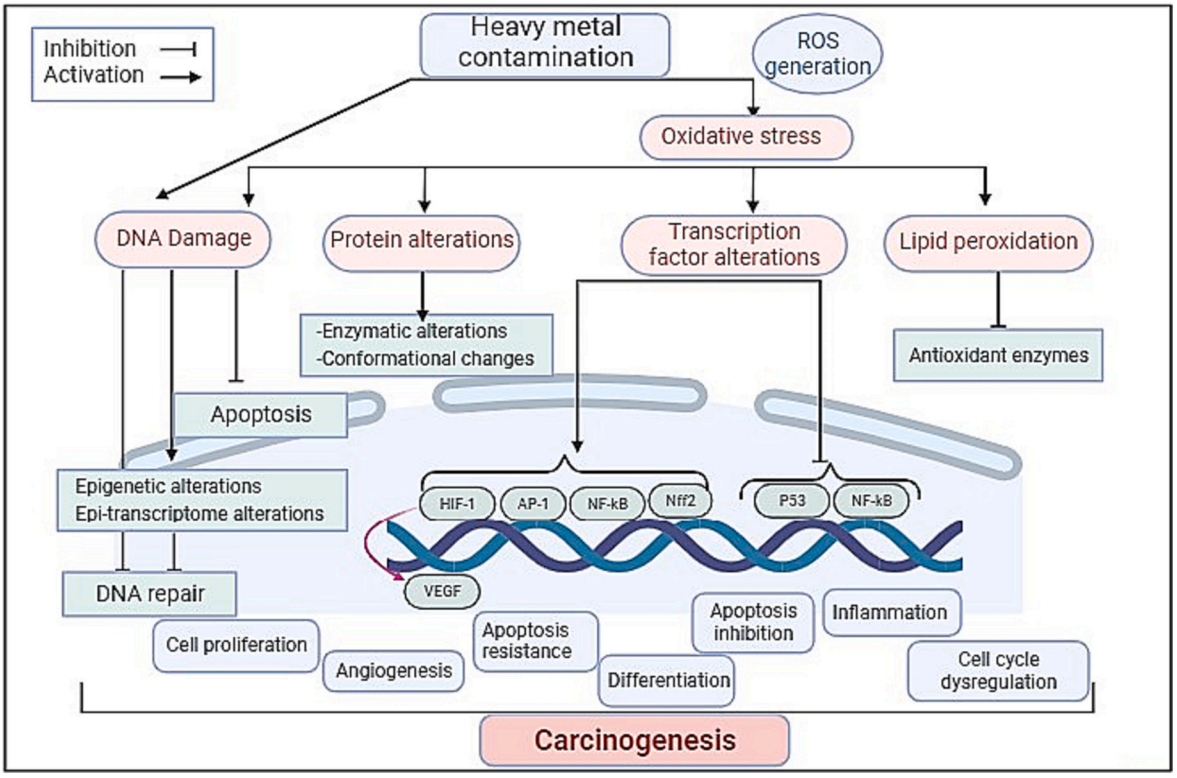


Fig. 2. Representation of heavy metals-induced carcinogenesis mechanisms [1,2].

damage as well as reduced DNA repair and detoxification gene expression in the young people group. It has been indicated that DNA destructions in airway cells were detected after arsenic exposure, and the amount of DNA 8-hydroxy-2′-deoxyguanosine (8OHdG; biomarker used for risk evaluation of cancer and degenerative disorders) was higher compared to the non-exposed group [2]. DNA damage is believed to be induced by oxidative stress via lipid peroxidation and could lead to ultimate brain cell death [2,81]. Furthermore, binding to DNA-binding protein, as could disrupt DNA repair, increasing carcinogenesis risk. Furthermore, it has been recognized that arsenic exposure was correlated with prostate, liver, skin, and Kupffer cell cancers.

In another study, Pb was found to be carcinogenic because of its effective disruption of the genetic process, resulting in DNA injury and incapability to repair itself, promoting the dysfunction of tumor-regulating genes [64].

Moreover, Cr(VI) is classified as a group1 carcinogen due to its

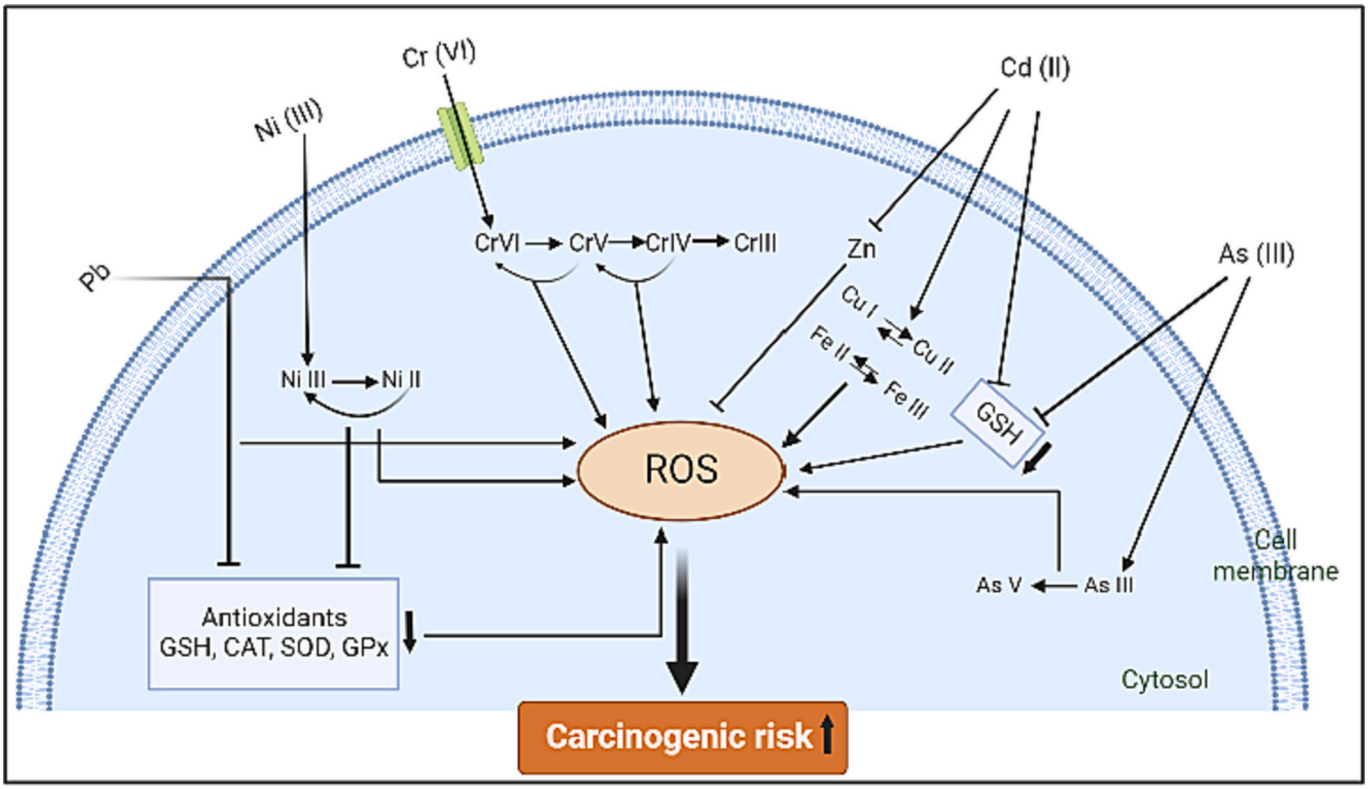


Fig. 3. Cellular ROS induction by heavy metal interactions and their increased carcinogenic risk.

mutagenic effects caused by ROS generation [3]. Single Strand Breaking (SSB) was identified during an "in vivo" study on albino mice after Cr (VI) exposure, showing SSB in the liver and kidney but a minor level was minor in the spleen, lung, and brain [55]. Cd also causes chromosomal aberrations through DNA damage, even if it is known to have a weak DNA binding activity [65,82].

As well, some studies revealed that Ni is implicated in oxidative stress, apoptosis, and DNA damage, via single (SSB)- and double (DSB)-Strand Breaking [36]. Kawanishi et al., [83] used different Ni compounds Nickel sulfide (Ni_3S_2), Nickel(II) oxide (NiO), and Nickel(II) sulfate ($NiSO_4$) to map SSB and DSB in cultured cells, they revealed that Ni_3S_2 was the most carcinogenic, and produced both types of DNA strand breaks. However, others reported an unclear mechanism used by Ni to induce oxidative stress [37].

4.3. Protein damage and enzymatic alterations

HMs target certain macromolecules (lipids, proteins, and nucleic acids). Binding to signaling proteins, cellular regulatory proteins, and enzymes usually occur via the thiol (–SH) group, which modifies cysteine residues. As a result, various cellular processes such as apoptosis, cell cycle regulation, DNA repair, DNA methylation, cell growth, and differentiation are altered [36]. Through this process, Pb was revealed to be effective in many enzymatic reactions involved in DNA transcription by substituting Zn, a metal catalyzer [64]. Therefore, the mechanism to maintain homeostasis in the cell requires principally cysteine (Cys-)-rich metal-binding peptides like glutathione (GSH) and proteins such as metallothionein (MT; small proteins rich in cysteine, playing a central role in metal homeostasis), as well as phytochelatins in plants and microorganisms, which could establish this function [84]. For example, Cd binds to metallothionein protein because of its high level of cysteine and induces Cd sequestration [85,86]. However, Cd has been identified as a histone demethylase inhibitor by substitution of Zn in its coordination center function of this family of enzymes [66].

In addition, the p53 protein which plays a significant function in DNA repair and possesses a zinc finger domain has been demonstrated to be affected by HMs. The disruption of p53 original conformation results in the inhibition of its binding capacity to DNA [87]. According to previous research, Co(II) and Ni(II) are responsible for p53's alteration capacity and as a result, cell cycle arrests [59]. Furthermore, Poly (ADP-ribose) polymerase (PARP) is implicated in several cell activities, mainly detecting DNA breaks and signaling them for enzymatic machinery reparation through zinc finger domains [88]. However, this function has been identified as being reduced in lymphoma cells after arsenic exposure [89]. Similarly, Co, Cd, and Ni demonstrated inhibition of H_2O_2-induced PARP activity in the HeLa cell line [90].

4.4. Activation of hypoxic signaling

Hypoxia is a state characterized by low oxygen levels in the body's tissues, triggered by several factors and conditions, including HMs exposure. It is widespread in tumors due to the rapid development of tumor cells which exceeds the formation of new blood vessels to bring oxygen [58]. The major regulator that controls the cell's adaptation to this oxygen tension situation is the hypoxia-inducible factor-1 (HIF-1) [91]. The activation of its transcription factor could be linked with various cancer progressions, including ovarian, breast, lung, and prostate cancers [92]. Furthermore, in response to hypoxia, HIF-1 is highly expressed, promoting the activation of the vascular endothelial growth factor (VEGF), which triggers angiogenesis stimulation and tumor progression. Therefore, HIF-1 pathway induction is essential for the carcinogenesis process. As a result, HMs may similarly stimulate the hypoxia pathway as a part of their carcinogenic-induced mechanism [58]. This directly affects HIF-1 hydroxylase (the enzyme that directs HIF-1 protein) activation or ROS generation [80]. Additional studies showed that Ni ions induce HIF-1 activation via PI3K/Akt dependent and the p70S6K independent pathways [52,93].

Unlike metals implicated in oxidative stress induction, Ni generates a

hypoxic response as a crucial mechanism in Ni-induced carcinogenesis. So, under regular oxygen amounts, a Ni-induced hypoxia-like state could be the mechanism promoting cancer development. The Ni-induced hypoxia-like state under normal oxygen tension may be a mechanism for promoting cancer development, which justifies the low mutagenic but elevated transforming activity of Ni compounds [58]. Some investigations have indicated that Co imitates hypoxia by its direct effect on the liver, kidney and erythropoietin generating cells. This could be produced by the metal-induced stimulation of the HIF transcription factor. Hyperoxia represses the erythropoietin impact of cobalt, but hypoxia improves this effect [94]. Also, arsenic exposure could as well affect the hypoxia signaling pathway [52]. It has been revealed that the prostate cancer cells (DU145) exposed to arsenite prompted HIF-1α expression, with a remarkable increase in VEGF level, involving the stimulation of the PI3K/Akt signaling pathway [52,93]. Unlike the arsenic-induced hypoxia mechanism, Cr (VI) was revealed independently of HIF-1α and VEGF expression. Alternatively, the MAP/p38 kinase signaling pathway might perform a key role in that process [95]. Thus, different pathways could be implicated in the hypoxia response promoted by metal agents.

4.5. Dysregulation of transcription factors and signaling pathways

The transcription factor's role consists of regulating targeted gene expression by binding to specific sites in the DNA. From several investigations, certain heavy metals (Pb, Ni, Cr, and Vanadium (V)) have been found to be able to activate some transcription factors related to the carcinogenic process. This could occur through ROS generation after HMs exposure by transferring the signal to redox-sensitive transcription factors NF-kB (Nuclear Factor-kappa B), AP-1 (Activating Protein-1), and p53 [70]. The protective genes implicated in the vital functions of the cell, such as DNA repair, apoptosis, proliferation, and the immune system, are controlled by these transcription factors [96]. In addition to altering key processes involved in carcinogenesis, Cr(VI) has shown to activate some mitogen-activated protein (MAP) kinase family elements [56]. The two pathways with the most critical metal effect on signal transduction are the MAP kinase/AP-1 and NF-kB pathways. NF-kB targets the inflammatory system; however, AP-1 is involved in cell proliferation and differentiation [96]. The P53 gene has a role in cell division activity through the control of cell cycle checkpoints, its disruption is associated with more than half of all human cancers [96]. Moreover, AP-1 and NF-kB transcription factors are known to be involved in cell death, cell proliferation, and p53 regulation [5]. Since AP-1, NF-kB, and p53 are the transcriptional factors targets of Cd and As the control of the protective genes expression could fail, resulting in anarchical cell growth and division [2].

Three main MAP kinase subfamilies have been identified to be affected by different metal exposures via several pathways: Extracellular signal-Regulated Kinases (ERK), C-Jun N-terminal Kinases (JNK), and the p38 MAP kinases [97]. On the other hand, AP-1 induction by H_2O_2 or by metals is mediated principally by JNK and p38 kinase pathways, knowing that AP-1 activation increases cell proliferation [97]. A further effect of the AP-1 protein is the regulation of apoptosis, either positively or negatively.

The Cr exposure could activate all of them (ERK, JNK, and p38) or only one or two, depending on the level and duration of exposure [98]. While, As was seen to cause phosphorylation of ERKs and JNKs in JB6 cells and induced AP-1 and NF-kB activation, but not p53. Consequently, ERKs activation is essential for As-induced transformation but JNKs and NF-kB activation are involved in As-induced apoptosis [70]. However, from other studies, the arsenite down-regulates NF-kB [99]. The utilization of various cell lines might justify this contradiction as a model using different concentrations and duration of exposure. For example, sodium arsenite treatment at low doses for a short duration activated NF-kB DNA binding, while As (III) chronic exposure at 0.1 or 0.5 μM reduced NF-kB DNA binding activity [100].

4.6. Epigenetic alterations

Heavy metal-induced carcinogenicity appears to be not only related to genetic alterations but also to DNA methylation and histone modification. These alterations can obstruct chromatin accessibility to controlling factors by its condensation and thus, alter gene expression on transcription initiation sites and involve gene splicing [101].

The accurate mechanism of epigenetic modifications related to heavy metals exposure is not well established. However, the silencing of certain tumor suppressor genes and rise in protooncogene expression following the ROS generation in the cell were suggested. This could be explained by DNA methylation recognized to prevent some tumor suppressor expression. Consequently, the modification in gene expression and cell transformation occurs due to disruption in the cell cycle process [2].

According to several studies, Ni could induce mutations by deletion, DNA protein crosslink damages, and chromosome aberrations [39,102,103]. However, it showed a weak mutagenic capacity particularly in prokaryotic assays, suggesting that the epigenetic modifications induced by Ni exposure are more involved in carcinogenesis induction. Moreover, across DNA methylation, Ni can replace Mg in the heterochromatin, leading to its condensation [60]. Ni has been shown to stimulate DNA methylation of E-cadherin and p16 tumor suppressor genes, which are essential in carcinogenesis induction, in which the capacity of Ni to prevent heterochromatin spreading events was suggested, leading to gene expression silencing [104].

The same p16 gene could also be methylated under the Cr exposure effect [57]. Moreover, specific histone modification marks were shown to be correlated with exposure to Cd and As [67]. It was also reported from in vivo and in vitro experiments that Ni exposure could alter global histone changes [105].

4.7. Epitranscriptome dysregulation

Different biochemical changes in the cellular transcriptome (RNA) are known as epitranscriptome [106]. Regarding non-coding RNA including microRNAs (miRNAs), endogenous small interfering RNAs (*endo*-siRNAs), and PIWI-interacting RNAs (piRNAs), which represent the highest portion in the human genome compared to the 2 % translated to protein, a potential factor in cancer etiology has emerged [107].

There is increasing indication demonstrating that heavy metal toxicity could occur through miRNA (non-coding RNA expression) alterations, which trigger a disorder in physiological conditions and signaling pathways of the cell. As a result, they promote the onset of a different kind of cancer [108].

For instance, Ni might dysregulate miRNA (non-coding sequence) which can assemble with mRNA (coding RNA), consequently, certain modifications will impact a series of gene expressions [61]. Furthermore, miRNA-21 (the most elevated miRNA in a large array of cancers) was found up-regulated in lung cancer induced by Ni exposure [109]. In addition, arsenic has been investigated in non-coding RNA regulation. Data suggests that it could promote global changes in the expression of miRNA and that it might deregulate >30 different miRNAs [110]. The suppression of miR-182-5p after arsenic exposure was demonstrated to increase hypoxia-inducible factor expression, implicated in As-induced carcinogenesis [53]. However, the role of miRNA alterations in Cr induced carcinogenesis has not been well studied.

5. Microalgae potentials in the prevention of heavy metal-induced carcinogenicity

Microalgae are microorganisms that represent the most important constituents of phytoplankton. They are photoautotrophic and can be found in a variety of environments, predominantly in marine and freshwater [14]. Microalgae can be considered as a promising feedstock for several biotechnological applications [111], biodiesel production

[112], and waste remediation [17].

Extensive use of microalgae in the development of pharmaceutical products has recently emerged [15]. This is due to their high ability to produce biomass rich in metabolites and bioactive compounds including fatty acids, polysaccharides, carotenoids, proteins, and vitamins with excellent health benefits [113]. In addition, certain enzymes might be synthetized at high proportions by algae to adapt to difficult conditions of growth, which participate in the diversification and the high quality of the bioactive compounds obtained from microalgae [14].

For instance, pigments like chlorophyll and carotenoids are known for their antioxidant properties, offering protection against oxidative stress and related diseases [19]. Fatty acids, particularly EPA and DHA, found in some microalgae were demonstrated possessing varying degrees of antibacterial and antifungal activities on Gram-positive and Gram-negative pathogens [114]. Moreover, Polysaccharides from microalgae possess immunomodulatory effects, enhancing the body's immune response [115].

On the other hand, microalgae performance were widely investigated as HMs bioremidiator agents. Their cultivation and application properties are considered to be a sustainable alternative approach in contaminated soil and wastewater treatment with reduced ecological footprint [116,117]. They have been revealed to possess the mitigating ability against heavy metals toxicity through their antioxidant capacity and HMs chelation ability [118,119]. Different strategies used by microalgae to remove HMs is discussed below and summarized in Fig. 4.

5.1. Microalgal antioxidant potential

5.1.1. Direct neutralization of ROS

As mentioned before, human exposure to HMs can induce an increased level of ROS in living cells, affecting their homeostasis. However, when ROS reach toxic levels, the cellular antioxidant system fails its elimination. Consequently, they persist in the cell [120]. Inside the cell, ROS can engender dramatic effects through macromolecules damaging which will eventually lead to signaling pathways alteration and carcinogenicity initiation [121].

On the other hand, microalgae can establish an intrinsic complement of mechanisms containing antioxidant elements at different molecular weights to endure the oxidative stress created by HMs invasion [122]. Microalgae cells possess an antioxidant defense system involved in their protection from oxidative stress according to three main defense ways. The first one includes the enzymatic antioxidants such as SOD, CAT, and GPx as well as mineral antioxidants including selenium, zinc, and copper. Their role consists in the obstruction of new free radicals' generation. The second group involves antioxidants from endogenous and exogenous origins including flavonoids, carotenoids, glutathione (GSH), uric acid, and vitamins (A, C, and E). They prevent oxidative stress through free radicals scavenging. The improvement in the amount of microalgal antioxidant elements might be an indicator of oxidation, starting with the enzymatic indicators such as CAT, SOD, and APX, then the nonenzymatic molecules including ascorbate, carotenoids, and GSH [122]. For example, a rise in CAT activation in the Cr(VI) tolerance study of *Chlorella* species procures CAT to be considered as a robust biomarker of Cr cytotoxicity [123]. The third group includes certain enzymatic antioxidants that can repair macromolecule injuries (DNA damage, protein, and lipids deterioration), such as DNA repair enzymes, proteases, lipases, transferases… [124,125]. Microalgal biomass is known for its richness in antioxidants with a wide range of applications including in the biomedical field [126,127]. This can be attributed to their capacity to endure harsh conditions such as UV irradiation and high salinity level, by increasing the antioxidant cell molecules and promoting the antioxidant secondary metabolites production [128]. For example, a high antioxidant effect on lung cancer cells has been illustrated using crude microalgal extract [129]. Besides, the amino acid antioxidant compounds (dimethylsulfoniopropionate and mycosporine) extracted from microalgae strains are known to be effective chemicals in UV radiation blockage [130]. Pigments, phenolics, peptides, and lipids antioxidants have also been isolated from microalgae biomass and revealed a strong antioxidant potential [21,22,131,132].

Lipids, β carotene, lutein, and astaxanthin pigments are prominent microalgae antioxidants of the carotenoid family. They protect microalgal tissues from light and oxygen damage [133] due to the presence of double conjugated bonds and some particular groups (epoxy, acetyl, acetylene), which neutralize the free radicals by their scavenging [21,22].

As well, astaxanthin extracted from *Haematococcus pluvialis* and *Clorella zofingiensis* and lutein from *Scenedesmus* spp., *Muriellopsis* sp., *and C. sorokiniana* revealed an effective antioxidant capacity [134,135] by mean of their ROS scavenging potential [16].

Using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) “in vitro” scavenging method, the antioxidant properties of certain peptides isolated from microalgae have been analyzed [131]. The main process of peptide extraction from microalgae is enzymatic hydrolysis using different enzymes like trypsin, papain, and alcalase alpha. The obtained product could be applied either directly as a crude extract or undergo a purification process [26]. Through a “in vitro” study, it has been shown that the enzymatic extraction of *Chlorella* sp. and *Tetraselmis suecica*, demonstrated a powerful antioxidant potential in skin fibroblasts [136]. Similarly, a strong scavenging capacity on superoxide and DPPH radicals of two purified peptides isolated from *Chlorella* sp. using pepsin

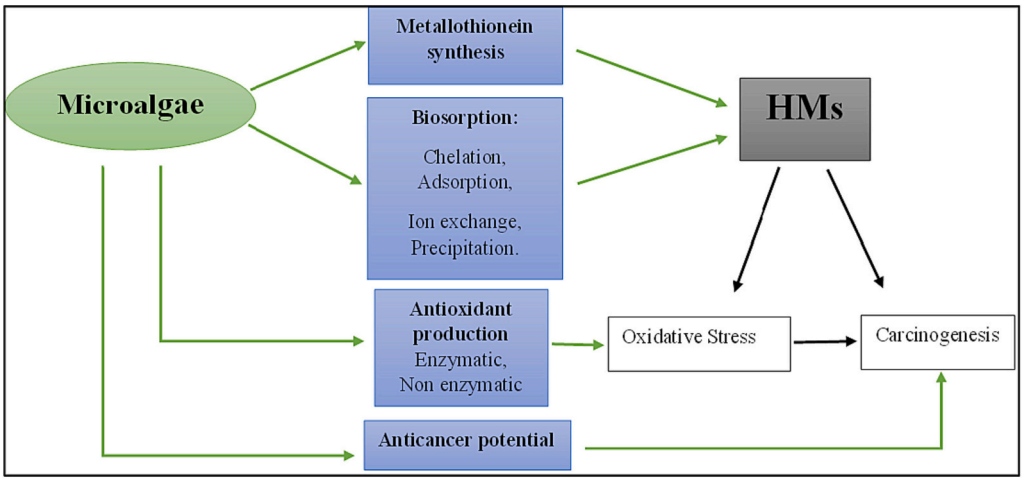


Fig. 4. Representation of different strategies applied by microalgae to protect from heavy metals toxicity

hydrolysate has been reported [21,137]. Moreover, polyphenols compounds isolated from different microalgae species also showed their antioxidant properties. A high level of phenolics was identified in *Euglena cantabrica* microalgae, showing more effective radical scavenging potential than that of conventional antioxidants. Haoujar et al., [132] also isolated *Phaeodactylum tricornutum* marine microalgae from Moroccan water, which produced protocatechuic acid with considerable antioxidant activity.

5.1.2. Indirect neutralization of ROS

According to some studies, microalgal carotenoids have been able to increase the expression of antioxidant genes in specific cells and tissues through the activation of Nrf2 transcription factor. Nrf2 regulates the antioxidant molecules to prevent oxidative stress. The elevated ROS level induces the activation of Nrf2 which acts as a transcription factor to stimulate the expression of intracellular antioxidative genes (CAT, SOD, GSH) by binding to a specific region of DNA (Antioxidant response element, ARE) [138]. Certain microalgae antioxidants such as carotenoids and flavonoids could contribute to this process through Nrf2 stimulation to emphasis the ARE expression leading to intracellular antioxidants (CAT, SOD, GSH) synthesis [36]. For example, β carotene has been found in a higher amount in *Dunaliella salina* reaching 14 % of dried biomass [139]. Due to its antioxidant and nutritional particularities, it is broadly used as a food product and in cosmetics [140]. In an "in vivo" study, it has been shown that mercury chloride ($HgCl_2$) induced oxidative stress in mice by decreasing the main antioxidant enzymes and glutathione in the liver through the induction of lipid peroxidation. However, the oral administration of *Spirulina fusiformis* extracts in specific conditions allowed lipid peroxidation to decrease and yield an ultimately higher GSH amount in the liver. Hence, the supplementation of *Spirulina* had an impact on preventing and protecting from $HgCl_2$-induced oxidative stress in mice [141]. Similarly, *Spirulina maxima* showed a protective effect against lead acetate-induced damage in rat's liver and kidney cells through its radical scavenging potential [138]. Table 2 summarizes the HMs mitigation strategies of the extracts and bioactive molecules of some microalgae species.

5.2. Microalgal anticancer potential

Various research investigated the anticancer activity of microalgae metabolites and derivative compounds to assess their effectiveness against different malignant cells and to improve understanding of the mechanisms involved in such a capacity.

Cellular toxicity, downregulation of cancer cell invasion, and improvement of the apoptosis cell death of cancer cells are also among these mechanisms [19,147]. According to Tavares-Carreón et al., [148] a methanolic extract of microalgae strains isolated from the Mexico desert (*Granulocystopsis* sp.) showed an antiproliferative effect on different cancer cell lines (breast, lung, colorectal, prostate, and melanoma), with an IC_{50} <20 μg/mL except in Vero normal cells and lung cancer cell line. Also, cell adhesion inhibition and proapoptotic activity were identified, as well as an increased caspase (3, 7) activity was revealed in a similar manner as doxorubicin (a conventional antitumor drug) [148]. Furthermore, a crude extract of the Qatari microalgae strain (*Chlorella* sp. QUCCCM3) demonstrated a significant antiproliferative potential on K562 myeloid leukemia cancer cells. This investigation was carried out using MTT assay ($p < 0.5$), showing an IC50 value of 21.37 ± 2.98 μg/mL [149].

Besides, several species of microalgae were investigated for their high quantities and even qualities of proteins and peptides that are demonstrated competitive with other well-known sources [150]. According to Deniz et al., [151], a phycocyanin rich extract made by *Spirulina platensis*, showed a significant cytotoxic effect on A549 lung cancer cell line, with an IC_{50} of 26.82 μg/mL. C-phycocyanin, a blue photosynthetic pigment, is highly abundant in Cyanobacteria, Cryptophytes, and Rhodophyta [152], its amount could attain >50 % in *Athrospira fusiformis* [153]. C-phycocyanin from *spirulina platensis* has been reported to possess anticancer activity against breast cancer cells (MDA-MB-231) through the MAPK pathway [24]. The latter is able to influence the behavior of cancer cells in several ways including proliferation, differentiation, and apoptosis, which are the key aspects in the development and progression of breast cancer [154]. Moreover, C-Phycocyanin isolated from *Spirulina platensis* demonstrated a high cytotoxic effect in HeLa and MCF7 cell lines. It seems to possess capacities to promote DNA fragmentation, Bcl-2 proteins down-regulation, Fas and ICAM upregulation, and caspases stimulation [14,155]. Additionally, a polypeptide from *Chlorella pyrenoidosa* (CPAP) exhibited an antiproliferative property against human liver cancer cells (HepG2) at an IC_{50} of 426 μg/mL. Its micro- and nano-encapsulation showed high resistance to the enzymatic degradation of the gastrointestinal tract [156].

On the other hand, polysaccharides generated by microalgae have been used in various domains, including food and biomedical applications due to their wide variety of activities against viruses, bacteria, oxidative stress, as well as cancer cells [26]. For example, a neutral polysaccharide has been isolated from *Gracilariopsis* sp. and demonstrated an interesting anticancer potential on lung cancer cells (A549 cell lines), by modulating their viability, morphology, and inducing cell apoptosis [157]. Furthermore, sulfated polysaccharides exhibit a remarkable effect on various cancer cell lines through their great potential for immunomodulatory activity. They can stimulate the activity of various immune cells like macrophages, natural killer cells, and lymphocytes, which play a crucial role in antitumoral immune system [158]. Their biological effect was associated with sugar structures and

Table 2
Microalgae bioactives with heavy metals mitigation capacity.

Algal bioactive molecules/ extracts	Algae species	Study type	Experimental model	Mitigation strategy	HMs targeted	References
Malondialdehyde (MDA)	*Chlorella vulgaris*	"In vitro"	*Chlorella vulgaris*	Increase the antioxidant enzyme activity (CAT, SOD, Apx, Gpx)	Cr (VI)	[123]
Astaxanthin	Not reported	Theoretical study	Density functional study	Scavenge free radicals, mainly superoxide radical anion	Ca^{+2}, Cu^{+2}, Pb^{+2}, Zn^{+2}, Cd^{+2} and Hg^{+2}.	[142]
Phycobiliproteins (C-phycocyanin)	*Spirulina maxima*	"In vivo"	Male NIH mice	Prevent oxidative stress	$HgCl_2$	[143]
Algal extracellular polymeric substances	*Synechocystis* sp.	"In vitro"	Sorption and transformation study on *Synechocystis* sp.	Biosorption through functional groups	As(III) and As (V)	[144]
Algal mixture	*Spirulina platensis* *Chlorella vulgaris*	"In vivo"	Seabass, *Dicentrarchus labrax*	increase in SOD and Gpx activities in the liver and induce ROS scavenging.	CdCl2 + Pb $(NO_3)_2$	[145]
Crude extract	*Spirulina fusiformis*	"In vivo"	Swiss albino mice	Decrease of lipid peroxidation and increase of GSH amount	$HgCl_2$	[141]
Crude extract	*Spirulina maxima*	"In vivo"	Swiss albino mice	ROS scavenging	Lead acetate Pb $(C_2H_3O_2)_2$	[146]

properties (composition, position, and sulfation degree) [159]. Through an "in vivo" experiment, fucoidan obtained from *Fucus vesiculosus* has been illustrated by applying phagocytic activity and activation of TNF production to fight against Lewis lung adenocarcinoma [160]. Also, some studies have shown the possibility of using microalgal polysaccharides with other chemotherapeutic agents already used in conventional approaches to remediate drug resistance and reduce its side effects [161].

Moreover, lipids extracted from microalgae could attain >25 % of dry weight, depending on the extraction process, and they reach around 34 % in *Botryococcus braunii,* [162,163]. Different enzymes utilized in their synthesis have been developed via genetic engineering to enhance lipids production to prevent and treat certain disorders such as cancer and inflammatory diseases [26]. Similarly, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), essential omega-3 polyunsaturated fatty acids (PUFA) possess a valuable potential for plenty of diseases, [25,26]. EPA and DHA administration in mice food resulted in a low proliferation of their lung cancer cells [164].

As liposoluble pigments, carotenoids from *Chlorella ellipsoidea* at 40.73 μg/mL showed an antitumor effect on colon carcinoma (HCT-116) [14]. Besides, they were identified for their anti-allergic, pro-vit A synthesis and antioxidant capacities after isolation from *Dunaliella salina* species [165]. As well, astaxanthin has been revealed to prevent the antiproliferative effect of KATOIII and SNU1 gastric cancer cell lines through the cell cycle arrest effect and the increase of p27 expression [166]. It has also been reported that astaxanthin repressed the expression of pro-inflammatory genes in macrophages through suppressing stimulation of NF-kB that is implicated in diverse carcinogenic processes, by acting as ROS scavengers [16]. Similarly, the antioxidant phytochemicals extracted from blue-green microalgae (C-phycocyanin, scytonemin) have also demonstrated high cytotoxic and anticancer effects [14,125]. Thus, certain antioxidant molecules isolated from microalgae have also been shown to possess an anticancer activity (Table 3).

5.3. Microalgal potential for HMs removal

Microalgae have gained important consideration in recent years for their remarkable potential in bioremediation processes. Their capacity to adsorb, absorb, and accumulate HMs makes them valuable tools in environmental restoration [173]. Their capacity to sequester HMs through chelation and biosorption mechanisms has been widely studied for the remediation of contaminated sites and industrial effluents. The versatility of microalgae, coupled with their rapid growth and photosynthetic capabilities, presents a sustainable and eco-friendly approach to address pollution issues, offering the potential to enhance the quality of water, soil, and air in various ecosystems .

The removal of HMs by microalgae involves different complex processes. The first mechanism is based on their ability to produce enzymatic and/or non-enzymatic antioxidant molecules. Also, they react to the toxicity induced by HMs through either the regulation of gene expression of specific proteins implicated in the detoxification (metallothionein) [174] or by means of a metal biosorption system [175]. The latter inhibits the HMs uptake via the release of phytochelatins on the surface of cells or through different chemical interactions including ion exchange, adsorption, complexation, and precipitation [175]. The complex and exclusive structure of microalgae cell walls, as well as its richness in functional groups, offers them this capacity [176].

As unicellular cells with simple structure and photosynthetic ability, microalgae have been usually favored for HMs remediation. In particular, two microalgae genera, *Chlorella* and *Scenedesmus* are preferably chosen for removal of heavy metals with specific attention to some species including *Chlorella salina*, *C. vulgaris*, *C. sorokiniana*, *Chlamydomonas reinhardtii*, *Scenedesmus abundans*, *S. subspicatus*, *Stigeoclonium tenue*, and *Arthrospira platensis* [177]. Moreover, a variety of species were investigated as biosorbents of plenty of HM such as Cu, Ni, Cd, Se, Pb, Fe, Mg [177].

5.4. Microalgae metal-binding proteins synthesis

Microalgae can synthesize specific encoded proteins capable of chelating HMs cations and inhibiting their effects to reduce HMs toxicity [118]. Among metal-binding proteins, metallothionein (MT), or metallothionein-like protein (MTLP) in aquatic organisms, is an mRNA translation product, rich in cysteine, and categorized as low molecular weight protein (6 to 7 kDa) [178]. In marine species, the metal-binding proteins have been established as likely biomarkers of HMs toxicity [179]. From "in vitro" studies, metallothionein could bind to HMs forming a stable complex [118,180]. For example, several metallothioneins were found to be able to chelate Cd traces and were involved in Zn and Cu homeostasis, consequently decreasing the cytotoxic free metal ion concentration [181].

Some microalgae species (*S. subspicatus, S. tenue, Stichococcus bacillaris*, and *Thalassiosira weissflogii*) were identified to biosynthesize metallothioneins following "in vivo" and "in vitro" exposure to a variety of HMs including Pb^{2+}, $Cd^{2+,}$ As^{3+}, Zn^{2+}, and Ni^{2+} [178,180,181].

Fitting to the same concept of bioremediation applied in wastewater decontamination, the application of microalgae-based metal-binding protein can be an effective device in the biomedical field for the detoxification of HMs. Metallothioneins may well be employed to eliminate heavy metals from contaminated tissues of living organisms [118]. In humans, different isoforms of metallothioneins are expressed [182], however, their distribution has been associated with cancer. For instance, the gene expression of certain isoforms was linked to prostate, breast, thyroid, and bladder cancers [183], in contrast to liver cancer where it was downregulated [184].

Table 3
Microalgae antioxidant bioactives with anticancer potential.

Antioxidants	Approximative inhibition concentration	Microalgal source	Cell line experiment (target) Cancer cell lines	References
Fucoxanthin	IC_{50}:19 μg/mL	*Chaetoceros calcitrans*	Human liver cancer cells (HepG2)	[167]
Carotenoids (especially lutein)	IC_{50}: 40.3 μg/mL	*Chlorella vulgaris*	Human colon cancer cell lines (HCT116)	[168]
Siphonaxanthin	IC_{95}: 20 μM	*Codium fragile*	Human leukemia cells (HL-60)	[169]
astaxanthin	IC_{58}: 25 μg/mL	*Haematococcus pluvialis*	Human hepatoma cancer cell line (HepG2)	[170]
Polyunsaturated fatty acids (PUFA)	IC_{50}: 0.45 μg/mL	*Nannochloropsis salina*	Human breast cancer cells (MCF-7)	[171]
Sulfated polysaccharides	IC_{60}: 250 μg/mL	*Phaeodactylum tricornutum*	HepG2	[172]
C-Phycocyanin	IC_{50}: 190 μg/mL	*Arthrospira platensis*	(MDA-MB-231)	[24]

5.5. Microalgal biosorption capacities (chelation)

Further strategies adopted by microalgae to eliminate toxic HMs consist of two processes. The primary one entails the attachment of HMs to the cell surface, known as biosorption [178]. This process is realizable by both live and dead algae biomass due to its non-metabolic nature. Biosorption is facilitated by the presence of negative groups (hydroxyl, carboxyl, phosphate, amine, and sulfhydryl…) at the external cell surface, allowing the adsorption of HMs by delivering more metal binding sites [185]. In addition to the adsorption mechanism, HMs can be attached to the microalgae cell surfaces through various mechanisms, such as ion exchange, microprecipitation, and chelation or complexation process [186]. The latter process involves chelating agents or phytochelatins (PCs), which reduce the bioavailability of heavy metals. PCs are produced enzymatically from glutathione oligomers in the presence of phytochelatin synthase [187]. This enzyme is activated at increasing levels of metal ions triggering the production of PCs. Then, metallic ions form complexes with PCs and they are transferred into the vacuoles and effectively removed from the cell, consequently decreasing heavy metal-induced toxicity [36]. The majority of algae have the ability to produce PCs agents [118]. This production is achieved after a few minutes of exposure to HMs and occurs independently of protein synthesis [188]. According to several studies, various elements (Pb, Cd, Zn, Hg, As, Cu…) can activate the phytochelatin synthase enzyme either "in vitro" or "in vivo" [178,187].

It has been demonstrated that *Chlorella* supplementation in the diet was efficient in improving mercury clearance from bones, the digestive tract, ligaments, and muscle [189]. *Chlorella* chelates HMs, particularly lead, and mercury because of its elevated chlorophyll content [12]. The most involved microalgae mechanisms in heavy metals detoxification are represented in Fig. 5.

Moreover, in the case of HMs ingestion, the algal extracts were shown to play the role of chelating agents by reducing the bioavailability and gastrointestinal absorption of HMs and inducing a faster toxicant excretion due to amplifying intestinal movements. Also, several high-value products present in these extracts are engaged in the heavy metals chelating activity, mainly phycobiliproteins and astaxanthin [142,190]. However, their mechanisms to bind with HMs are still unknown, which limits their extensive applications. According to Bermejo et al., [191], the fluorescence emission spectra of *S. platensis* protein extract, especially phycocyanin decreased in presence of iron ions, which was an indicator of the metal-chelating activity of these proteins. In more recent study, it has been shown that the fluorescence of cyanobacterial phycobiliproteins could be reduced after HMs binding, making them very attractive as sensors and scavengers of HMs. Using high-resolution native mass spectrometry, Phycocyanin demonstrated a high affinity to copper and silver and was subjected to a severe changes in its native oligomerization upon exposure to copper and silver ions [190].

Furthermore, different metal cations (Calcium (Ca^{2+}), Cu^{2+}, Pb^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+}) were shown in theoretical studies to form complexes with astaxanthin, forming Metal-Oxygen bonds. These complexes (astaxanthin-metal) were shown to have the free radical scavenging capacity, in particular against a superoxide radical anion [142]. Another investigation has been done on the arsenic sorption capacity of extracellular polymeric substances (EPS) extracted from a cyanobacteria strain, it showed an increase in EPS amount after arsenic cell treatment. Moreover, using FTIR, they revealed that As is bound to EPS by complexation interactions through their functional groups including C═O, —NH, and —OH [144]. The second process occurs after the adhesion of HMs to the cell surface, they get internalized inside the cell allowing the bioaccumulation process to occur. This step requires the mediation of some carrier proteins to be completed due to the hydrophilic nature of HMs [178]. Then, compartmentalization is achieved by the entry of HMs in specific organelles including chloroplasts and mitochondria, for ultimate detoxification. Few statements suggest that this step is carried out only by living cells [178]. However, others indicate that dead microalgal biomass can accumulate HMs ions similarly or at a higher extent than living cells. In some studies, the comparison of HMs uptake between living microalgae cells and their respective biomass was analyzed. For instance, a faster Cd removal by dried biomass than by living microalgae was suggested. However, in a bioremediation trial of contaminated seawater, >190 species of microalgae used, and a high Cd removal capacity of approximately 50 % was attributed to *Chlorella* sp. Noting that the intracellular accumulation was estimated at 67 %, while, 25 % was the adsorbed proportion of cadmium on the microalgae wall [192].

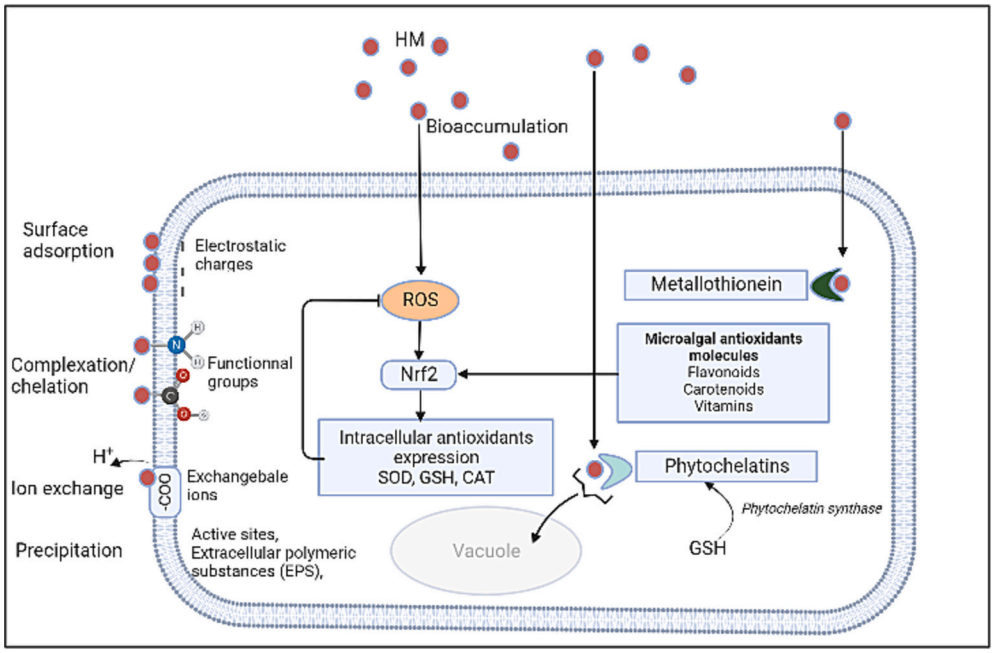


Fig. 5. Scheme of the most involved microalgae mechanisms in heavy metals detoxification.

5.6. Living cells vs. dead biomass for biosorption

As previously stated, biosorption is a fast metabolic independent process that could be triggered by both living and dead cells. However, due to its advantages, dead biomass is the most used. It requires neither nutrients nor specific conditions or parameters to adjust. In addition, it could remain effective even after a long time without the specific condition of conservation [193]. Moreover, the regeneration and ability for further uses of the non-living biomass compared to the living biomass are also considered a frequently reported advantage of its use [194]. Most prominently, HMs' adsorption rate of dead biomass has been identified to be higher than that of living cells [119,195]. However, living cells can accumulate HMs, which are considered toxic and have impacts on their metabolism. Also, the enzymatic process provided by live cells could be more difficult and take a longer time, since it involves biotransformation and biodegradation to recover HMs [196]. It has been shown that the biosorption rate of As III was clearly higher using many kinds of microalgal biomass [197].

6. Conclusion and recommendation

Humans are subjected to heavy metal exposure through various routes including inhalation, dermal contact, and ingestion of contaminated food and water, which leads to several toxic effects on human health. The principal key mechanisms implicated in heavy metal-induced carcinogenicity are their capacities to generate reactive oxygen species (ROS), which are involved in cell macromolecule damage such as DNA, proteins, and lipids. Toxic heavy metals could also disrupt DNA repair, cell proliferation, and apoptosis, as well as gene expression via epigenetic alterations. Heavy metals are difficult to avoid due to their prevalence as major contaminants in the environment. However, it is important to use natural products to protect human cells from their carcinogenicity. Here, microalgae were addressed as potential agents to prevent the carcinogenicity induced by heavy metal exposure. Based on the current review, this prevention can be achieved through various microalgal strategies, including HMs biosorption, antioxidant, and anticancer activities.

In this context, more studies on microalgae extracts need to be conducted to assess their possible applications against heavy metal carcinogenesis. Likewise, molecular investigations related to purification strategies of bioactive compounds from microalgae and their mechanisms of action on the cellular system to mitigate heavy metal toxicity are also needed. Clinical trials that would explore the effectiveness of microalgal bioactive compounds as new dietary supplements with the heavy metal binding capacity to prevent a wide range of HMs-induced cancers are also desired. This could be a new microalgae research axe to be considered in the future.

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CRediT authorship contribution statement

Hadjira Hamai-Amara: Writing – review & editing, Writing – original draft, Conceptualization. **Haissam Abou-Saleh:** Writing – review & editing. **Mohammad A. Al-Ghouti:** Writing – review & editing. **Sergio Crovella:** Writing – review & editing. **Imen Saadaoui:** Writing – review & editing, Supervision, Conceptualization. **Lama Soubra:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated and/or analyzed in this study were included in the published article.

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