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Metal and metalloid containing natural products and a brief overview of their applications in biology, biotechnology and biomedicine

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Abstract Bioinorganic natural product chemistry is a relatively unexplored but rapidly developing field with enormous potential for applications in biology, biotechnology (especially in regards to nanomaterial development, synthesis and environmental cleanup) and biomedicine. In this review the occurrence of metals and metalloids in natural products and their synthetic derivatives are reviewed. A broad overview of the area is provided followed by a discussion on the more common metals and metalloids found in natural sources, and an overview of the requirements for future research. Special attention is given to metal hyperaccumulating plants and their use in chemical synthesis and bioremediation, as well as the potential uses of metals and metalloids as therapeutic agents. The potential future applications and development in the field are also discussed.

Keywords Natural products · Metals · Bacteria · Fungi · Hyper accumulators · Therapeutic agents

Introduction

Metals and metalloids are widespread in both biological systems and the environment. Many are able to easily lose electrons to form cations that are soluble in biofluids, such as blood. It is in this cationic form that they play important roles in biology. This is because many bio-molecules (e.g. nucleic acids and proteins) as well as many small molecules and ions important to living systems are electron rich and therefore have a high tendency to form co-ordinate bonds with metals and metalloids (Orvig and Abrams 1999; Turel 2015). Chemically, there is wide scope for such interactions

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and metals are involved in many crucial biological functions. Important biomolecules that make use of metal ions include, but are not limited to, vitamin B_{12} (cobalt), haemoglobin (iron), insulin (zinc), chlorophyll (magnesium), plastocyanin (copper), urease (nickel) and calmodulin (calcium). Calcium is also important for structural integrity in many organisms, for example bones in mammals, while silicates are used for a similar function in various species of algae (e.g. diatoms) (Ceresia and Brusch 1955).

Secondary metabolites, commonly referred to as natural products are a broad class of compounds and can be defined as any chemical substance produced by a living organism that are not involved in normal growth and are typically produced as a result of particular environmental stress events and/or for chemical defence. The term is commonly used to refer to a class of compound(s) found in nature that have distinctive pharmacological effects and/or are used as potential pharmaceutical drugs and more recently, FDA approved phytobotanicals (David et al. 2015; Mishra and Tiwari 2011). Natural products originate from the vast biodiversity of Earth's terrestrial and aquatic organisms and their derivatives often have potent physiological activities. As such they continue to play important roles as both frontline treatments for many diseases and as the inspiration for chemically synthesised therapeutics (Dias et al. 2012). They are also increasingly being used in biotechnology applications. The physico-chemical properties of natural products are the result of millions of years of evolution and as such they are a challenging route to the development of new compounds, albeit one with an enviable track record (David et al. 2015, Lamottke et al. 2011). Nevertheless, since more than 95 % of the world's biodiversity has not yet been evaluated for any useful, biological active compounds, there remains a major opportunity/challenge to efficiently and effectively access and utilise this natural chemical diversity (Mishra et al. 2011).

The majority of natural products contain the standard elements of organic compounds (e.g. C, H, O, N, and S) and other heteroatoms depending on the synthetic route taken. Natural products (both natural and/or semi-/synthetic) sometimes also exhibit the surprising incorporation of semi-metals (metalloids) and metals. For example, inorganic arsenic based compounds seem to play an important role in the biochemistry of many plant and animal species. For example, boron-containing natural products have been shown to possess antibiotic activity. Selenium rich microorganisms, such as the cyano-bacterium *spirulina,* show promise as a food/health supplement (as selenium is essential to human health) as well as being a source of general nutrition, especially in third-world countries. More recently, both natural and synthetically derived natural products have shown to be useful metal chelators with possible applications in the treatment of neurogenerative disease; others may be useful for cleaning up metal contamination resulting from rapid industrialisation and economic development in both developed and developing countries (Chakraborty et al. 2014). Examples of metal and metalloid containing natural products are discussed in this review, along with their potential uses, in what might be termed bioinorganic natural products chemistry. Each example is critically examined and further comment on the potential future for the field is presented.

Common metals and metalloids in biological systems

Arsenic

Arsenic is well known to be toxic to humans and indeed it has had a well-deserved reputation as a poison of choice for hundreds of years (Winter 2015). Interestingly, despite their known toxicity, arsenic compounds, especially organic ones, can be integral components of food chains and so may play potentially important biological roles in many organisms. As such, arsenic containing natural products can be found in a broad variety of terrestrial and aquatic species (Rezanka and Sigler 2008) and have been the focus of a number of reviews, most notably by Cullen (2008) and Lansdown (2014). The aim of the following section is not to repeat the work of these authors but merely to provide a brief insight into the role arsenic can play in natural products.

Byrne et al. (1995) detected arsenobetaine in abundance for the first time in the terrestrial environment in a the arsenic accumulating mushrooms *Sarcosphaera coronaria*, *Agaricus haemorrhoidaius* and *A. placomyces*. Dimethylarsinic acid was also found to be the major arsenic compound in another mushroom, *Laccaria amethystina* collected in Slovenia (Byrne et al. 1991). It is of note that some mushrooms accumulate arsenic to potentially toxic

levels, as recently reported from China (Zhang et al. 2015). Rice can also accumulate arsenic from water or soil (Fransisca et al. 2015) and this may be a significant risk in some parts of the world (Williams et al. 2006). Other examples of arsenic based compounds identified included, arsenocholine and the tetramethylarsonium ion (Byrne et al. 1991). A detailed study by Kuehnelt et al. (2000) found a large variety of arsenic compounds including arsenic acid, dimethylarsinic acid, methylarsonic acid, arsenobetaine, arsenocholine and four arsenoriboses present in two lichens and twelve green plants growing near an old arsenic smelter site in Austria. The authors showed that arsenic containing compounds were able to accumulate in terrestrial lichens and be integrated into their biochemistry, as well as functioning as indicators of pollution and metal toxicity (Kuehnelt et al. 2000).

Arsenic based natural products have also been reported in the marine environment. Indeed, marine organisms have been known to accumulate arsenic concentrations enough to be harmful to humans. Marine algae, for example, can contain arsenic at concentrations of 0.1–382 days wt (mg kg^{-1}), which is significantly higher than the level commonly found in in seawater (Edmonds et al. 1987; Rahman et al. 2012). As such, arsenic species need to be monitored in seafood in order to establish and monitor potential risks to consumers (Tukai et al. 2002). Algae have various physiological mechanisms to deal with arsenic. Edmonds and colleagues for example found that the marine algae, *Hizikia fusiforme* stored half of its arsenic load as arsenic-containing ribofuranosides and the other half as inorganic arsenic (Edmonds et al. 1987). The concentrations of the three arsenicals were also determined in thirty-seven marine organisms comprising of algae, crustaceans, bivalves, fish and oceanic mammals which shows just how widespread such compounds are in marine species (Sloth et al. 2005).

The incorporation of arsenic into complex organic molecules such as arsenosugars and arsenobetaines by marine algae and invertebrates, and fungi and bacteria can include volatile methylated arsenic compounds (Bird et al. 1948; Rezanka and Sigler 2008; Vidal and Vidal 1980). Honschopp and co-workers for example isolated an arsenic resistant and arsenic methylating bacterium belonging to the *Flavobacterium-Cytophaga* group, which had an arsenic content of 1.5 ppm with a tolerance of 200 ppm of arsenic (Honschopp et al. 1996).

Marine phytoplankton and terrestrial fungi can produce phospholipids containing arsenic-arsoniumphospholipids, in the presence of arsenate. Vidal and Vidal studied the metabolism of arsenic in two marine microorganisms: a facultative anaerobic bacterium (*Serratia marinorubra*) and the obligate, aerobic yeast (*Rhodotorula rubra*) (Vidal et al. 1980). Both the bacterium and the yeast produced arsenite (As III) and methylarsonic acid [$CH_3AsO(OH)_2$]. However, the yeast produced dimethylarsinic acid $(CH_3)_2AsO(OH)$ and volatile alkylarsines, while the bacterium, which grew anaerobically, did not synthesize gaseous forms of arsenic (i.e., methylarsines). Interestingly, neither organism synthesized arsoniumphospholipids, such as those produced by marine phytoplankton or terrestrial fungi (Vidal and Vidal 1980).

Recent findings have indicated that the As III *S*-adenosylmethionine methyltransferase (*arsM*) gene in bacteria was responsible for releasing volatile arsenic compounds from the bacteria (Yuan et al. 2008). The volatile compounds were trapped on H_2O_2-impregnanted paper and detected through the use of trimethylarsine oxide being eluted from the paper. These findings highlighted indirect evidence for the bacterial release of volatile trimethylarsine, with the authors developing a direct speciation analysis of volatile arsenic species in the headspace of the bacterial culture, and thus confirming *ArsM's* role in producing the volatile arsenic species (Yuan et al. 2008).

Wickenheiser et al. (1998) developed and applied gas and liquid chromatographic speciation methods with inductively coupled plasma-mass spectrometry (ICP-MS) detection to study anaerobic arsenic metabolism. Instrumental analysis included the use of high performance ion chromatography, hydride generation gas chromatography–mass spectrometry (GC–MS) purge and trap gas chromatography and ICP-MS, to study the formation of volatile and ionic arsenic compounds produced in culture of anaerobic methanogen, *Methanobacterium formicium*. Arsenite, mono- and di- methylated arsenic acid, arsine, mono-, di- and tri-methylarsine and certain unknown volatile arsenic species were detected which demonstrates the large variety of biochemical pathways that arsenic can be involved in (Wickenheiser et al. 1998).

More recently, Meyer et al. (2006) determined the biogenic production of volatile metalloid species in soils of different origin through methylation and hybridization (Meyer et al. 2006). Hybrids and methylated derivatives of a variety of elements were detected, namely arsenic, antimony, bismuth, selenium, tellurium, mercury, lead and tin. High versatility in the transformation of metalloid ions to volatile derivatives was observed by isolating a strictly anaerobic gram-positive strain ASI-1 (which is related to the species *Clostridium glycolicum*), and fluorescence in situ hybridization showed that ASI-1 amounts to about 2 % of the total microbial flora of the alluvial soil (Meyer et al. 2006).

Islam and co-authors developed an enumeration method for arsenic methylating bacteria from mixed culture samples through the use of the anaerobic-culture-tube, the most probable number method (MPN), and detection by GC–MS (Islam et al. 2005). The advantages of this method is that it can simultaneously enumerate AsMB and acetate and formate-utilising methanogens, as the carbon source is based on the growth of methanogens. Overall, the method simplifies the estimation and isolation of AsMB populations in different samples, including environmental samples.

Boron

Boron is an essential trace element for plants, is beneficial to animals and humans, and is also a semiconductor possessing both metal and non-metal properties (Winter 2015). The most well-known boron-containing NP is the polyketide antibiotic, boromycin, first isolated from *Streptomyces antibioticus* collected from soil in the Ivory Coast, Africa. It shows considerable therapeutic potential and as such is discussed further in "Inorganic medicinal chemistry" section. There are also a number of other boron containing antibiotics; Okazaki et al. reported the isolation of aplasmomycin, from *Streptomyces griseus* SS-20, found in shallow sea sediments. This compound chelated boron and was effective in controlling *Plasmodium berghei* (Okazaki et al. 1975). Subsequently, Sato and co-workers described the isolation of several structurally related compounds from *S. griseus*, namely aplasmomycins B and C, of which aplasmomycin B showed antibacterial activity (Sato et al. 1978). The same group also described that the chelation with metals/metalloids other than boron did not directly correspond with antibacterial activity (Stout et al. 1991).

Irschik and colleagues isolated the antibiotics, tartrolon A and tartrolon B from a soil sample collected near Braunschweig, Germany (Irschik et al. 1995). The origin of these antibiotics which were active against Gram-positive bacteria and mammalian cells was identified as the cellulose-degrading myxobacterium, *Sorangium cellulosum* (Irschik et al. 1995). In another example, a boron-containing antibiotic, tartrolon E, produced by the symbiotic cellulose-degrading bacteria, *Teredinibacter turnerae* (found in the gills of marine shipworms) was also recently discovered by Elshahawi et al. (2013). This compound showed significant antibacterial activity against *Pseudomonas aeruginosa* and methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MRSA). It also possessed an IC_{50} of 2 μM against the MCF-7 breast cancer cell line but interestingly did not show any inhibition activity against the fungus *Candida albicans.*

Boronated compounds also show promise against larger organisms. Lewer and co-authors isolated tartrolon C, from the extract of a *Streptomyces* strain CP1130 on the basis of its insecticidal activity (Lewer et al. 2003). This compound was found to be active against two major crop pests, the beet armyworm, also known as the small mottled willow moth (*Spodoptera exigua*) and the tobacco bud worm (*Heliothis virescens*), with MELCs (minimum emergent larvicide concentration) of 125 ppm for both insects. This showcases its potential as a novel insecticide (Henstock et al. 2015; Lewer et al. 2003).

Selenium

Selenium is considered to be an essential trace element in human health, assisting in protection against chronic degenerative, neurological or neoplastic diseases (Rezanka and Sigler 2008). It is also an essential micronutrient for plants and microorganisms, but can also occur is some soils in amounts high enough to produce serious effects on animals feeding on plants such as locoweed (*Astragalus* sp.) (Winter 2015).

The blue-green alga *Spirulina platensis* (cyanobacterium) has been studied as a possible source of selenium containing pharmaceuticals and most recently as a commercially available dietary

supplement (Cases et al. 2001; deMorais et al. 2015; Li et al. 2015; Rezanka and Sigler 2008). Selenium containing natural products are well documented in the literature from selenium-accumulating plants, which can be divided into the following three subgroups: selenite-accumulators (broccoli and cucumber), selenomethionine accumulators (grains, such as wheat, and mushrooms), and Se-methyl selenomethionine accumulators (e.g. garlic and onion) (Whanger 2002). In these plants, selenium is often present in methylated forms such as selenocystathione, Se-methyl selenocysteine, methyl selenol, *C*-glutamyl selenocystathione. *C*-glutamyl-Se-methyl selenocysteine is the major selenium compound in natural and selenized garlic and has been reported to be an effective carcinogenic agent against mammary gland cancer in rats (Whanger 2002).

Silicon

Biogenic silica is found in relatively low abundance in the tissues of living organisms and is essential for the growth and biological function in a variety of plant and microbial systems; however, the metabolic pathways of these interactions are still unknown (Henstock et al. 2015; Rezanka and Sigler 2008). The process of converting soluble silicon into the mineral phase of silica is termed, biosilification and an incredible variety of structures with unique shapes are generated from silica by aquatic creatures such as sponges, diatoms, and radiolarians (Greene 2008). Various researchers have also studied the ability of homologous enzymes to catalyse the formation and cleavage of siloxane bonds, which ultimately allow us to understand the role of various proteins in the biosilification process (Greene 2008). Furthermore, through genetic engineering and biotechnological methods, new, environmentally benign routes have been developed towards the synthesis of organyl-substituted siloxanes that can be used in manufacturing (drug delivery, cosmetics, diagnostics and biosensors, and coating materials) (Greene 2008; Rezanka and Sigler 2008).

Microbes and microbial enzymes have also been used in the biotransformation/bioremediation of organosilicon compounds. Silicate bacteria, (genus *Bacillus*), release silicon from aluminosilicates through the secretion of organic acids (Groudev et al. 1996). For example, Sabourin and co-workers described the biodegradation of dimethylsilanediol in soil under aerobic conditions within a controlled environment (Sabourin et al. 1996). More recently, Lehmann and co-workers described the degradation pathway of polydimethylsiloxane (the monomer of dimethylsilanediol) in soils in a plot trial over a 12-month period (Lehmann et al. 2000). They found that degradation decreased over winter months and extensive degradation was observed during the warmer months—peaking during summer. This demonstrated that polydimethylsiloxanes will degrade under aerobic field conditions. Grümping and co-workers demonstrated the anaerobic degradation of polydimethylsiloxanes in composted sewage sludge was also possible (Grümping et al. 1999).

Many have demonstrated the ability of microorganisms to metabolise metalloids for the bioremediation of wastes and the production of commercial products (Kumar et al. 2015). For example, van Hullebusch et al. observed the bio-alteration of metallurgical waste in the presence of *P aeruginosa,* which accrue in bulk as dissolved Fe, Si, Ca and Mg (van Hullebusch et al. 2015). It is hypothesised that this release is most likely due to the discharge of soluble complexing organic molecules, such as siderophores (van Hullebusch et al. 2015). Similarly, Tang developed an organic fertiliser that utilized *Bacillus subtilis* bacteria and a selenium enriched waste source (Tang 2013) and in a study by Hashimoto and co-workers, a nano-micrometer-architectural acidic silica was prepared from a natural amorphous iron oxide with structural silicon, (a product of an iron-oxidising bacterium *Leptothrix ochracea*) for the use in ceramics (Hashimoto et al. 2013).

In some instances, microorganisms are being genetically engineered to address the challenge of the biomass feedstock supply for sustainable industrial applications and to modify the metabolic pathway for the more efficient production of high-value products (Qin et al. 2012). For example, silicon is an effective agent in controlling various plant pests and diseases caused by fungi and bacteria and has been known to alleviate various abiotic stresses, such as salt stress, metal toxicity, drought stress, radiation damage, nutrient imbalance, high temperature and freezing (Rezanka and Sigler 2008).

A study by Sommer and co-workers, for example, found microbiological and rhizosphere processes to be the primary contributor to silicon mobilization, plant uptake, and formation of phytogenic Si in plants, and

release due to microbial decomposition (Sommer et al. 2006).

The beneficial effects of Si are usually expressed more clearly in Si-accumulating plants, and are mainly attributed to the protection of the plant from multiple abiotic and biotic stresses. For example, silicon deposition in the exodermis and endodermis of the root of rice plants reduces the transport of sodium through the apoplastic pathway, which is strongly associated with salt tolerance (Gao et al. 2007). Adeyemi and Gadd (2005) studied the ability of selected filamentous fungi to mediate biogenic weathering. They found that *Aspergillus niger, Serpula himantioides and Trametes versicolour* produced organic acids resulted in corrosion of mineral surfaces, modification of the mineral substrate through transformation into secondary minerals (i.e. crystal formation) and hyphal penetration of the mineral substrate (Adeyemi and Gadd 2005). Bacteria such as *Leptospirillum ferrooxidans* and *Acidithiobacillus thiooxidans* that are highly motile have been shown to possess a chemosensory system that allows them to have the capacity to detect gradients of oxidizable substrates such as those extracted from ores (Jerez and Moo-Young 2011). Such bacteria could be used to remediate contaminated sites and or extract and concentrate minerals from soils.

Tellurium

Tellurium is a relatively rare element that has no significant biological role, and within biological systems, both tellurium and tellurium compounds have been found to be toxic (Rezanka and Sigler 2008); organotellurium compounds are known to damage cells by oxidising sulfhydryl groups and depleting endogenous reduced glutathione (Taylor 1996). However, many organisms that have the ability to grow in the presence of these toxic metalloid salts have been known to reduce them to elemental, insoluble forms or methylate these metalloids in order to produce volatile derivatives which can then be released (Chasteen and Bentley 2002). Additionally, some microorganisms have exploited this tolerance and exhibit the ability to bioremediate tellurium contaminated wastes. For example, the fungus, *Acremonium falciforme*, has been found to reduce tellurite via volatilisation and produce both dimethyl telluride and dimethyl ditelluride (Chasteen and Bentley 2002). Similar results have been seen for the fungi *Scopulariopsis brevicaulis*, *Candida humicola*, *S. brevicaulis* and *Penicillium* sp. (Boriova et al. 2014; Chasteen and Bentley 2002). Ollivier and co-workers also described a marine tellurite-resistant strain of yeast, *Rhodotorula mucilaginosa*, that both precipitates intracellular Te(0) and volatilises methylated Te compounds when grown in the presence of oxyanion tellurite (Ollivier et al. 2008). It was found that the use of such microbes provided a *"green"* pathway for the production of Te(0)-containing nanostructures and for the remediation of Te-oxyanion wastes. Furthermore, continuous aeration using low oxygen concentrations strongly promoted Te volatilisation while inhibiting Te(0) precipitation. Lastly, it was concluded that volatile Te species may be further degraded rapidly by *R. mucilaginosa* and converted to the particulate form (Ollivier et al. 2011).

Metal hyperaccumulating plants and their use in chemical synthesis and bioremediation

Plants which have the ability to uptake and store extreme concentrations of metal ions in their tissues are known as hyperaccumulators and approximately 500 such species, accumulating a broad range of metals and metalloids, have been identified worldwide (Krämer 2010). Proposed uses of these plants are phytoremediation (using plants to clean up the environment), biofortification (improvement of mineral nutrition in crops) and biomining (using plants to extract and concentrate minerals from soils). Recently, several novel applications for these unique plants have been applied in the chemical sciences, in particular, as plant-based sources for green catalysts and for the synthesis of nanoparticles.

Research into the synthesis of nanoparticles is a rapidly growing area with applications in many areas, such as biomedicine, (Salata 2004) drug delivery, (Han et al. 2007) applications as electronic semiconductors and highly active catalysts (Ikeda et al. 2006). Methods for green synthesis of nanoparticles are being sought which require sources of renewable feedstocks. So far, successful biosynthesis of nanoparticles has been carried out using algae, fungi, lichen and bacteria (Thakkar et al. 2010).

Hyperaccumulating plants offer a new and potentially renewable source of a metal-rich organic

substrate which has been shown to be useful in nanoparticle synthesis. Using wood from the nickel hyperaccumulating tree, *Pycnadra acuminate*, for example, Lerch and co-authors successfully synthesised carbon supported nickel nanoparticles using pyrolysis (Lerch et al. 2010). It is questionable if this is truly a renewable source as *S. acuminata* is a rare tree, endemic to New Caledonia. Other studies however, have successfully shown the formation of nanoparticles from metal accumulating plant tissues in common glass house grown plants (Marchiol et al. 2014).

Nanoparticles are particularly useful in organic chemistry as catalysts. The use of metal rich plant extracts in chemical synthesis has been termed *"eco-catalysis"* and examples of this have been demonstrated with different metals from both field collected and glasshouse grown biomass. For example, two species of nickel hyperaccumulating shrubs, *Psychotria douarrei* and *Geissois pruinosa*, both endemic to New Caledonia, can accumulate up to 4.7 and 0.8 % Ni dry mass respectively, some of the highest nickel concentrations even found in plants (Jaffre et al. 1979; Kelly et al. 1975). These plants have been used for phytoremediation and re-vegetation of disturbed land and produce considerable amounts of nickel rich biomass. Grison and co-authors proposed a novel use for the biomass produced from these restoration projects, successfully demonstrating that extracts from the nickel rich tissue could be used for plant-based catalytic chemistry in the Biginelli reaction (Grison et al. 2013).

The use of the model Zn hyperaccumulating plant *Noccaea caerulescens* has also been used as a catalytic substrate for a number of reactions such as the manufacture of Lucas reagent (Sabourin et al. 1996). With similar work being carried out using Mn hyperacuumulators (Escande et al. 2015). New applications for the metal rich biomass produced from phytoremediation further enhances the economic viability of this method of soil decontamination and restoration and it is anticipated that this will spur future interest in phytoremediation.

Inorganic therapeutic agents

Metals and metalloids as therapeutic agents

Both human and veterinary medicine have long made use of both metals and metalloids as therapeutic agents, usually without a defined molecular basis for their mechanism of action, and, until recently, with little or no attempt to discover or refine it. Copper was used as sterilisation agent for drinking water and wounds by the ancient Egyptians for example (Dollwet and Sorenson 1985) and cinnabar (mercury(II) sulphide, HgS), containing natural medicines can be traced back over 2000 years to India and China (Beers and Mousavi 2013). Mercury was also historically used, both as an ointment and internally, to treat syphilis in Europe (Tampa et al. 2014).

The organoarsenic compound arsphenamine, (Salvarsan) was introduced circa 1910 for the treatment treat of both syphilis and trypanosomiasis (Williams 2009). This followed work showing that Atoxyl, the monosodium salt of para-arsanilic acid, had some activity against sleeping sickness was too toxic for routine medical use (Williams 2009). Arsanilic acid itself, along with roxarsone, carbarsone and nitarsone, was also long used as a veterinary feed additive promoting growth and to prevent or treat disease in chickens, sheep, cows and pigs (Calvert and Smith 1980; Hanson et al. 1956). Aside from nitarsone however, these were voluntary withdrawn from the market by the manufacturers in 2013 following safety concerns over the potential transfer of arsenic from the drugs into the human food chain (FDA 2011).

As the above examples are well known of course but illustrate that the use of inorganic compounds in medicine depends heavily on overcoming the problem of their inherent toxicity, this has been the focus of much research in recent years and this is where natural products provide inspiration. The biological activity of many proteins and enzymes can be ascribed to their metal centres, with the organic backbone acting as a scaffold to grasp the metal ion in place. Since biological systems make use of metals and metalloid naturally the question then arises can metal ions be incorporated into drugs for therapeutic use, and could natural products provide useful influence into the design of potential drugs? Answering this question is a topic of great interest in inorganic medicinal chemistry.

Inorganic medicinal chemistry

Metals, and in particular transition metals, offer a range of advantages for the design of medicinal compounds and there are many detailed reviews on this subject to which the interested reader is directed

(Bertrand and Casini 2014; Casini and Reedijk 2012; Mjos and Orvig 2014; Orvig and Abrams 1999). They are structural diverse and have a wide range of coordination numbers, geometries and accessible redox states. This allows for a high degree of 'tuneability' of the thermodynamics and kinetics of associated ligand substitutions which in turn allows for the modification of the physico-chemical properties of the underlying complex (van Rijt and Sadler 2009). This large diversity of options has led to a similarly large number of inorganic compounds being created for use in human health and medicine.

Two areas of work have highlighted the potential of inorganic medicinal chemistry in recent years: the gadolinium compounds, used as contrast agents in magnetic resonance imaging (MRI), and the platinum anticancer drugs. There are now four complexes of Gd^{3+} on the imaging market for example, and they and other commonly used compounds including the gamma-emitting radiopharmaceuticals such as 99mTc (a coordination complex consisting of the radioisotope technetium-99m bound to six methoxyisobutylisonitrile ligands) and X-ray contrast agents such as barium sulphate ($BaSO_4$) are all in heavy clinical use.

The anti-cancer ability of platinum complexes was first demonstrated using cisplatin [*cis*-$PtCl_2(NH_3)_2$], which interestingly contains no carbon atoms in its structure, in 1969 (Rosenberg et al. 1969). Once inside the cell cisplatin undergoes hydrolysis, producing a highly reactive charged platinum complex $[Pt(NH_3)_2ClH_2O]^+$ (Siddik 2003). This complex binds (intercalates) to DNA through either adenine or guanine. Further hydrolysis displaces the remaining chloride ligand, allowing platinum to bind to a second nucleotide base (Siddik 2003). The cisplatin–DNA adduct is recognised by (amongst other DNA repair proteins) a high mobility group (HMG)-domain protein which binds strongly to the complex; the resulting adduct causes destacking of the nucleotide bases, resulting in the DNA helix becoming kinked and ultimately triggering apoptosis (Siddik 2003). Since 1969, second and third generation water soluble, platinum containing drugs have been created with lower therapeutic doses and fewer side effects and remain in common use; these include including carboplatin, oxaliplatin, ormaplatin and zeniplatin. These compounds are all very effective and platinum based chemotherapy, including use of cisplatin itself, is still a large part of modern cancer therapy.

Some tumours can become resistant to platinum based drugs and the compounds themselves can exhibit serious side effects such as nephron- and myelo-toxicity. This has led to the development of platinum-acridine antitumor agents (Dutta et al. 2013; Graham et al. 2011) as well as analogue complexes containing metals such as gold, osmium and ruthenium (Bruijnincx and Sadler 2009). For example, titanocene dichloride was both the first non-platinum coordination complex and the first metallocene to undergo a clinic trail (Bruijnincx and Sadler 2009). Work by Ang et al. (2011) also demonstrated a class of ruthenium based complexes which interacted strongly with proteins but weakly with DNA. Interestingly, these compounds had high antitumor activity in vivo but were only weakly effective in vitro.

Gold has a long history of use in medicine and Gold(I)-based coordination compounds have been a major focus area in inorganic drug design since the anti-bacterial activity of potassium dicyanoaurate was discovered by (Koch 1890). For the interested reader, a detailed review of the use of gold in medicine is given by Shaw (1999). Additional, recent work has also shown that gold complexes are also effective at inhibiting tumour growth, most likely via interference with mitochondrial thioredoxin reductase, demonstrating the potential application of gold in cancer therapy (Baker et al. 2006; Martins et al. 2001; Ott et al. 2009). Gold complexes are also commonly used in the treatment of rheumatoid arthritis and other autoimmune diseases (Tiekink 2003).

Eiter et al. (2009) showed that gold based analogues of a platinum-acridine antitumor agents are only weakly cytotoxic (likely due to the fact that gold does not form permanent DNA adducts) but do show high antibacterial activity, as do several other gold complexes such as sodium *bis*(thiosulfato-*S*)aurate(I) (sanocrysin) (Corbi et al. 2010; Eiter et al. 2009; Shukla et al. 2005). Gold nanoparticles have also been shown to be none toxic in vivo (Shukla et al. 2005) but have been used in both the diagnosis and treatment (via drug delivery) of tumors (Brown et al. 2010; Yezhelyev et al. 2006).

Semi-metals have also been shown to be of use in medical science. A recent example is the discovery of boron containing polyether-macrolide antibiotic compounds such as boromycin and borophycin. Chemical

synthesis has aimed to incorporate boron into different biologically active molecules, particularly for medicinal applications, for example, boron neutron capture therapy of brain tumors (Rezanka and Sigler 2008). Recently, Anacor Pharmaceuticals has discovered several boron-based compounds for the treatment of various skin disorders. Boromycin inhibited the growth of Gram-positive bacteria, but showed no inhibition on some Gram-negative bacteria and fungi (Hutter et al. 1967) and also strongly inhibited the replication of HIV-1 (Hemscheidt et al. 1994; Kohno et al. 1996). A structurally related analogue of boromycin, borophycin (cytotoxin) has been isolated from the lipophilic extract of a marine strain of the blue-green alga (*Cyanobacterium*), *Nostoc linckia* (Roth). The discovery of natural analogues, to boromycin and related compounds, or the synthesis of artificial ones, perhaps containing different semi metals could potentially be of great benefit to addressing the problem of antibiotic resistance in both human and veterinary medicine (Banker and Carmeli 1998; Hemscheidt et al. 1994).

Natural products and metal chelation in human health

Chelating agents are capable of binding to toxic metal ions to form complex structures, which are easily excreted from the body. Some chelation agents, e.g. dimercaprol, used to treat arsenic poisoning, may themselves be toxic and or have limited efficacy (Muckter et al. 1997). Metal chelation in natural products has been investigated previously. Lutz and co-workers for example, examined the potential of the NP, isomaltol as an M^{3+} binding group. Using isomaltol complexes of aluminum, gallium, and indium they showed that the isomaltol moiety is a useful chelating group for several trivalent non-transition-metal ions (Lutz et al. 1989). Similar work carried out by Picciano and co-authors showed curcumin to be effective in preventing or reversing development of amyloid fibrils formed from $A\beta$ peptides ($A\beta$). Curcumin was found to simultaneously bind to Cu^{2+} and $A\beta$, functioning, as both as a chelator and an $A\beta$ binding partner, and thus may be able to participate in the treatment of Alzheimer's disease.

Natural products have also aided in the design templates for several multi-target drug discovery design studies. Geldenhuys and colleagues recently showed that stilbenes (a type of natural phenol) and stilbene scaffolds are an important target, particularly for recreating the neuroprotective effects of the non-flavonoid natural product, resveratrol (McMaster 2013). In their work the stilbene scaffold-based compounds were developed through chelation with metal ions that interact with and reduced levels of β-amyloid protein aggregation and reactive oxygen species (ROS) (Geldenhuys and Van Der Schyf 2013).

Kloss et al. (2013) described the potential of the Clostridium derived natural product, closthioamide [a selective copper (I) ligand] to act as a selective copper chelator. This is the first report of a metal complex of a NP from the anaerobic microbial world. Closthioamide may lead to bio-inspired Cu-selective chelators with therapeutic potential, since copper mis-trafficking has been implicated in various health problems such as Menkes and Wilson's disease. Similar work by Dimise et al. described a class of natural products called the fuscachelins, produced by the moderately thermophilic actinomycete, *Thermobifida fusca.* These compounds present some of the only known secondary metabolites isolated from thermophilic bacteria (Dimise et al. 2012). Fuscachelin A in particular has a good ability to chelate iron and thus has potential application as an iron-sequester.

A study by Bouriche and colleagues examined the medicinal uses of *Malva parviflora* L (Egyptian mallow) a small perennial herb widely distributed throughout Africa. Leaves of this plant are used in the treatment of some inflammatory disorders and the authors demonstrated the ability of *M. parviflora* leaf extracts to scavenge free radicals and chelate ions which the authors speculated was the mechanism underlying the anti-inflammatory activity (Bouriche et al. 2011). A similar study by Wang et al. (2010) described the NP (-)-*N*-formylanonaine isolated from the leaves of *Michelia alba* D.C. (an evergreen, tropical tree), which was found to inhibit mushroom tyrosinase with an IC_{50} of 74.3 μM and to have tyrosinase and melanin reducing activities in human epidermal melanocytes without apparent cytotoxicity to human cells.

With continuing interest the involvement of metals in human disease, e.g. aluminium in neurological disorders, as well as the use of gallium and indium in diagnostic nuclear medicine procedures interest in NP based chelating agents is both timely and relevant.

The work described above shows the potential of the field but at present there is only a small range of

inorganic therapeutic agents that take advantage of diverse reactivity and properties of metals. It should perhaps be born in mind that metal-based therapeutics bring their own challenges. The reactivity of metals and metalloids, which offers so many options for new mechanisms of action, is a double edged sword—and one which may be blunted by unintended reactions with none target molecules. Therapeutic metal complexes should also not be too stable, as this may reduce their therapeutic effect.

Other characteristics of metal-containing compounds that can have a major influence on their cytotoxic properties include geometrical isomerism as well as redox potential although such properties can potentially be altered via ligand modification and may be harnessed via the design of (photo) activation at target sites (the so called cancer bomb approach). Structure is also an important component of cytotoxic activity. For example whereas *cis*platin is highly cytotoxic, its *trans*-isomer, *trans*platin, has low toxicity and is clinically ineffective (Blisard et al. 1991).

Conclusion

As observed by Sadler, almost a quarter of a century ago, the majority of the elements in the periodic table, up to and including bismuth have potential uses in the design of both new therapeutic agents (Sadler 1991), and today they also increasingly have use in novel biotechnology applications. Active metal complexes, metal ions and ligands can also be used for such purposes (Sadler 1991). For example, Cefixime is a broad spectrum semi synthetic cephalosporin antibiotic. When complexes of cefixime with Cu(II), Zn(II), Cd(II), Fe(III) and Ni(II) were synthesised they showed a slightly higher antimicrobial activity than the drug itself with the Fe(III) complex being the most potent against various bacterial species (Pillai and Latha 2012). In future, the improved design of metallo-compounds will depend on gaining a detailed knowledge of their coordination chemistry under specific, biologically relevant conditions. Knowledge will also be needed of reaction kinetics, mechanisms, pathways and ligand-exchange dynamics of such compounds. Despite these challenges it is likely that there is a great deal of potential in new applications of natural products containing metals, metalloids and metal complexes and much useful work remains to be undertaken in this area.

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