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Evaluation of Medicinal Properties Exhibited by Various Metal Compounds: A Review

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ABSTRACT: A metallopharmaceutical is a drug that contains a metal as an active ingredient.[1][2] Most commonly metallopharmaceuticals are used as anticancer or antimicrobial agents. The efficiency of metallopharmaceuticals is crucially dependent on the respective trace metal binding forms.[3]

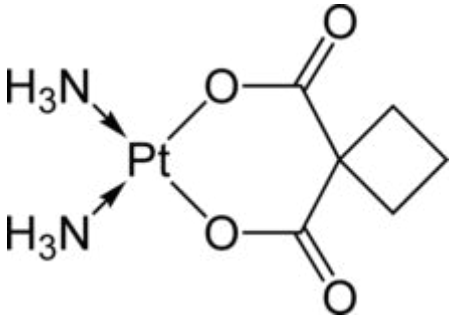
Examples of metallopharmaceuticals include:

- bismuth subsalicylate – a mild anti-diarrheal also used in treating peptic ulcers caused by antibiotic-resistant *H. pylori*
- cisplatin and carboplatin – platinum containing anticancer agents[6][7]
- gold salts such as auranofin – anti-inflammatory for treatment of arthritis[8][9]
- silver sulfadiazine – antibacterial
- zinc pyrithione – antibacterial and antifungal

KEYWORDS : metallopharmeceutical, metal, active ingredient, trace, binding, anticancer, antimicrobial, mild

I.INTRODUCTION

Coordination chemistry offers much scope for the design of novel and therapeutic agents, including metallopharmaceuticals.



Carboplatin, an example of a metallopharmaceutical

The widespread use of metal complexes as effective pharmaceuticals, e.g. cancer therapeutic, anti-inflammatory[1], antidiabetic drugs or antimicrobial and diagnostic agents, demonstrates that the cytotoxicity of metal ions can be finely controlled via the appropriate choice of ligands. The successful targeting of radioisotopes again depends on the ligand design and metal oxidation state. The complexes of platinum, ruthenium, cobalt, copper and other d-block metal ions have been used in medicine for a long time but only recent advances have been made in understanding the molecular basis of mechanism of their action[2]. Due to the above mentioned purpose, we decided to prepare a detailed description of target-based research, directed towards a design[3] and application possibilities, with the known mechanisms of action of metal ion complexes in the broad sense of therapy definition. The detail also covers the progress, limitations and challenges of the above-mentioned approaches and emphasizes the advantages of well known and new metallopharmaceuticals in medicine and pharmacy[4].

Bismuth subsalicylate, sold generically as pink bismuth and under the brand names Pepto-Bismol and BisBacter, is an antacid medication used to treat temporary discomforts of the stomach and gastrointestinal tract, such as nausea, heartburn, indigestion, upset stomach, and diarrhea.[5]

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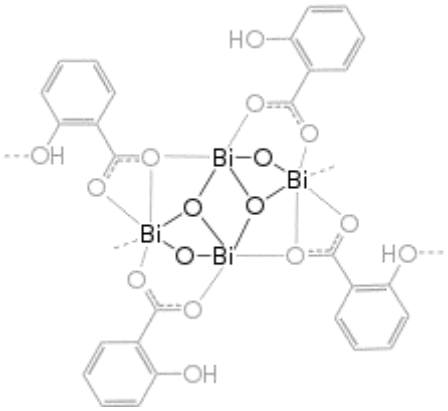


Bismuth subsalicylate has the empirical chemical formula $C_7H_5BiO_4$,[1] and is a colloidal substance obtained by hydrolysis of bismuth salicylate ($Bi(C_6H_4(OH)CO_2)_3$).[5]

As a derivative of salicylic acid, bismuth subsalicylate displays anti-inflammatory[2] and bactericidal action.[3] It also acts as an antacid. There are some adverse effects. It can cause a black tongue and black stools in some users of the drug when it combines with trace amounts of sulfur in saliva and the colon to form bismuth sulfide.[4] Bismuth sulfide is a highly insoluble black salt, and the discoloration seen is temporary and harmless.

Long-term use (greater than six weeks) may lead to accumulation and toxicity.[5] Some of the risks of salicylism can apply to the use of bismuth subsalicylate.[6][7][8]

Children should not take medication with bismuth subsalicylate while recovering from influenza or chicken pox, as epidemiologic evidence points to an association between the use of salicylate-containing medications during certain viral infections and the onset of Reye syndrome.[9] For the same reason, it is typically recommended that nursing mothers not use medication containing bismuth subsalicylate because small amounts of the medication are excreted in human breast milk, and these pose a theoretical risk of Reye's syndrome to nursing children.[10]

Salicylates are very toxic to cats, and thus bismuth subsalicylate should not be administered to cats.[11]

The British National Formulary does not recommend bismuth-containing antacids (unless chelated), cautioning that absorbed bismuth can be neurotoxic, causing encephalopathy, and that such antacids tend to be constipating.[12]

There is an increased risk of bleeding when using bismuth subsalicylate and anticoagulation therapy, like Coumadin (Warfarin) [13][14][15] Bismuth subsalicylate is used as an antacid and antidiarrheal, and to treat some other gastrointestinal symptoms, such as nausea. The means by which this occurs is still not well documented. It is thought to be some combination of the following:[16]

- Stimulation of absorption of fluids and electrolytes by the intestinal wall (antisecretory action)
- As a salicylate, reducing inflammation/irritation of stomach and intestinal lining through inhibition of prostaglandin G/H synthase 1/2
- Reduction in hypermotility of the stomach[17]
- Inhibits adhesion and filmogenesis by *Escherichia coli*
- Bactericidal action of a number of its subcomponents, including salicylic acid[17]
- Bactericidal action via a so-called oligodynamic effect in which small amounts of heavy metals such as bismuth damage many different bacteria species.[18]
- Weak antacid properties

In vitro and *in vivo* data have shown that bismuth subsalicylate hydrolyzes in the gut to bismuth oxychloride and salicylic acid and less commonly bismuth hydroxide. In the stomach, this is likely an acid-catalyzed hydrolysis.[19] The salicylic acid is absorbed and therapeutical concentrations of salicylic acid can be found in blood after bismuth subsalicylate administration. Bismuth oxychloride and bismuth hydroxide are both believed to have bactericidal effects, as is salicylic acid for enterotoxigenic *E. coli* a common cause of "traveler's diarrhea."[17]

Organobismuth compounds have historically been used in growth media for selective isolation of microorganisms.[20] Such salts have been shown to inhibit proliferation of *Helicobacter pylori*, other enteric bacteria, and some fungi.[18]

Despite its common usage and commercial significance, the exact structure of the pharmaceutical long remained undetermined, but was revealed, through the use of advanced electron crystallography techniques, to be a layered

coordination polymer with the formula $BiO(C_7H_5O_3)$.[19] In the structure, both the carboxylate and phenol groups of the salicylate coordinate towards the bismuth cations. [21]The determination of bismuth subsalicylate had long been hindered due to the small particle size as well as defects within the structure, arising from variations in the stacking arrangement of the bismuth subsalicylate layers, which could be observed as part of the structural investigation.[20] While bismuth salts were in use in Europe by the late 1700s, the combination of bismuth subsalicylate and zinc salts for astringency with salol (phenyl salicylate) appears to have begun in the US in the early 1900s as a remedy for life-threatening diarrhea in infants with cholera. At first sold directly to physicians, it was first marketed as *Bismosal* in 1918.[21]

Pepto-Bismol began being sold in 1900[21] or 1901[22] by a doctor in New York. It was originally sold as a remedy for infant diarrhea by Norwich Pharmacal Company under the name "Bismosal: Mixture Cholera Infantum".[21] It was renamed Pepto-Bismol in 1919. Norwich Eaton Pharmaceuticals was acquired by Procter and Gamble in 1982.[23]

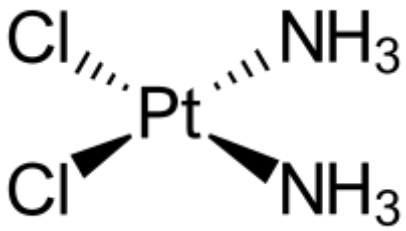
As of 1946 and 1959, Canadian advertisements placed by Norwich show the product as Pepto-Besmal both in graphic and text.[24][25]

Pepto-Bismol is an over-the-counter drug currently produced by the Procter & Gamble company in the United States, Canada and the United Kingdom. Pepto-Bismol is made in chewable tablets[26] and swallowable caplets,[27] but it is best known for its original formula, which is a thick liquid. This original formula is a medium pink in color, with a teaberry (methyl salicylate) flavor.[28]

Generic bismuth subsalicylate, and other branded versions of the drug, are widely available in pill and liquid form.[29]

II.DISCUSSION

Cisplatin is a chemotherapy medication used to treat a number of cancers.[2] These include testicular cancer, ovarian cancer, cervical cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain tumors and neuroblastoma.[2] It is given by injection into a vein.[2]



Common side effects include bone marrow suppression, hearing problems, including total irreversible hearing loss, usually restricted to one ear, kidney damage, and vomiting.[2][3][4] Other serious side effects include numbness, trouble walking, allergic reactions, electrolyte problems, and heart disease.[2] Use during pregnancy can cause harm to the developing fetus.[1][2] Cisplatin is in the platinum-based antineoplastic family of medications.[2] It works in part by binding to DNA and inhibiting its replication.[2]

Cisplatin was discovered in 1845 and licensed for medical use in 1978 and 1979.[5][2] It is on the World Health Organization's List of Essential Medicines.[6][7]

Cisplatin is administered intravenously as short-term infusion in normal saline for treatment of solid and haematological malignancies. It is used to treat various types of cancers, including sarcomas, some carcinomas (e.g., small cell lung cancer, squamous cell carcinoma of the head and neck and ovarian cancer), lymphomas, bladder cancer, cervical cancer,[8] and germ cell tumors.[30]

Because of its widespread use, the cure rate for testicular cancer has increased from 10% to 85%.[9]

Cisplatin has a number of side effects that can limit its use:

- Nephrotoxicity (kidney damage) is the primary dose-limiting side effect and is of major clinical concern. Cisplatin selectively accumulates into the proximal tubule via basolateral-to-apical transport, where it disrupts mitochondrial energetics and endoplasmic reticulum Ca^{2+} homeostasis and stimulates reactive oxygen species and pro-inflammatory cytokines.[10] Multiple mitigation strategies are being explored clinically and pre-clinically, including hydration regimens, amifostine, transporter inhibitors, antioxidants, anti-inflammatories, and epoxyeicosatrienoic acids and their analogues.[10][11]
- Neurotoxicity (nerve damage) can be anticipated by performing nerve conduction studies before and after treatment. Common neurological side effects of cisplatin include visual perception and hearing disorder, which

can occur soon after treatment begins.[12] While triggering apoptosis through interfering with DNA replication remains the primary mechanism of cisplatin, this has not been found to contribute to neurological side effects. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE-1.[12] It is primarily found on cells of the peripheral nervous system, which are aggregated in large numbers near the ocular and aural stimuli-receiving centers.[25] This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo. However, NHE-1 inhibition has been found to be both dose-dependent[17] (half-inhibition = 30 µg/mL) and reversible.[12] Cisplatin can increase levels of sphingosine-1-phosphate in the central nervous system, contributing to the development of post-chemotherapy cognitive impairment.[13][14]

- Nausea and vomiting: cisplatin is one of the most emetogenic chemotherapy agents, but this symptom is managed with prophylactic antiemetics (ondansetron, granisetron, etc.) in combination with corticosteroids. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone.[22]
- Ototoxicity and hearing loss associated with cisplatin can be severe and is considered to be a dose-limiting side effect.[4] Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs (such as the aminoglycoside antibiotic class) may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear[25] or the generation of reactive oxygen species. In September 2015, the U.S. Food and Drug Administration (FDA) approved sodium thiosulfate under the brand name Pedmark to lessen the risk of ototoxicity and hearing loss in people receiving cisplatin.[15][16][17] There is ongoing investigation of acetylcysteine injections as a preventative measure.[4][18]
- Electrolyte disturbance: Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin.[13]
- Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis.[19]

Cisplatin interferes with DNA replication, which kills the fastest proliferating cells, which in theory are cancerous. Following administration, one chloride ion is slowly displaced by water to give the aquo complex *cis*-$[PtCl(NH_3)_2(H_2O)]^+$, in a process termed aquation. Dissociation of the chloride is favored inside the cell because the intracellular chloride concentration is only 3–20% of the approximately 100 mM chloride concentration in the extracellular fluid.[20][21]

The water molecule in *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ is itself easily displaced by the *N*-heterocyclic bases on DNA. Guanine preferentially binds. A model compound has been prepared and crystals were examined by X-ray crystallography[22]

Subsequent to formation of $[PtCl(guanine\text{-}DNA)(NH_3)_2]^+$, crosslinking can occur via displacement of the other chloride, typically by another guanine.[23] Cisplatin crosslinks DNA in several different ways, interfering with cell division by mitosis. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible. In 2008, researchers were able to show that the apoptosis induced by cisplatin on human colon cancer cells depends on the mitochondrial serine-protease Omi/Htra2.[24] Since this was only demonstrated for colon carcinoma cells, it remains an open question whether the Omi/Htra2 protein participates in the cisplatin-induced apoptosis in carcinomas from other tissues.[24]

Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. These include 1,2-intrastrand d(GpG) adducts, which form nearly 90% of the adducts, and the less common 1,2-intrastrand d(ApG) adducts. Coordination chemists have obtained crystals of the products of reacting cisplain with small models of DNA. Here is a POVray plot of the platinum binding to a small model of DNA.[25]

1,3-intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER). Other adducts include inter-strand crosslinks and nonfunctional adducts that have been postulated to contribute to cisplatin's activity. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action.[26]

Carboplatin, sold under the trade name Paraplatin among others, is a chemotherapy medication used to treat a number of forms of cancer.[1] This includes ovarian cancer, lung cancer, head and neck cancer, brain cancer, and neuroblastoma.[1] It is used by injection into a vein.[1]

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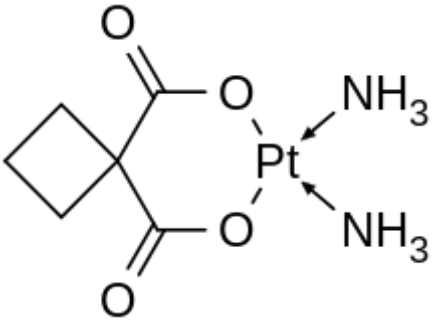


Side effects generally occur.[1] Common side effects include low blood cell levels, nausea, and electrolyte problems.[2][1] Other serious side effects include allergic reactions and increased future risk of another cancer.[1][Use during pregnancy may result in harm to the baby.[1] Carboplatin is in the platinum-based antineoplastic family of medications and works by interfering with duplication of DNA.[1][3]

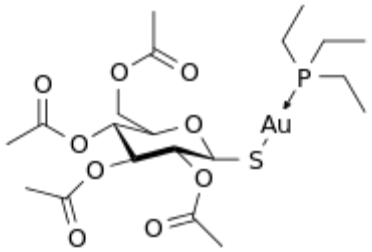
Carboplatin was patented in 1972 and approved for medical use in 1989.[4] It is on the World Health Organization's List of Essential Medicines.[5] Carboplatin is used to treat a number of forms of cancer. This includes ovarian cancer, lung cancer, head and neck cancer, brain cancer, and neuroblastoma. It may be used for some types of testicular cancer but cisplatin is generally more effective.[1] It has also been used to treat triple-negative breast cancer. Relative to cisplatin, the greatest benefit of carboplatin is its reduced side effects, particularly the elimination of nephrotoxic effects. Nausea and vomiting are less severe and more easily controlled.[20]

The main drawback of carboplatin is its myelosuppressive effect. This causes the blood cell and platelet output of bone marrow in the body to decrease quite dramatically, sometimes as low as 10% of its usual production levels.[21] The nadir of this myelosuppression usually occurs 21–28 days after the first treatment, after which the blood cell and platelet levels in the blood begin to stabilize, often coming close to its pre-carboplatin levels. This decrease in white blood cells (neutropenia) can cause complications, and is sometimes treated with drugs like filgrastim. The most notable complication of neutropenia is increased probability of infection by opportunistic organisms, which necessitates hospital readmission and treatment with antibiotics.

In terms of its structure, carboplatin differs from cisplatin in that it has a bidentate dicarboxylate (the ligand is CycloButane DiCarboxylic Acid, CBDCA) in place of the two chloride ligands, which are the leaving groups in cisplatin. For this reason, "CBDCA" is sometimes used in the medical literature as an abbreviation referring to carboplatin. Carboplatin exhibits lower reactivity and slower DNA binding kinetics[22], although it forms the same reaction products *in vitro* at equivalent doses with cisplatin. Unlike cisplatin, carboplatin may be susceptible to alternative mechanisms. Some results show that cisplatin and carboplatin cause different morphological changes in MCF-7 cell lines while exerting their cytotoxic behaviour.[6] The diminished reactivity limits protein-carboplatin complexes, which are excreted. The lower excretion rate of carboplatin means that more is retained in the body, and hence its effects are longer lasting (a retention half-life of 30 hours for carboplatin, compared to 1.5-3.6 hours in the case of cisplatin).[25]

III.RESULTS

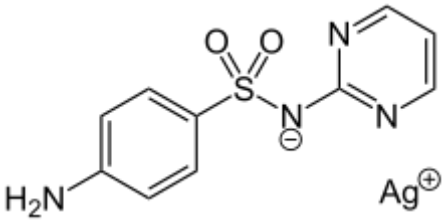
Auranofin is a gold salt classified by the World Health Organization as an antirheumatic agent. It has the brand name Ridaura. Auranofin is used to treat rheumatoid arthritis. It improves arthritis symptoms including painful or tender and swollen joints and morning stiffness.[3] Auranofin is a safer treatment compared to the more common injectable gold thiolates (gold sodium thiomalate and gold thioglucose), but meta-analysis of 66 clinical trials concluded that it is somewhat less effective.[4]



The drug was approved for the treatment of rheumatoid arthritis in 1985. No longer a first-line treatment for rheumatoid arthritis, due to its adverse effects, "most of which are associated with long-term use for chronic disease. The most common adverse effects are gastrointestinal complaints such as loose stools, abdominal cramping and watery diarrhea, which can develop in the early months of treatment. The development of loose stools occurs in 40 % of patients, while watery diarrhea is reported in just 2–5 % of patients, and in most cases these symptoms were alleviated by reducing or splitting the dose".[5]

Auranofin is under investigation as a means of reducing the viral reservoir of HIV that lies latent in the body's T-cells despite treatment with antiretroviral therapy.[6] The drug was shown to reduce the amount of latent virus in monkey trials.[7] A human study testing auranofin and other investigational treatments is ongoing in Brazil.[8] Preliminary results show that auranofin contributed to a decrease in the viral reservoir.[9] Auranofin has been identified in a high-throughput drug screen as 10 times more potent than metronidazole against *Entamoeba histolytica*, the protozoan agent of human amebiasis. Assays of thioredoxin reductase and transcriptional profiling suggest that the effect of auranofin on the enzyme enhances the sensitivity of the trophozoites to reactive oxygen-mediated killing in mouse and hamster models; the results are marked reductions of the number of parasites, the inflammatory reaction to the infestation, and the damage to the liver.[10][11][12] Auranofin may be useful in the prevention and control of *Acanthamoeba* infections, and in the treatment of primary amoebic meningoencephalitis, caused by pathogenic free-living amoebae *Acanthamoeba* spp. and *Naegleria fowleri*, respectively.[13][14] In a cell-based screen, auranofin showed potent activity against replicating and non-replicating *M. tuberculosis* as well as other gram-positive bacteria. Auranofin protected mice from an otherwise lethal infection with methicillin-resistant *S. aureus* (MRSA). The drug acts in a similar manner in bacteria as in parasites by inhibiting thioredoxin reductase (TrxR). Studies in humans are needed to evaluate the potential of this drug to treat Gram-positive bacterial infections in humans.[15] When mice with Protein kinase Cι (PKCι)–dependent KP adenocarcinoma tumors that exhibited resistance to anti–PD-1 antibody therapy (α-PD-1) were treated with auranofin, the PKCι inhibitor auranofin inhibited KP tumor growth and sensitized these tumors to α-PD-1. [18] The Mayo clinic is running a clinical trial to research the effects of auranofin and sirolimus on squamous, ras mutated lung adenocarcinoma, and small cell lung cancer. [19]

Silver sulfadiazine, sold under the brand Silvadene among others, is a topical antibiotic used in partial thickness and full thickness burns to prevent infection.[1] Tentative evidence has found other antibiotics to be more effective, and therefore it is no longer generally recommended for second-degree (partial-thickness) burns, but is still widely used to protect third-degree (full-thickness) burns.[2][3]



Common side effects include itching and pain at the site of use.[4] Other side effects include low white blood cell levels, allergic reactions, bluish grey discoloration of the skin, red blood cell breakdown, or liver inflammation.[4] Caution should be used in those allergic to other sulfonamides.[4] It should not be used in pregnant women who are close to delivery.[4] It is not recommended for use in children less than two months of age.[4]

Silver sulfadiazine was discovered in the 1960s.[5] It is on the World Health Organization's List of Essential Medicines.[6] It is available as a generic medication.[4]

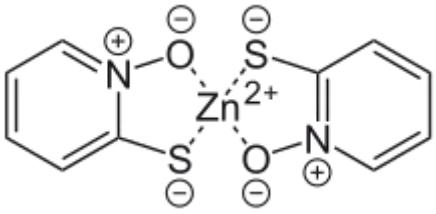
Tentative evidence has found other antibiotics to be more effective in the healing of superficial and partial thickness burn injuries; therefore, it is no longer generally recommended.[2][3] A Cochrane review from 2013 found that most of the trials that met inclusion criteria for the review had methodological shortcomings and thus are of little use in assessing the efficacy of silver sulfadiazine in the healing of burn injuries.[2] Another Cochrane systematic review from 2010 concluded, "There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection".[7] Other reviews of the evidence have also concluded, "[the] quality of the trials was limited".[8] Cochrane has raised concerns about delays in time to wound healing when SSD is used.[2] In addition to concerns regarding delayed wound healing, silver sulfadiazine is associated with sloughing of the wound surface that makes reassessment of wound depth difficult, and requires daily reapplication.[9] For this reason, application of silver sulfadiazine is not recommended for most burns due to altered wound appearance and the frequency of required dressing changes.[9] A noninfection-related clear fluid may form on the wound's surface. Burning and painful sensations are not uncommon, but are only temporary.

Application to large areas or to severe burns may lead to systemic absorption and lead to adverse effects similar to those of other sulfonamides.[10] About 0.1 to 1.0% of people show hypersensitivity reactions such as rashes or erythema multiforme.[11] This reaction is known from other sulfonamides including antibacterials, thiazide diuretics, [24] and sulfonylurea antidiabetics; but data on the likelihood of cross-allergies are inconsistent.

Incorporation of the silver ions can lead to local argyria (discoloration of the skin), especially if the treated area is exposed to ultraviolet light. [30]Generalised argyria with silver accumulation in kidneys, liver, and retina has only been found in association with excessive long-term use, or repeated use on severe and heavily inflamed burns. Possible consequences of generalised argyria include interstitial nephritis and anemia.[11]

IV.CONCLUSIONS

Zinc pyrithione (or pyrithione zinc) is a coordination complex of zinc. It has fungistatic (inhibiting the division of fungal cells) and bacteriostatic (inhibiting bacterial cell division) properties and is used in the treatment of seborrhoeic dermatitis[2] and dandruff.



The pyrithione ligands, which are formally monoanions, are chelated to Zn^{2+} via oxygen and sulfur centers. In the crystalline state, zinc pyrithione exists as a centrosymmetric dimer (see figure), where each zinc is bonded to two sulfur and three oxygen centers.[3] In solution, however, the dimers dissociate via scission of one Zn-O bond. This compound was first described in the 1930s.[4]

Pyrithione is the conjugate base derived from 2-mercaptopyridine-*N*-oxide (CAS# 1121-31-9), a derivative of pyridine-*N*-oxide[29]

Zinc pyrithione can be used to treat dandruff and seborrhoeic dermatitis.[5][6][7] It also has antibacterial properties and is effective against many pathogens from the *Streptococcus* and *Staphylococcus* genera.[8] Its other medical applications include treatments of psoriasis, eczema, ringworm, fungus, athletes foot, dry skin, atopic dermatitis, tinea versicolor,[9][8] and vitiligo. Because of its low solubility in water (8 ppm at neutral pH), zinc pyrithione is suitable for use in outdoor paints and other products that protect against mildew and algae.[27] It is an algaecide. It is chemically incompatible with paints relying on metal carboxylate curing agents. When it is used in latex paints with water containing much iron, a sequestering agent that preferentially binds the iron ions is needed. It is decomposed by ultraviolet light slowly, providing years of protection in direct sunlight. A process to apply zinc pyrithione to cotton with washable results was patented in the United States in 1984.[11] Zinc pyrithione is used to prevent microbe growth in polyester.[12] Textiles with applied zinc pyrithione protect against odor-causing microorganisms.[28] Export of antimicrobial textiles reached US$497.4 million in 2015.[13] Zinc pyrithione is approved for over-the-counter topical use in the United States as a treatment for dandruff and is the active ingredient in several anti-dandruff shampoos and body wash gels[30]. In its industrial forms and strengths, it may be harmful by contact or ingestion. Zinc pyrithione can in the laboratory setting trigger a variety of responses, such as DNA damage in skin cells.[15]

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