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GOLD MAKES BOLD TO HOLD THE THIO GROUP IN AUROTHERAPY

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ABSTRACT

The mechanisms of action of gold salts are still poorly understood. While auranofin has a direct anti–inflammatory action in animal models, Sodium aurothiomalate has not. Both gold compounds inhibit various enzymes. Among these, lysosomal enzymes are of particular interest. Gold is known to accumulate in the lysosomes and gold salts modulate certain macrophage functions in the immune system. The role of organic gold salt ligands containing, like D–penicillamine, a thiol group is still unclear. Positive data characterizing responders versus non–responders are not yet available. As in other clinically heterogeneous diseases, medical action has mainly been based on clinical empiricism which, although resting on false premises, has helped to find a comparatively efficacious treatment. In fact, the proposals for further studies to shed light on the mode of action presented here may equally be ill conceived. However, these studies would at least expand our understanding of rheumatoid arthritis and thus be beneficial in the long run.

KEYWORDS: Chrysotherapy, Auranofin, Aurothioglucose, Disodium aurothiomalate, Sodium aurothiomalate, Disodium aurothiosulfate.

INTRODUCTION

Aurotherapy (AW–roh–THAYR–uh–pee) is a procedure that uses gold salts (a salt form of the metal element gold) to treat diseases, such as rheumatoid arthritis. The gold salts stop cells from releasing chemicals that can harm tissues also called chrysotherapy and gold therapy. Gold salts are ionic chemical compounds of gold. The term, a misnomer, is a synonym for the gold compounds used in medicine. Chrysotherapy and Aurotherapy are the applications of gold compounds to medicine. Contemporary research on the effect of gold salts treatment began in 1935, primarily to reduce inflammation and to slow disease progression in patients with rheumatoid arthritis. The use of gold compounds has decreased since the 1980s because of numerous side effects and monitoring requirements, limited efficacy, and very slow onset of action. Most chemical compounds of gold, including some of the drugs discussed below, are not salts, but are examples of metal thiolate complexes.[1-3] Gold compounds are of following types but bold letter drugs are used in medicine: Auranofin, Aurothioglucose, Aurotioprol, Bromo (tetrahydrothiophene) gold(I), Caesium auride, Chloro (dimethyl sulfide)gold(I), Chloro (tetrahydrothiophene) gold(I), Chloro (triphenylphosphine) gold(I), Chloroauric acid, Disodium aurothiomalate, Disodium aurothiosulfate, Fulminating gold, Gold chalcogenides, Gold cluster, Template: Gold compounds, Gold halide, Gold heptafluoride, Gold monoiodide, Gold salts, Gold triiodide, Gold(I,III) chloride, Gold(I) bromide, Gold(I) chloride, Gold(I) fluoride, Gold(I) sulfide, Gold(III) bromide, Gold(III) chloride, Gold(III) fluoride, Gold(III) hydroxide, Gold(III) oxide, Gold(V) fluoride, Organogold chemistry, Potassium dicyanoaurate, Sodium aurothiomalate, Tetrabromoauric acid, Tetraxenonogold(II), (2,4,6–Trimethylphenyl)gold.

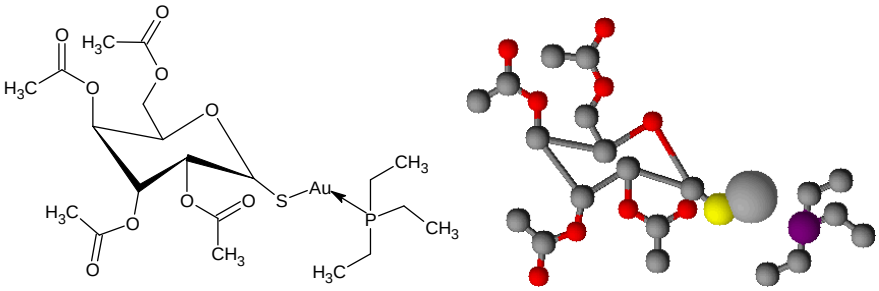
Auranofin is a gold complex classified by the World Health Organization as an anti–rheumatic agent. It has the brand name Ridaura. Auranofin is an organogold compound classified by the World Health Organization as an antirheumatic agent. Auranofin appears to induce heme oxygenase 1 (HO–1) mRNA. Heme oxygenase 1 is an inducible heme–degrading enzyme with anti–inflammatory properties.

Use: Antiinflammatory and Antirheumatic Products. Auranofin is used to treat rheumatoid arthritis. It improves arthritis symptoms including painful or tender and swollen joints and morning stiffness. 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.[4-6]

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. The

drug was shown to reduce the amount of latent virus in monkey trials. A human study testing auranofin and other investigational treatments is ongoing in Brazil. Preliminary results show that auranofin contributed to a decrease in the viral reservoir.[7]

Mode of action: The mode of action of auranofin, an oral organic gold compound used in the treatment of rheumatoid arthritis, is probably similar to the previously available parenteral gold compounds. Auranofin affects polymorphonuclear cells and monocytes at lower concentrations than gold sodium thiomalate and generally affects humoral and cell–mediated immunity in the same direction as the latter drug.



Figure–1: Auranofin.

Pharmacokinetic data: The pharmacokinetics of auranofin is different from the intramuscular gold compounds. Auranofin is 20–25% orally absorbed and has less total body retention, greater fecal excretion and less urinary excretion than gold sodium thiomalate. This may be due in part to its differing chemistry, including its lipophilicity and monomeric structure (at least *in–vitro*). While many clinical studies are not yet complete, auranofin (6 mg/day) is clearly more effective than placebo for treating rheumatoid arthritis. Its efficacy relative to gold sodium thiomalate is not clear. Auranofin may be slightly less effective than gold sodium thiomalate, but because it is generally less toxic than intramuscular gold compounds, its therapeutic index may be more favorable. Bioavailability: 40%, Protein binding: 60%, Metabolism: Plasma membrane of the cell removes the acetyl groups of the glucose moiety, Elimination half–life: 21 to 31 hours, Excretion: Urine–(60%), faeces. Approximately 60% of the absorbed gold (15% of the administered dose) from a single dose of auranofin is excreted in urine; the remainder is excreted in the feces. In plasma, 95–99% of the drug is bound to albumin fraction.

Pharmacodynamics data: Auranofin is a gold salt used in treating inflammatory arthritis. Gold salts are called second–line drugs because they are often considered when the arthritis progresses in spite of anti–inflammatory drugs (NSAIDs and corticosteroids).

IUPAC name: (1–Thio–β–D–glucopyranosato) (triethylphosphine) gold–2,3,4,6–tetraacetate, 2,3,4,6–Tetra–O–acetyl–1–thio–beta–D–glucopyranosato –S (triethylphosphine)gold, Gold(+1) cation; 3,4,5–triacetyloxy–6–(acetyloxymethyl) oxane–2–thiolate; triethylphosphanium, *CAS Number:* 34031–32–8, *Formula:* $C_{20}H_{34}AuO_9PS$, Molar mass: 678.483g/mol.

Toxicity: Oral, rat: LD_{50}> 2000mg/kg. Symptoms of overdose may include diarrhoea, vomiting, abdominal cramps and symptoms of hypersensitivity (such as skin rash, hives, itching and difficulty breathing).

***Amoebiasis*:** 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.

***Tuberculosis*:** In a cell–based screen, auranofin showed potent activity against replicating and non–replicating *Mycobacterium tuberculosis* as well as other gram–positive bacteria. Auranofin protected mice from an otherwise lethal infection with methicillin–resistant *Staphylococcus 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.

Ovarian cancer: Drug–screening reveals auranofin induces apoptosis in ovarian cancer cells *in–vitro*.

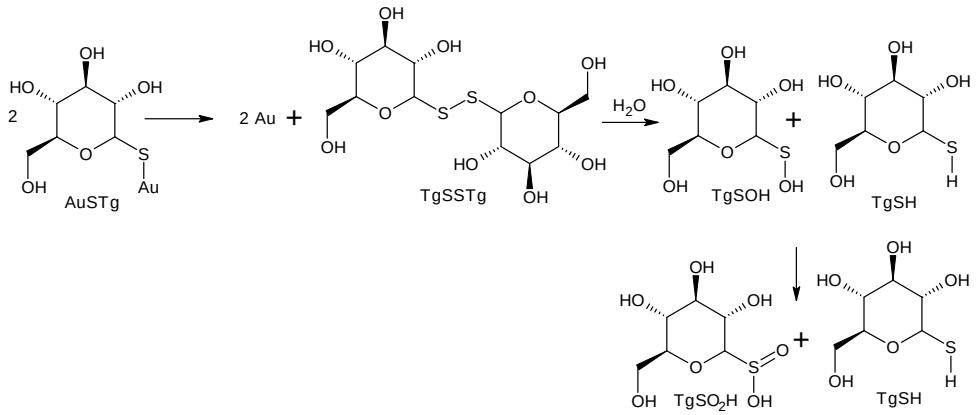
***Dosage forms*:** Capsule (3 mg/1), *Water Solubility*: 0.151 mg/mL, *logP*: 2.99, *pKa* (Strongest Basic): –4.3.

Aurothioglucose, also known as gold thioglucose, is a chemical compound with the formula $AuSC_6H_{11}O_5$. This derivative of the sugar glucose was formerly used to treat rheumatoid arthritis.

History: Throughout history, gold was used to cure diseases, although the efficacy was not established. In 1935, gold drugs were reported to be effective for the treatment of rheumatoid arthritis. Although many patients reacted positively to the drug, gold thioglucose was not uniformly effective. Only 1 gold drug remains in active clinical use for this purpose in the United *States:* auranofin although sodium aurothiomalate (gold sodium thiomalate) and aurothioglucose were still used until recently. In the United Kingdom, only sodium aurothiomalate and auranofin were used recently. In 2001, aurothioglucose was withdrawn from the Dutch market, where it had been the only injectable gold preparation available since 1943, forcing hospitals to change medication for a large number of patients to aurothiomalate. The drug had been in use for more than 70 years, and four years later the reasons for its sudden disappearance remained unclear. It was recently discontinued from the US market along with sodium aurothiomalate leaving only Auranofin as the only gold salt on the US market.

Mode of action: Rheumatoid arthritis is an autoimmune disease in which the body's immune system mistakenly attacks the lining of various skeletal bone joints of the body. These attacks are facilitated by various pro–inflammatory immune cells and agents like cytokines, histamines, mast cells, macrophages, monocytes, lymphocytes, leukocytes and many others. The long–term result of this unwanted immune response is chronic inflammation and painful tissue damage. The cause of the malfunctioning immune system in rheumatoid arthritis is unknown and there is no definitive cure for the condition. Similarly, the mode of action of aurothioglucose is also not well elucidated. Nevertheless, some studies have suggested that the combination of both the sulfhydryl ligand and aureus cation present in aurothioglucose elicits an inhibitory effect on adenylyl cyclase activity in human lymphocyte membranes and in membranes of T and B lymphocyte subsets. In particular, such inhibition of the activity of adenylyl cyclase and its various isoforms would theoretically also limit the cyclases' ability to induce mast cell degranulation and histamine release, to enhance respiratory burst effects, to stimulate the action of resting macrophages, to induce and activate phagocytes, to induce neutrophil chemotaxis, etc. All of which are pro–inflammatory actions. The effect of aurothioglucose, on basal and forskolin–activated adenylyl cyclase activity in human total lymphocyte membranes and in membranes of T and B lymphocyte subsets was studied. The gold compounds inhibited adenylyl cyclase activity. This inhibitory effect required the presence of both the sulfhydryl ligands and aurous cation. Regulation of lymphocyte adenylyl cyclase by gold compounds represents a potential mode of action of these drugs in rheumatic disease. Transcription factor NF–kappaB controls the expression of a number of genes including those for cell adhesion molecules such as E–selectin, ICAM– 1 and VCAM– 1. These cell adhesion molecules are known to play important roles in a critical step of tumor metastasis; the arrest of tumor cells on the venous or capillary bed of the target organ. NF–kappaB is activated by extracellular signals such as those elicited by the pro–inflammatory cytokines, TNF and IL–1. The adhesion of tumor cells to IL–1β–treated HUVEC human umbilical vein endothelial cells was inhibited by gold compounds such as aurothioglucose.

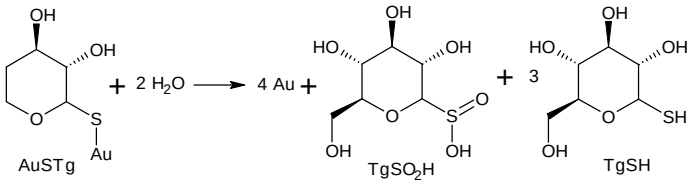
Medicinal chemistry: Gold thioglucose features gold in the oxidation state of +I, like other gold thiolates. It is a water–soluble, non–ionic species that is assumed to exist as a polymer. Under physiological conditions, an oxidation–reduction reaction leads to the formation of metallic gold and sulfinic acid derivative of thioglucose.[8]



$2\ AuSTg \rightarrow 2\ Au + TgSSTg$

$TgSSTg + H_2O \rightarrow TgSOH + TgSH$

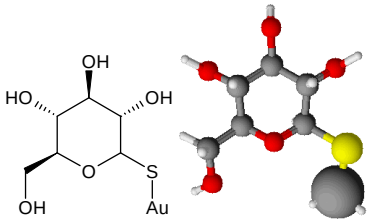
$2\ TgSOH \rightarrow TgSO_2H + TgSH$



Overall: 2 H_2O + 4 AuSTg → 4 Au + $TgSO_2H$ + 3 TgSH.
(where AuSTg=gold thioglucose, TgSSTg=thioglucose disulfide, $TgSO_2H$=sulfinic acid derivative of thioglucose)

***IUPAC name*:** gold(I) (2S,3S,4R,5S)3,4,5–trihydroxy–6–(hydroxymethyl)–oxane–2–thiolate, *CAS Number*: 12192–57–3, *Formula:* $C_6H_{11}AuO_5S$, *Molar mass:* 392.181g/mol, *Water Solubility:* 96.4 mg/mL, *logP:* –1.8, *pKa (Strongest Acidic):* 12.51, *pKa (Strongest Basic):* –3.

Preparation: Gold thioglucose can be prepared by treating gold bromide with thioglucose solution saturated with sulfur dioxide. Gold thioglucose is precipitated with methanol and recrystallized with water and methanol.



Figure–2: Aurothioglucose.

Miscellaneous observations: In recent research, it was found that injection of gold thioglucose induces obesity in mice. Aurothioglucose has an interaction with the antimalarial medication hydroxychloroquine.[9,10]

Pharmacokinetics data: Absorption: In general, aurothioglucose is administered via intramuscular injection preferably intragluteally after which the resultant absorption is typically slow and erratic. Gold is absorbed from injection sites, reaching peak concentration in blood in about 4 to 6 hours. After a single intramuscular injection of 50mg of aurothioglucose suspension in two subjects, peak serum levels were observed at approximately 235g/dL and 450g/dL. Storage of gold in human tissues depends upon organ mass as well as the concentration of gold. Subsequently, tissues having the highest gold levels (w/w) may not necessarily have the largest total amounts of gold. The highest concentrations of gold are generally found in the lymph nodes, adrenal glands, liver, kidneys, bone marrow and spleen. Relatively small concentrations are actually found in the articular structures. In particular, following the administration of aurothioglucose doses, about 85% of the resultant plasma gold will be stored in the major bodily gold depots, which in decreasing order of total gold content are, the lymph nodes, bone marrow, liver, skin and bone.

Route of Elimination: Following a single intramuscular injection of 50mg aurothioglucose in each of two patients, one study determined that approximately 70% of the agent is eliminated in the urine and 30% in the faeces. In general, excretion is primarily in the urine.

Volume of Distribution: Readily accessible data regarding the volume of distribution of aurothioglucose is not available.

Clearance: When a standard weekly treatment schedule of aurothioglucose administrations is followed, about 40% of the given dose is excreted each week, while the remainder is excreted over a longer period. The true potential of gold compounds, including aurothioglucose, to cumumulate has not been clearly defined, but it is clear that substantially larger amounts of gold are retained in the body during therapy with parenteral gold compounds than during therapy with auranofin.

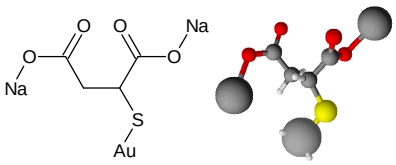
Biological Half–Life: The biological half–life of gold salts (like aurothioglucose) following a single 50mg dose demonstrates a biological half–life of about 3–27days, where the half–life seemingly increases with increased number of doses. Following successive weekly doses, the half–life increases and may become 14–40days after the third dose and up to 168days after the eleventh weekly dose. The biological half–life of gold salts following a single 50mg dose has been reported to range from 3 to 27days. Following successive weekly doses, the half–life increases and may be 14 to 40days after the third dose and up to 168days after the eleventh weekly dose.

Toxicity: Overdose as a result of too rapid increases in dosing with aurothioglucose will be manifested by rapid appearance of toxic reactions, including those that are particular to renal damage, like hematuria and proteinuria, while hematologic effects include thrombocytopenia and granulocytopenia. Other toxic effects, including fever, nausea, vomiting, diarrhea, and various skin disorders like papulovesicular lesions,

urticaria and exfoliative dermatitis, each of which are typically combined with severe pruritus can also develop. The intramuscular TD_{Lo} (Toxic Dose Low) for males is reported to be approximately 3.357mg/kg when considering sense organs and special senses like eye vision and about 5.5mg/kg for affects on the lungs, thorax, or respiration. For women, the intramuscular TD_{Lo} for effects on the liver, gastrointestinal tract, and cholestatic jaundice is between 2.6–2.7mg/kg while the value for effects on the kidney, ureter, bladder and acute renal failure, acute tubular necrosis, and other changes in urine composition is about 14.402mg/kg.

Disodium aurothiomalate is a chemical compound with the formula $AuSCH(CO_2Na)CH_2CO_2Na$. In conjunction with its monoprotonated derivative, this coordination complex or closely related species are used to treat rheumatoid arthritis, under the tradename (Myochrysine). The thiomalate is racemic in most formulation.

Structure: Disodium aurothiomalate is a coordination polymer. The salt $CsNa_2Au_2T(TH)$ salt (T=thiomalate^{3-}, TH=monoprotonated thiomalate^{2-}) is related to disodium aurothiomalate but is easier to crystallize and characterize by X–ray crystallography. The compound is polymeric with Au–S–Au–S chains with succinoyl groups attached to the sulfur atoms. The structure of the related drug Aurothioglucose is also polymeric with two–coordinate gold(I) centers. In such compounds, the efficacy results from the compound in solution, the structures of such solution species are often poorly understood. Medical texts sometimes suggest that free Au^+ ions exist in this and related gold(I) compounds, but the Au–thiolate bonding is highly covalent and free gold ions do not exist in solution. Whereas simple gold thiolates are lipophilic, the carboxylate substituent renders disodium aurothiomalate soluble in water. Disodium aurothiomalate contains no Au–C bonds, so it is not an organometallic compound in the formal sense.[11]



Figure–3: Disodium aurothiomalate.

Pharmacokinetic data: Gold sodium thiomalate solutions are rapidly absorbed following IM injection, with peak serum concentrations occurring in 3–6hours. The apparent volume of distribution is 0.26+/–0.051 kg^{-1}. *Bioavailability:* 0%, *Excretion:* The major route of elimination of an IV dose of gold sodium thiomalate is urinary excretion, with a mean of 35% of the dose found in the urine in ten days. Fecal elimination accounts for an additional 9.4% of the IV dose excreted in ten days, probably as a result of biliary secretion. Renal, very slow, *Clearance:* 7.0 ml/kg/day. *Formula:* $C_4H_3AuNa_2O_4S$, *CAS Number:* 12244–57–4, *Molar mass:* 390.076g/mol. *Half life:* 12.5 days. *Water Solubility:* 35.2 mg/mL, *logP:* –0.14, *pKa (Strongest Acidic):* 3.18.

Pharmacodynamics data: It may decrease prostaglandin synthesis or may alter cellular mechanisms by inhibiting sulfhydryl systems. About 85–90% of the drug is protein bound.

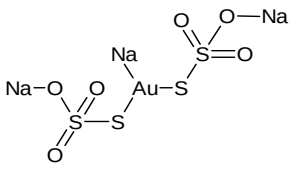
Mode of action: It is known that sodium aurothiomalate inhibits the synthesis of prostaglandins. The predominant action appears to be a suppressive effect on the synovitis of active rheumatoid disease.

Toxicity: Over dosage symptoms are those of heavy metal toxicity; they include pruritus, dermatitis, stomatitis, vague gastrointestinal discomfort, albuminuria with or without a nephrotic syndrome, hematuria, agranulocytosis, thrombocytopenic purpura and aplastic anemia.

Side effects: Disodium aurothiomalate can cause photosensitive rashes, gastrointestinal disturbance, and kidney damage.

Dosage forms: Injection (Intramuscular): 50mg/mL, Solution (Intramuscular): 10mg/mL, Solution (Intramuscular): 25mg/mL, Solution (Intramuscular): 50mg/mL.

Disodium aurothiosulfate is the inorganic compound with the formula $Na_3Au(S_2O_3)_2{\cdot}2H_2O$. This salt contains an anionic linear coordination complex of gold(I) bound to two thiosulfate ligands. Like several other gold compounds, this species is used as an antirheumatic. The first placebo–controlled trial was probably conducted in 1931, when sanocrysin was compared with distilled water for the treatment of tuberculosis.[12]



Figure–4: Disodium aurothiosulfate.

Clinical data: Routes of administration: Intramuscular injection.

IUPAC name: Trisodium dithiosulphate aurate(I), dehydrate, *CAS Number:* 18497–75–1, *Formula:* $AuNa_3O_6S_4$, *Molar mass:* 490.192276g/mol.

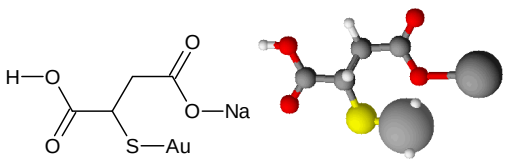
Sodium aurothiomalate is a gold compound that is used for its immunosuppressive anti–rheumatic effects which is hydroxy succinic acid (malic acid) derivative. Along with an orally–administered gold salt, auranofin, it is one of only two gold compounds currently employed in modern medicine. Sodium aurothiomalate is a variable mixture of the mono– and disodium salts of gold thiomalic acid used mainly for its anti–inflammatory action in the treatment of rheumatoid arthritis. It is most effective in active progressive rheumatoid arthritis and of little or no value in the presence of extensive deformities or in the treatment of other forms of arthritis. Gold Sodium Thiomalate is the sodium salt of gold thiomalic acid, an organogold compound with antirheumatic and potential antineoplastic activities. Gold Sodium Thiomalate (GST) appears to inhibit the activity of atypical protein kinase C iota (PKCiota) by forming a cysteinyl–aurothiomalate adduct with the cysteine residue Cys–69 within the PB1 binding domain of PKCiota. This prevents the binding of Par6 (Partitioning defective protein 6) to PKCiota, thereby inhibiting PKCiota–mediated oncogenic signaling, which may result in the inhibition of tumor cell proliferation, the promotion of tumor cell differentiation, and the induction of tumor cell apoptosis. Atypical PKCiota, a serine/threonine kinase overexpressed in numerous cancer cell types, plays an important role in cancer proliferation, invasion and survival; Par6 is a scaffold protein that facilitates atypical PKC–mediated phosphorylation of cytoplasmic proteins involved in epithelial and neuronal cell polarization.

Mode of action: It is known that sodium aurothiomalate inhibits the synthesis of prostaglandins. The predominant action appears to be a suppressive effect on the synovitis of active rheumatoid disease. The effects of aurothiomalate, on basal and forskolin–activated adenylyl cyclase activity in human total lymphocyte membranes and in membranes of T and B lymphocyte subsets were studied. The gold compounds inhibited adenylyl cyclase activity. This inhibitory effect required the presence of both the sulfhydryl ligands and aurous cation. Regulation of lymphocyte adenylyl cyclase by gold compounds represents a potential mode of action of these drugs in rheumatic disease. Transcription factor NF–kappaB controls the expression of a number of genes including those for cell adhesion molecules such as E–selectin, ICAM–1 and VCAM–1. These cell adhesion molecules are known to play important roles in a critical step of tumor metastasis; the arrest of tumor cells on the venous or capillary bed of the target organ. NF–kappaB is activated by extracellular signals such as those elicited by the pro–inflammatory cytokines, TNF and IL–1. The adhesion of tumor cells to IL–1 β–treated HUVEC human umbilical vein endothelial cells/ was inhibited by gold compounds such as aurothiomalate.

Medical uses: It is primarily given once or twice weekly by intramuscular injection for moderate–severe rheumatoid arthritis although it has also proven itself effective in treating tuberculosis.[13-15]

Adverse effects: Overdosage symptoms are those of heavy metal toxicity; they include pruritus, dermatitis, stomatitis, vague gastrointestinal discomfort, albuminuria with or without a nephrotic syndrome, hematuria, agranulocytosis, thrombocytopenic purpura and aplastic anemia. Its most common side effects are digestive (mostly dyspepsia, mouth swelling, nausea, vomiting and taste disturbance), vasomotor (mostly flushing, fainting, dizziness, sweating, weakness, palpitations, shortness of breath and blurred vision) or dermatologic (usually itchiness, rash, local irritation near to the injection site and hair loss) in nature, although conjunctivitis, blood dyscrasias, kidney damage, joint pain, muscle aches/pains and liver dysfunction are also common. Less commonly, it can cause GI bleeds, dry mucous membranes and gingivitis. Rarely it can cause: aplastic anaemia, ulcerative enterocolitis, difficulty swallowing, angiooedema, pneumonitis, pulmonary fibrosis, hepatotoxicity, cholestatic jaundice, peripheral neuropathy, Guillain–Barré syndrome, encephalopathy, encephalitis and photosensitivity.

Pharmacology: Its precise mode of action is unknown but is known that it inhibits the synthesis of prostaglandins. It also modulates phagocytic cells and inhibits class II major histocompatibility complex–peptide interactions. It is also known that it inhibits the following enzymes: Acid phosphatase, β–glucuronidase, Elastase, Cathepsin G, Thrombin, Microsomal prostaglandin E synthase–1.[16-18]



Figure–5: Sodium aurothiomalate.

History of use: Reports of favorable use of the compound were published in France in 1929 by Jacques Forestier. The use of gold salts was then a controversial treatment and was not immediately accepted by the

international community. Success was found in the treatment of Raoul Dufy's joint pain by the use of gold salts in 1940; "(The treatment) brought in a few weeks such a spectacular sense of healing, that Dufy boasted of again having the ability to catch a tram on the move." It was recently discontinued from the US market along with Aurothioglucose leaving only Auranofin as the only gold salt on the US market.

Pharmacokinetic data: Protein binding: High, Elimination half–life: 6 to 25 days, Biological Half–Life: 12.5days. Following single 10–mg doses of gold sodium thiomalate, serum gold concentrations showed a biphasic decline with a relatively rapid early phase (serum half–life about 43hours) and a slow late phase (serum half–life about 6 days).
Excretion: Urine (60–90%), Faeces (10–40%).

Absorption: Gold sodium thiomalate solutions are rapidly absorbed following IM injection, with peak serum concentrations occurring in 3–6 hours. *Route of Elimination:* The major route of elimination of an IV dose of gold sodium thiomalate is urinary excretion, with a mean of 35% of the dose found in the urine in ten days. Fecal elimination accounts for an additional 9.4% of the IV dose excreted in ten days, probably as a result of biliary secretion.

Volume of Distribution: The apparent volume of distribution is 0.26+/– 0.051 kg^{-1}. *Clearance:* 7.0ml/ kg/day.

IUPAC name: Sodium 3–(auriosulfanyl)–3–carboxypropanoate, *CAS Number:* 12244–57–4, *Formula:* $C_4H_4AuNaO_4S$, *Molar mass:* 367.93.

Use in rheumatoid arthritis: Investigation of medical applications of gold salts began at the end of the 19th century, when gold cyanide demonstrated efficacy in treating *Mycobacterium tuberculosis* in *in–vitro*.

Indications: The use of injected gold salts is indicated for rheumatoid arthritis. Its uses have diminished with the advent of newer compounds such as methotrexate and because of numerous side effects. The efficacy of orally administered gold is more limited than injecting the gold compounds.

Mechanism in arthritis: The mechanism by which gold drugs affect arthritis is by inhibiting the cyclooxygenase pathways.

Administration: Gold salts for rheumatoid arthritis are administered by intramuscular injection but can also be administered orally (although the efficacy is low). Regular urine tests to check for protein, indicating kidney damage, and blood tests are required.

Efficacy: A 1997 review reports that treatment with intramuscular gold (parenteral gold) reduces disease activity and joint inflammation. Gold salts taken by mouth are less effective than by injection. Three to six months are often required before gold treatment noticeably improves symptoms.

Auranofin **Aurothioglucose** **Sodium aurothiomalate**

Figure–6: Gold compounds.

Side effects: Chrysiasis (Gk, chrysos – 'gold', osis – 'condition of') is a dermatological condition induced by the parenteral administration of gold salts, usually for the treatment of rheumatoid arthritis. Such treatment has been superseded as the best practice for treating the disease because of numerous side effects and monitoring requirements, their limited efficacy and very slow onset of action. Similar to silver, a gold preparation used parenterally for a long period may rarely produce permanent skin pigmentation – especially if the skin is exposed to sunlight or artificial ultraviolet radiation. The skin's pigmentation (in this condition) has been described as uniformly gray, grayish purple, slate gray, or grayish blue and is usually limited to exposed portions of the body. It may involve the conjunctivae over the scleras but usually not the oral mucosa. Location of pigment predominantly in the upper dermis leads to the blue component of skin color through the scattering phenomenon. It is much less likely to be deposited in the nails and hair. Chrysiasis was said to have been much more common when medicines containing traces of gold were used for treatment of tuberculosis (commonplace forms of treatment nearly fifty years ago). Treatments containing gold traces were also used to treat cases of

rheumatoid arthritis – but because the dose used for tuberculosis was higher than for arthritis, it has not afflicted many subscribing to such treatments. Gold can be identified in the skin chemically by light microscopy, electron microscopy, and spectroscopy. There is no way to reverse or treat chrysiasis. A noticeable side–effect of gold–based therapy is skin discoloration, in shades of mauve to a purplish dark grey when exposed to sunlight. Skin discoloration occurs when gold salts are taken on a regular basis over a long period of time. Excessive intake of gold salts while undergoing chrysotherapy results – through complex redox processes – in the saturation by relatively stable gold compounds of skin tissue and organs (as well as teeth and ocular tissue in extreme cases) in a condition known as chrysiasis. This condition is similar to argyria, which is caused by exposure to silver salts and colloidal silver. Chrysiasis can ultimately lead to acute renal failure (such as tubular necrosis, nephrosis, glomerulitis), severe heart conditions, and hematologic complications (leukopenia, anemia). While some effects can be healed with moderate success, the skin discoloration is considered permanent.

Other side effects: Other side effects of gold salts include kidney damage, itching rash, and ulcerations of the mouth, tongue, and pharynx. Approximately 35% of patients discontinue the use of gold salts because of these side effects. Kidney function must be monitored continuously while taking gold salts.[19,20]

CONCLUSION

Gold therapy is generally recognized as the process of treating the body with gold, through compounds known as gold salts, to help deal with specific conditions such as rheumatoid arthritis. Aurotherapy and chrysotherapy are other names for this kind of process. Gold therapy is built on a long human tradition of revering and prizing this precious metal. As one of the heaviest known elements, gold has a lot of intrinsic value on world markets. Its popular use as currency in prior times demonstrates the collective value that gold has had, and continues to have, for the human community. With gold therapy, even more value is added to this element as a potential solution for healing. The main potential for gold salt applications, according to some scientists and medical experts, is in limiting inflammation in the joints. Gold therapy is often a considered treatment for juvenile forms of arthritis. It is sometimes valuable in treating patients who would not respond favorably to more complex chemical solutions. Gold supplements can be injected into the body or administered through oral supplements. Some forms may require testing after application to see that the gold compound was properly received. Results from these compounds, according to medical resources, can take up to six months. Gold salts, which are now used only occasionally to treat severe rheumatoid arthritis, are a rare cause of peripheral neuropathy described for the first time more than 70 years ago. Although the incidence of gold salt neuropathy is low, it must always be considered in differential diagnoses, particularly when high cumulative doses of gold have been administered. However, peripheral neuropathy has been reported with cumulative doses of gold ranging from 30 to 2600 mg. Sodium aurothiomalate is the most common preparation associated with neuropathy. The onset is generally slow and secondary to axonal damage, but cases with sudden motor weakness (sometimes asymmetrical) and prominent segmental demyelization have also been reported. In both chronic and acute neuropathies, motor signs (weakness, muscle cramps and atrophy, myokymia) predominate over sensory impairment and recovery is invariably slow. The neurophysiological examination is often normal or a mild reduction in nerve conduction velocity may be demonstrated, but denervation in affected muscles is not uncommon. The presence of elevated cerebrospinal fluid levels in some patients has raised the possibility of radicular involvement. The pathogenesis of gold–induced neuropathy is unknown, although the different clinical presentations suggest that the medication may act with different mechanisms. Administration of gold salts (chrysotherapy) has found greatest application in canine medicine in the treatment of autoimmune disorders, particularly autoimmune polyarthritis (e.g. rheumatoid arthritis, idiopathic polyarthritis) and the autoimmune skin diseases (e.g. pemphigus foliaceus, bullous pemphigoid). In the cat, gold salts have been used as therapy for pemphigus foliaceus, chronic gingivostomatitis, plasma cell pododermatitis and lesions of the eosinophilic granuloma complex. The majority of reported studies have been with aurothiomalate rather than auranofin as the latter drug is more expensive and reportedly less effective.

***Mode of action*:** By inhibition of lymphocyte proliferation (possibly T–helper cells), inhibition of immunoglobulin production, inhibition of complement component Cl, inhibition of neutrophil and monocyte–macrophage function, particularly the release of lysosomal enzymes and prostaglandins, inhibition of connective tissue enzymes (elastase, collagenase, hyaluronidase), protection from oxygen radicals.

Formulations and dose rates: Gold salts are available for oral administration as auranofin (Ridaura®; 3 mg tablets containing 29% gold) or in an injectable form as aurothiomalate (Myocristin®; 20, 40 or 100mg/mL suspension containing 50% gold). These drugs are not currently licensed for companion animal use.

***Pharmacokinetics*:** Following oral administration, gold is absorbed from the intestine (approximately 20–25% of the gold content of the drug) and binds plasma proteins with moderate affinity. Gold particularly concentrates within liver, kidney, spleen, lungs and adrenal glands. At the cellular level, gold also accumulates predominantly within macrophages. Approximately 60% of the absorbed dose is excreted in urine and unabsorbed gold is excreted in the feces. After IM injection, gold is

rapidly absorbed, with peak serum concentrations achieved in 4–6hours and up to 95% of the agent is bound to plasma proteins. The half–life in blood is approximately 6days. The drug is predominantly concentrated in the synovium, with lower levels in liver, kidney, spleen, bone marrow, adrenals and lymph nodes. Approximately 70% of the absorbed dose is excreted in urine and the remainder is lost in the feces.

***Adverse effects*:** Gold salts are contraindicated in patients with SLE (Systemic Lupus Erythematosus), diabetes mellitus or hematological, hepatic, renal or cardiac disease. Recorded adverse effects include diarrhea (more commonly with auranofin than aurothiomalate), blood dyscrasias (especially thrombocytopenia, hemolytic anemia, leukopenia), hemorrhage or ulceration of mucous membranes, mucocutaneous disease of the erythema multiforme–toxic epidermal necrolysis spectrum, encephalitis, neuritis, hepatotoxicity or renal disease (damage to proximal tubules). Nephrotoxic effects are particularly marked in cats and may lead to proteinuria.

***Known drug interactions*:** There are few data for veterinary patients, but in humans the potential for toxicity is elevated with concurrent administration of penicillamine or antimalarial drugs. Gold salts should not be administered concurrently with cytotoxic immunosuppressive drugs.

Special considerations: The use of gold salts should only be considered following unsuccessful trials of other less toxic and expensive immunosuppressive agents. Animals receiving chrysotherapy should have regular monitoring of hematological and renal (urinalysis) parameters at baseline, then every 2weeks initially and then every 1–2months. Gold salts are potentially teratogenic and their use is contraindicated in pregnancy.

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