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## Drugs Contain Metals – A short Review on the Application of drug Contains Gold

Ab. Rashid Wani\*<sup>1</sup>, Ghulam Mohammad Jan<sup>1</sup>

*1. Department of Chemistry, Govt. Degree College Boys Dooru Anantnag J&k (India)*

### ABSTRACT

Pharmaceutical Chemistry combines knowledge of the biological, medical, and physical sciences in the study of the scientific aspect of drug therapy. The emphasis is on the chemical nature of the reactions and interactions involved in drug therapy. The students will receive a solid background in the aspects of chemistry the most relevant to drugs: physical, organic, and analytical chemistry. They will also learn the fundamental aspects of the synthesis, manufacture, use, and mode of action of drugs. Pharmaceutical drug, also referred to as a medicine or medication, can be loosely defined as any chemical substance - or product comprising such - intended for use in the medical diagnosis, cure, treatment, or prevention of disease.

**Keywords:** Biological Medical, Physical Science, Drugs, Disease

\*Corresponding Author Email: [abwani001@gmail.com](mailto:abwani001@gmail.com)

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## INTRODUCTION

Credited with curing or warding off everything from smallpox to measles, for centuries, the Gold was a common treatment for rheumatoid arthritis from the late 1920s until the 1990s<sup>1-4</sup>. According to the Johns Hopkins Arthritis Center, gold flakes were injected into muscles, into the veins and even given orally<sup>5-7</sup>. Though gold could sometimes be an effective treatment, it is unclear exactly how it improves the patient's condition. New treatments with fewer side effects are now preferred. One of the most exciting uses of gold in medicine is precision delivery of medication to fight cancer. Microscopic gold covered "medicine bullets" are fired at targeted cells then activated to release their load.<sup>8-9</sup>

### **Implants**

Most people associate gold body parts with gold fillings or caps on teeth. It can also be used in medical implants from stents to pace makers because it is resistant to bacteria and deterioration.

### **Health Supplement**

The Japanese originated the tradition of ingesting thin films of gold in beverages and food as a sort of "vitamin". In India and Egypt, it is taken as a powder or a tablet.

### **Gold and Rheumatoid Arthritis**

Gold is most notably used in modern medicine as a treatment for rheumatoid arthritis, although newer drugs have supplanted it as the treatment of choice. It helps to relieve joint stiffness and pain and helps to prevent bone deformation, according to the University of Washington. Gold is injected into a muscle in the buttocks or arm or it is taken in a pill form. It does not work for everyone and can take up to 6 months to see any benefit.

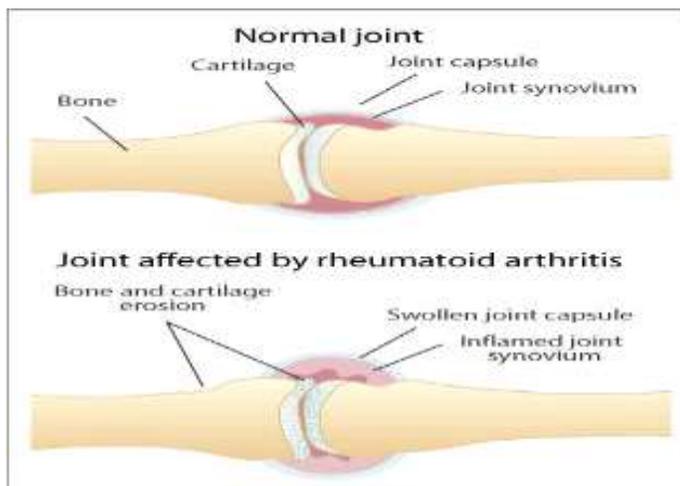
### **Gold and Cancer**

Gold is used in treating cancer in various ways. Doctors can insert gold into the prostate to help line up radiation equipment to more accurately zero in on the organ, according to the "Daily Mail." Some anti-cancer drugs also have trace amounts of gold in them that help to attack the tumor. A new therapy is looking into covering silica particles in gold. These particles will then attach to the tumor and illuminate under radiation, allowing doctors to see the tumor more effectively.

### **Gold Antiarthritics Drugs**

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder that affects one to two percent of people worldwide and five percent of women over the age of 55<sup>10</sup>. Women between the ages of forty and sixty are most susceptible to the disease. It is a painful, incurable disease, and can lead to total loss of joint use within ten years of onset<sup>39</sup>. Symptoms are pain and swelling of

the affected joint and over time the soft tissue surrounding the joint erodes away. People with advanced rheumatoid arthritis often have deformed hands or feet due to uncontrollable hyperextension or hyperflexion. The causes of rheumatoid arthritis are unknown.



**Figure 1: Joint Erosion**

Two classes of drugs are used to treat rheumatoid arthritis. The first class of drugs, called “first-line” drugs, are non-steroidal anti-inflammatory drugs (NSAIDs), which include drugs such as aspirin and ibuprofen. These drugs simply alleviate pain and swelling. The second class of drugs, or the “second-line” drugs, are disease-modifying anti-rheumatic drugs (DMARDs), and include such drugs as methotrexate, D-penicillamine and various gold salts<sup>11</sup>. DMARDs “modify” rheumatoid arthritis, and are able to slow its advance, allowing patients to retain flexibility and motion for longer periods of time. In general, these are dangerous drugs and are only prescribed for patients with severe rheumatoid arthritis who are not responding to other treatments.



**Figure 2: Rheumatoid Arthritis Hand**

Gold salts have been used to treat rheumatoid arthritis since the early twentieth century. They are immunosuppressants. Unlike other DMARDs, gold salts have been known to reverse erosive damage<sup>41</sup>. Examples of gold salts are gold sodium thiomalate (“Myocrisin”), gold thioglucose (“Solganal”) and gold thiosulfate. Gold sodium thiomalate is the only gold salt that is FDA approved. Countries outside the United States use other gold salts as well.

### The Immune System

Rheumatoid arthritis patients are interested in anything that reduces pain and swelling. The fact that gold salts are also able to reverse erosive damage makes them especially attractive as a treatment option.

The one biochemical reaction that gold ion is known to have in the body is binding to sulfhydryl groups (-SH) and interfering with reactions that rely on these functional groups<sup>12,13</sup>. This gives gold salts the potential to affect a wide range of reactions. Links have been found between gold salt therapy and reduced activity of certain areas of the immune system. For instance, gold salts inhibit the activity of lysosomal enzymes, which are important for the action of phagocytotic cells<sup>14</sup>. In the immune response, infected cells are targeted and attacked by phagocytotic cells, which engulf the infected cells and digest them using lysosomal enzymes. In another example, studies have found that patients with inflammatory autoimmune disorders have greater levels of “substance P,” a neuropeptide found around nerve cells. Gold therapy reduces levels of substance P in the blood serum<sup>45</sup>. Several studies have found that gold therapy affects relative levels of prostaglandins (PGs) and leukotrienes. Specifically, gold salts lower levels of PGF-2 $\alpha$  and increases levels PGE2. PGF-2 $\alpha$  is involved in stimulating the release of lysosomal enzymes, while PGE2 inhibits lysosomal enzyme release<sup>15</sup>. By changing relative levels of these prostaglandins, gold salts affect the immune response.

**Table 1: Immune Response of Gold Salt**

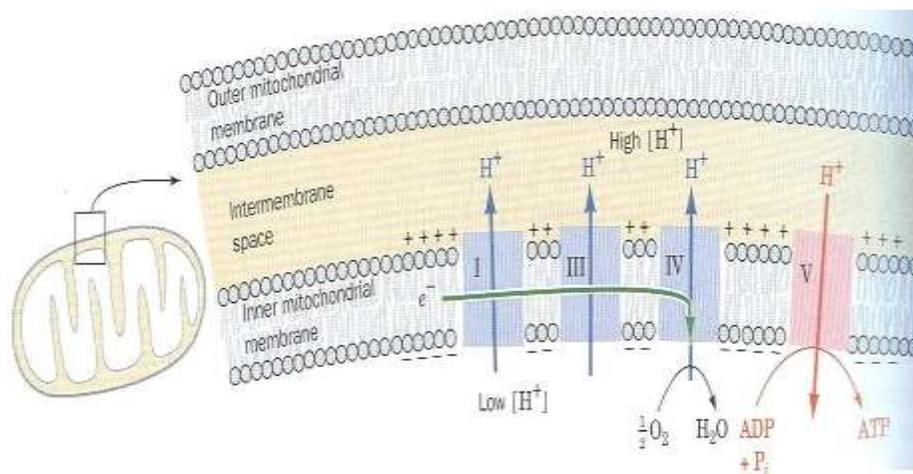
Therapy Used	Number Of Subjects	Substance P Plasma	Substance P Synovial Fluid
Group I (Ongoing Gold Salt Therapy)	11	185 $\pm$ 70	103 $\pm$ 48
Group II (Forgoing Gold Salt Therapy)	21	188 $\pm$ 74	119 $\pm$ 47
Group III (No Gold Salt Therapy)	10	174 $\pm$ 74	138 $\pm$ 94
Total Cumulative Dose Of Gold Salts			
< 1000 mg	13	204 $\pm$ 93	141 $\pm$ 47
> 1000 mg	19	176 $\pm$ 56	92 $\pm$ 32*
*P = 0.0018			

In short, gold salts suppress the immune response in such a way that the effects of rheumatoid arthritis are greatly reduced and in some cases reversed, making them very attractive to patients.

## Mitochondria and Oxidative Stress

Doctors want to prescribe medicine that will treat their patients as well as possible, as fast as possible and as safely as possible. Gold therapy has the potential to lead to some serious side effects that make doctors leery to prescribe gold salts.

The ability of gold ion to bind to a thiol group allows it to bind to proteins in the mitochondrial membrane. When this happens, the mitochondrial membrane becomes more permeable to positively charged ions. This results in decoupling of the oxidative phosphorylation reaction that synthesizes adenosine triphosphate (ATP)<sup>16</sup>. Mitochondria rely on a charge gradient to catalyze ATP production, and when this gradient is disrupted, ATP synthesis is severely inhibited and leads to cell death. In addition, studies have found that gold may be retained in mitochondria of liver, kidney and bone marrow cells, all areas where gold treatment are the most devastating<sup>48</sup>. The presence of any heavy metal in the liver or kidneys interferes with their filtration function, and can lead to damage that is shown by the secretion of proteins or blood in the urine. The effect of gold on bone marrow and blood cells (blood cells originate in the bone marrow) are the most serious side effect of gold therapy. Patients on gold therapy have lower levels of red blood cells, white blood cells and blood platelet cells. In severe cases, aplastic anemia can occur, where normal bone marrow stem cells are being replaced by fat cells, and the body is physically unable to replenish the blood cells that it is losing<sup>17</sup>. If left untreated, this can lead to death.



**Figure 3: Oxidative Decoupling**

Thus, while gold salts may have some very beneficial treatment effects, their side effects are common enough and serious enough that doctors shy away from prescribing them.

## Drug Comparison

In recent years, gold salts have largely been replaced by other drugs for rheumatoid arthritis treatment, especially the anti-cancer drug methotrexate. Methotrexate may not be a “better”

treatment so much as it is a newer treatment whose track record is not long enough to be as bad as that of gold salts.

In terms of dosage and effect, methotrexate has an advantage over gold sodium thiomalate. Methotrexate dosage is 7.5 mg per week, and improvement may be seen in three to six weeks. Gold sodium thiomalate, on the other hand, has a dosage between 25 and 50 mg per week and it may take three to six months for improvement to be detected. In addition, the half-life of gold in the body (3-27 days) is much longer than that of methotrexate (3-10 hours). So less methotrexate is required for a faster response with less of a chance to cause adverse reactions than gold salts.

Where methotrexate loses out is in side effects and drug interactions. Overall, methotrexate has fewer side effects than gold salts, and a lower percentage of patients are affected by these side effects. However, where gold salt side effects are almost always completely reversible upon cessation of treatment, methotrexate side effects, especially lung and liver damage, are not and can cause health problems later. Also, methotrexate interacts with a wide range of other drugs, including NSAIDs used to treat pain, and cause unexpected adverse reactions. It is never used in conjunction with other drugs. Gold sodium thiomalate, however, interacts with very few drugs, the most dangerous being penicillamine, another DMARD. It is always used as part of a drug regime. Finally, on a more economic basis, gold sodium thiomalate is much cheaper than methotrexate, costing less than \$50 for a solution of 10mg/mL<sup>18-20</sup>.

## CONCLUSION

Pharmaceutical chemistry is a discipline at the intersection of chemistry, pharmacology, and biology involved with designing, synthesizing and developing pharmaceutical drugs. Inorganic compounds and organometallic compounds have many interesting applications. Many metallodrugs are “prodrugs” they undergo ligand substitution and/or redox reactions before they reach the target site. Metallopharmaceuticals used as anticancer agents, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics, and radiosensitizing agents have been reported.

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