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The Future of Metallodrugs: Cost, Environmental Impact, Research Investments, and Clinical Trials

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ABSTRACT

Metallodrugs are unique prodrugs developed from metals and provide distinctive benefits as they supply the human body with vital nutrients and chemical compounds not present in organic medications. Historically, metallodrugs have primarily been platinum-based and have been utilized in cancer treatment. This has resulted in high levels of cytotoxicity for patients, high costs, and low variability in treatments. Based on this literature review using ScienceDirect, Pubmed, and Google Scholar, including published academic, scientific, and medical research articles relating to the use and manufacturing of metallodrugs, this study explores the scope and impact that metallodrugs could have in the future. Considering the rising demand for new medications and therapies for diseases, metallodrugs will play a key role in the future, especially with recent advancements. In terms of cost, metallodrugs have dropped in price due to innovations using more common, cost-effective materials in key processes such as metal catalysis. Furthermore, coinciding with recent environmental awareness, the new technique of mechanochemistry, which is being researched globally, represents a future of metallodrug development that causes minimal harm to the environment. Also, there has been an uptick in research for applications of metallodrugs in other fields, beyond cancer treatment. For example, IQG-607 has shown promising results for treating new, resistant strains of tuberculosis. In the future, expanding research into different fields for metallodrug application will help to improve medication and make it more accessible to a larger number of people.

Introduction

Metallodrugs

Metallodrugs are a form of prodrugs – medications that become activated once they enter the body and are activated by either ligand substitution or redox reactions (Anthony et al., 2020). Metallodrugs in their crude forms have been present for centuries, dating back to the 16th century when syphilis was treated with mercury (Wagner, 2019). The first therapeutic metallodrug was Salvarsan, introduced by Ehrlich in the early 20th century. It was used to treat syphilis and is often referred to as the catalyst of modern usage of metallodrugs in chemotherapy (Imberti et al., 2023). Later, in 1965, researchers at Michigan University discovered that cisplatin inhibited the replication of cancerous cells, which is what led to the modern research and development of anticancer metallodrugs (Mjos & Orvig, 2014).

Benefits of Metallodrugs

Although the majority of medications are organic, metallodrugs represent the future of the field of medicine. Metals are prevalent throughout the human body and provide vital nutrients and chemical functionalities not found in organic compounds (Anthony et al., 2020). Furthermore, the Community for Open Antimicrobial Drug Discovery (CO-ADD) screened metal-containing compounds, which had a rate of success 10 times higher than organic drugs (Frei et al.,

2020). In a world where humanity is constantly in rapid search of new medication and treatments, metallodrugs could represent the hopeful future of modern medicine.

Current Technologies in Clinical Use

Imaging Technology

Currently, the primary metal isotope used in cancer screening is technetium-99nm. First discovered at the University of Chicago in 1964, this isotope has been determined to be the optimal isotope for cancer screening due to cooperation with commercial γ-cameras (Bartholomä et al., 2010). Since then, over 67 imaging agents have been approved by the FDA. However, there is an ongoing shortage in its production because the two nuclear reactors which generate more than 70% of the global market of technetium-99 m's parent nuclide have become nearly obsolete. As an alternative, gallium isotopes have been investigated in countries such as Germany, despite a lack of FDA or EMA approval (Mjos & Orvig, 2014).

Anticancer Therapeutics

Cisplatin, one of the oldest and most well-known drugs, has become practically standard in cancer treatment. Derived from a square planar Pt^{2+} complex, cisplatin was FDA-approved in 1978 and became the first metallodrug to enter clinical usage worldwide (Mjos & Orvig, 2014). Since then, in an attempt to reduce the cytotoxicity of cisplatin, second-round platinum-based drugs oxaliplatin and carboplatin were developed. These were approved by the FDA between 1989 and 2002 (Mjos & Orvig, 2014). The only other metallodrug currently approved for anti-cancer clinical usage is arsenic. Originally used in ancient Chinese medicine, injectable solutions of arsenic trioxide have been approved for treating acute promyelocytic leukemia (Chen et al., 2011).

Methods

The literature utilized in this research paper includes published academic and medical research articles focused on the current and future uses of metallodrugs in various treatments and medical therapies. The dates of publication range from November 2006 to July 2024. The databases utilized include ScienceDirect, Pubmed, and Google Scholar. Additional sources include university research and textbook samples. The search terms used were “metallodrugs”; “cancer therapies”; “potential of metallodrugs”; “medicinal inorganic chemistry”; and “future of metallodrugs.” The literature focused on topics of future research into metallodrugs, how specific elements are utilized in metallodrugs, and how cancer treatment has evolved since advances have been made. In total, 58 published sources were reviewed, and 27 were included. A discussion of these findings is presented below.

Results

Cost

A key development in the drug industry is the revolutionization of metal catalysis. Traditionally, precious, expensive metals are used due to their higher catalytic activity, high thermal stability, chemical longevity, versatility, and overall performance (Trento, 2023). However, in 2023, UCLA researchers developed a method for metal catalysis using oxygen and an abundant metal, copper. This process costs only $3 per gram, a fraction of the usual cost which can go up to $3,200 per gram. The process, known as aminodealkenylation, used oxygen as the reagent and copper as the catalyst to break carbon-nitrogen bonds, creating amines, which are widely used in pharmaceuticals (Ober, 2023). This is especially prevalent in cutting costs of anti-cancer drugs, which are primarily metallodrugs. For example,

research using this technology produced a c-Jun N-terminal kinase inhibitor in three chemical steps as opposed to the original 12 steps previously needed (Ober, 2023).

Environmental Impact

Currently, pharmaceutical industrial processes use vast amounts of toxic and highly volatile solvents which can be a threat to the environment (James et al., 2012). However, a new technology, mechanochemistry, is set to revolutionize the pharmaceutical field. Mechanochemistry is a synthetic technique that has successfully been used to develop new metallodrugs in an environmentally friendly manner (Andre et al., 2021). Mechanochemistry is a method that achieves chemical transformations in a mechanical manner, such as through milling or grinding, eliminating the need for bulk dissolution of reactants. The success of this technique is rooted in catalytic additives to control reactivity, such as liquid-assisted grinding (LAG) (Do & Friščić, 2016). This process is revolutionary for the environment as chemical reactions can now proceed without excess solvents or heating (Bryce & Southern, 2021). Furthermore, the activity of important medications has been enhanced using this technique. For example, the activity of ibuprofen increased when formulated with MgO, a metallic compound (Quaresma et al, 2017). Additionally, a key framework ZIF-8 for anti-cancer drugs has been synthesized by mechanochemistry. This is especially important as this technique revealed a new metastable intermediate on a previously unreported topology (Quaresma et al, 2017).

Research Investments

The development of metallodrugs through mechanochemical methods has exploded over the past two decades across Europe. For example, Portugal has expanded the use of mechanochemical methods into bioinspired metal-organic frameworks, with an emphasis on antibiotic coordination frameworks, which are key for metallodrugs (André et al., 2021). Furthermore, the European Cooperation in Science and Technology (COST) funded the COST Action: CA18112 - Mechanochemistry for Sustainable Industry. This program has partners in 33 COST Member Countries and partners from Canada, China, Mexico, Russia, Singapore, and the USA to further research the field of mechanochemistry, which is directly tied to the development of metallodrugs (Hernández et al., 2020). Additionally, as of February 2023, the European Commission has awarded €7.7 million to IMPACTIVE, a project for green pharmaceuticals, for the investigation of mechanochemistry in the synthesis of active pharmaceutical ingredients (Eckford, 2023; IMPACTIVE, 2024).

Drugs in Clinical Trials

Although few metallodrugs have been used in cancer treatment, there are many more in clinical trials for the treatment of other diseases.

IQG-607

The drug IQG-607 has been developed in response to the new strands of *Mycobacterium tuberculosis* which are resistant to the current drug in the market, isoniazid (Santos, 2014). Tested on infected mice, IQG-607 showed much lower counts of bacterial loads compared to untreated controls after 1 month and 2 months of treatment (Rodrigues-Junior et al., 2019). Furthermore, the dosage of IQG-607 did not cause mortality or even any toxic clinical signs (Basso et al., 2010). These results were similar in minipigs, which are more similar to humans and will thus result in more accurate results (Rodrigues-Junior et al., 2019). Thus, IQG-607 shows promising results for clinical reproduction (Abbadi et al., 2018).

Platinum-Based Anti-Cancer Drugs

Usually, platinum complexes are the norm for metallodrugs. The most famous example is cisplatin. However, cisplatin often causes major side effects for patients because it is highly cytotoxic (Mjos & Orvig, 2014). To lower this level of cytotoxicity, further research is being conducted on liposome nanoparticle formulations of cisplatin which appear to reduce serious reactions (Charest et al., 2013). Furthermore, the drug satraplatin, which is also a platinum-based anti-cancer drug, is especially attractive due to its pill form, which increases patient convenience and decreases cost (Bhargava & Vaishampayan, 2009).

Ruthenium Complexes

Since the 1990s, scientists have researched organometallic complexes of ruthenium for anticancer therapies. The advantage of these agents is their effectiveness against metastasis and potency against a diverse range of tumors (Bergamo & Sava, 2007). Furthermore, they have been shown to have reduced toxicity in comparison to platinum-based anti-cancer drugs (Lucaciu et al., 2022). These are still in clinical trials and have not been officially approved for use.

Medical Applications

Although the field has made several strides, it still pales in comparison to traditional medicinal development fields (Kabir et al., 2023). In practice, metallodrugs are still typically only used in the field of cancer treatment, such as for chemotherapy. However, there is much more potential for the usage of metallodrugs in areas such as antiviral therapeutics, antimicrobial therapeutics, and anti-inflammatory therapeutics (Kabir et al., 2023). Even when metallodrugs are used to treat cancer, they are much more useful through combination therapy, through which multiple drugs fight against cancer cells, making it difficult for them to fight back (Zimmerman et al., 2007).

Discussion

The literature highlights that metallodrugs have a bright future in medicine. The rising demand for new medications and therapies creates a perfect market for their entry.

Metallodrugs have become increasingly cost-effective. Due to a new technology developed at UCLA in 2023, metal catalysis can now be performed using common metals, such as copper, and oxygen. This cuts the price from $3,200 per gram down to $3 per gram, increasing the accessibility of metallodrugs as it becomes more feasible to produce and implement metallodrugs (Ober, 2023). This can make metallodrugs more accessible to many lower-income communities globally.

Furthermore, mechanochemistry has made the development of metallodrugs environmentally friendly. As materials are mechanically ground, there is no need for bulk dissolution of chemicals. Furthermore, it eliminates emissions, as chemical reactions can occur without excess heat, benefitting the environment (Bryce & Southern, 2021). This makes the production of metallodrugs environmentally sustainable.

In the status quo, metallodrugs are primarily utilized in cancer treatments, such as cisplatin, the first metallodrug to be put into clinical practice in the modern era (Mjos & Orvig, 2014). They are particularly unique because they provide nutrients and other uses not found in organic compounds traditionally used in medicine (Anthony et al., 2020). Although most metallodrugs are platinum-based, there has been an increase in research done regarding other bases, such as ruthenium complexes and arsenic, primarily for cancer treatment. Furthermore, although metallodrugs have a large scope for treatment outside of cancers, little research has been done exploring this. For example, one of the only prominent drugs developed was IQG-607, in response to new strands of tuberculosis which are resistant to the current drugs on the market and has shown promising results with no signs of cytotoxicity (Rodrigues-Junior et al., 2019). Thus, further investigation into these opportunities would prove beneficial in fighting various diseases. In the future, increasing research and investment into metallodrugs will prove to be beneficial. Already, the COST

program and the European Commission's funding of research into mechanochemistry is making strides in this space. Investigating further into other uses for metallodrugs and increasing research endeavors will help to bring more drugs out of clinical trials and into practice to benefit a larger number of people.

Limitations

A key limitation of this research is that most of the available research is focused on the United States and Europe, making this review Eurocentric and US-centric. Thus, it does not include information on metallodrug developments, research investments, and approved metallodrugs coming from other medically advanced countries outside of Europe and the United States.

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References

A. Southern, S., & L. Bryce, D. (2021). *Annual Reports on NMR Spectroscopy* (Vol. 102). Elsevier Inc.

Abbadi, B. L., Da Silva Rodrigues-Junior, V., Da Silva Dadda, A., Pissinate, K., Villela, A. D., Campos, M. M., De França Lopes, L. G., Bizarro, C. V., Machado, P., Sousa, E. H. S., & Basso, L. A. (2018). Is IQG-607 a Potential Metallodrug or Metallopro-Drug With a Defined Molecular Target in Mycobacterium tuberculosis? *Frontiers in Microbiology*, *9*. https://doi.org/10.3389/fmicb.2018.00880

André, V., Duarte, M. T., Gomes, C. S. B., & Sarraguça, M. C. (2021). Mechanochemistry in Portugal—A Step towards Sustainable Chemical Synthesis. *Molecules*, *27*(1), 241. https://doi.org/10.3390/molecules27010241

Anthony, E. J., Bolitho, E. M., Bridgewater, H. E., Carter, O. W. L., Donnelly, J. M., Imberti, C., Lant, E. C., Lermyte, F., Needham, R. J., Palau, M., Sadler, P. J., Shi, H., Wang, F., Zhang, W., & Zhang, Z. (2020). Metallodrugs are unique: opportunities and challenges of discovery and development. *Chemical Science*, *11*(48), 12888–12917. https://doi.org/10.1039/d0sc04082g

Bartholomä, M. D., Louie, A. S., Valliant, J. F., & Zubieta, J. (2010). Technetium and Gallium Derived Radiopharmaceuticals: Comparing and contrasting the chemistry of two important radiometals for the molecular imaging era. *Chemical Reviews*, *110*(5), 2903–2920. https://doi.org/10.1021/cr1000755

Basso, L. A., Schneider, C. Z., Santos, A. J. a. B. D., Santos, A. a. D., Jr, Campos, M. M., Souto, A. A., & Santos, D. S. (2010). An inorganic complex that inhibits Mycobacterium tuberculosis enoyl reductase as a prototype of a new class of chemotherapeutic agents to treat tuberculosis. *Journal of the Brazilian Chemical Society*, *21*(7), 1384–1389. https://doi.org/10.1590/s0103-50532010000700026

Bergamo, A., & Sava, G. (2007). Ruthenium complexes can target determinants of tumour malignancy. *Dalton Transactions*, *13*, 1267. https://doi.org/10.1039/b617769g

Bhargava, A., & Vaishampayan, U. N. (2009). Satraplatin: leading the new generation of oral platinum agents. *Expert Opinion on Investigational Drugs*, *18*(11), 1787–1797. https://doi.org/10.1517/13543780903362437

Charest, G., Sanche, L., Fortin, D., Mathieu, D., & Paquette, B. (2013). Optimization of the route of platinum drugs administration to optimize the concomitant treatment with radiotherapy for glioblastoma implanted in the Fischer rat brain. *Journal of neuro-oncology*, *115*, 365-373.

Chen, S., Zhou, G., Zhang, X., Mao, J., De Thé, H., & Chen, Z. (2011). From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. *Blood*, *117*(24), 6425–6437. https://doi.org/10.1182/blood-2010-11-283598

Do, J., & Friščić, T. (2016). Mechanochemistry: a force of synthesis. *ACS Central Science*, *3*(1), 13–19. https://doi.org/10.1021/acscentsci.6b00277

Eckford, C. (2023, February 16). European Commission awards €7.7 million to Mechanochemistry Project. *European Pharmaceutical Review*. https://www.europeanpharmaceuticalreview.com/news/179571/european-commission-awards-e7-7-million-to-mechanochemistry-project/

Frei, A., Zuegg, J., Elliott, A. G., Baker, M., Braese, S., Brown, C., Chen, F., G Dowson, C., Dujardin, G., Jung, N., King, A. P., Mansour, A. M., Massi, M., Moat, J., Mohamed, H. A., Renfrew, A. K., Rutledge, P. J., Sadler, P. J., Todd, M. H., Willans, C. E., … Blaskovich, M. A. T. (2020). Metal complexes as a promising source for new antibiotics. Chemical science, 11(10), 2627–2639. https://doi.org/10.1039/c9sc06460e

Hernández, J. G., Halasz, I., Crawford, D. E., Krupicka, M., Baláž, M., André, V., Vella-Zarb, L., Niidu, A., García, F., Maini, L., & Colacino, E. (2020). European Research in focus: Mechanochemistry for Sustainable Industry (COST Action MEchSUSTINd). *European Journal of Organic Chemistry*, *2020*(1), 8–9. https://doi.org/10.1002/ejoc.201901718

Imberti, C., Lok, J., Coverdale, J. P. C., Carter, O. W. L., Fry, M. E., Postings, M. L., Kim, J., Firth, G., Blower, P. J., & Sadler, P. J. (2023). Radiometal-Labeled Photoactivatable PT(IV) anticancer complex for theranostic phototherapy. *Inorganic Chemistry*, *62*(50), 20745–20753. https://doi.org/10.1021/acs.inorgchem.3c02245

IMPACTIVE. (2024, July 16). *Our project - IMPACTIVE*. IMPACTIVE - Mechanochemistry Towards Greener Pharmaceuticals. https://mechanochemistry.eu/our-project/

James, S. L., Adams, C. J., Bolm, C., Braga, D., Collier, P., Friščić, T., Grepioni, F., Harris, K. D. M., Hyett, G., Jones, W., Krebs, A., Mack, J., Maini, L., Orpen, A. G., Parkin, I. P., Shearouse, W. C., Steed, J. W., & Waddell, D. C. (2012). Mechanochemistry: opportunities for new and cleaner synthesis. *Chemical Society Reviews*, *41*(1), 413–447. https://doi.org/10.1039/c1cs15171a

Kabir, E., Noyon, M. K., & Hossain, M. A. (2023). Synthesis, biological and medicinal impacts of metallodrugs: A study. *Results in Chemistry*, *5*, 100935. https://doi.org/10.1016/j.rechem.2023.100935

Lucaciu, R. L., Hangan, A. C., Sevastre, B., & Oprean, L. S. (2022). Metallo-Drugs in cancer therapy: Past, present and future. *Molecules*, *27*(19), 6485. https://doi.org/10.3390/molecules27196485

Mjos, K. D., & Orvig, C. (2014). Metallodrugs in Medicinal Inorganic chemistry. *Chemical Reviews*, *114*(8), 4540–4563. https://doi.org/10.1021/cr400460s

Ober, H. (2023, November 22). UCLA chemists use oxygen, copper 'scissors' to make cheaper drug treatments possible. *UCLA*. https://newsroom.ucla.edu/releases/chemists-oxygen-copper-less-expensive-drug-treatments

Quaresma, S., André, V., Fernandes, A., & Duarte, M. T. (2016). Mechanochemistry – A green synthetic methodology leading to metallodrugs, metallopharmaceuticals and bio-inspired metal-organic frameworks. *Inorganica Chimica Acta*, *455*, 309–318. https://doi.org/10.1016/j.ica.2016.09.033

Rodrigues-Junior, V. S., Villela, A. D., Abbadi, B. L., Sperotto, N. D., Pissinate, K., Picada, J. N., Da Silva, J. B., Bizarro, C. V., Machado, P., & Basso, L. A. (2019). Nonclinical evaluation of IQG-607, an anti-tuberculosis candidate with potential use in combination drug therapy. *Regulatory Toxicology and Pharmacology*, *111*, 104553. https://doi.org/10.1016/j.yrtph.2019.104553

Santos, D. (2014). Activity of IQG-607, a new orally active compound in a murine model of Mycobacterium tuberculosis infection. *BMC Proceedings*, *8*(S4). https://doi.org/10.1186/1753-6561-8-s4-o8

Trento, C. (2023, December 27). *Advantages of Precious Metal Catalysts*. samaterials.com. https://www.samaterials.com/advantages-of-precious-metal-catalysts.html

Wagner, P. (2019). Metallodrugs and their various impacts on disorders and diseases. *Chemistry & Biochemistry Student Projects*. https://pillars.taylor.edu/chemistry-student/23

Zimmermann, G. R., Lehár, J., & Keith, C. T. (2006). Multi-target therapeutics: when the whole is greater than the sum of the parts. *Drug Discovery Today*, *12*(1–2), 34–42. https://doi.org/10.1016/j.drudis.2006.11.008