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Revisão

SILVER COMPLEXES FOR TUBERCULOSIS TREATMENT: A SHORT REVIEW

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This paper is a brief review of silver complexes that have been identified as antibacterial drugs with promising use for the treatment of tuberculosis (TB). This treatment aims to cure and discontinue the transmission of the disease. The excessive and inappropriate use of drugs has jeopardized the effectiveness of antibiotics for the TB treatment, bringing bacterial resistance to them. To achieve these objectives, the drugs used must be able to eliminate rapidly the bacterial population, avoiding the selection of drug-resistant strains and preventing its recurrence. The number of new cases of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) continues to rise. So, it is important to develop more research to introduce new drugs or improve existing ones, which can reduce the treatment time, increasing drug adherence and reducing MDR-TB and XDR-TB. The Ag(I) complexes were described with different types of ligands, and bonds to Ag(I) occur by N, O, P, and S atoms. Metal complexes are presented as options for anti-TB treatments. There are no cases of TB treatments using metal complexes but research in this area show that they could be used in the future to eradicate the bacteria that contaminate environments, surgical materials and other objects.

Keywords: *Mycobacterium tuberculosis*; silver(I) compounds; drugs.

INTRODUCTION

Tuberculosis (TB) is one of the ten leading causes of human deaths, the most lethal caused by a single infectious agent (above HIV/AIDS). This disease affects 1/3 of the world's population and approximately 10 million people develop TB each year, resulting in 2 million deaths.[1]

Although standard medical treatment with TB drugs is highly effective, more therapies are necessary to reduce the number of infectious cases. The number of new cases of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) continues to increase.[2] Understanding TB epidemiological profile is fundamental to reduce the time between the first symptoms, the diagnosis and the beginning of supervised medical treatments. It is also important to develop researches to introduce new drugs or improve the already existent, which can reduce the treatment time from 6 to 3 months, for example, therefore avoiding abandonment and increasing adherence, which prevent MDR-TB and XDR-TB.

While some initiatives against TB aim to eradicate social conditions that increase TB cases (such as extreme poverty, malnutrition and smoking), other actions seek to increase the population's immunity to the bacteria via Bacillus Calmette–Guérin (BCG) vaccine; there are also numerous efforts to eliminate *Mycobacterium tuberculosis* as cause of the active (and lethal) form of TB, creating new drugs for potential use. This paper also presents the state of the art in the research of metal complexes as possible drugs for treatment of TB.[1–3]

Drugs used in the treatment of TB

Standard treatment for TB consists of four first-line drugs: isoniazid, rifampicin, pyrazinamide and ethambutol, and resistance of bacilli can occur to all first-line drugs.[3] Tuberculosis treatment aims to cure (preventing its morbidity and mortality) and to discontinue the disease transmission (making patients noninfectious). To achieve these objectives, the drugs used should be capable of rapidly eliminating the bacterial population, preventing the selection of drug-resistant strains (consequently, the appearance of MDR-TB and XDR-TB) and sterilizing the lesion, preventing its recurrence.[4]

Since 1960, in the face of bacterial resistance and the increase in cases of TB deaths, the treatment regimen has been standardized and the current recommended treatment for cases of drug-susceptible TB is a six-month regimen with the four first-line drugs.[4] The structural formulas of these substances are shown in Figure 1.

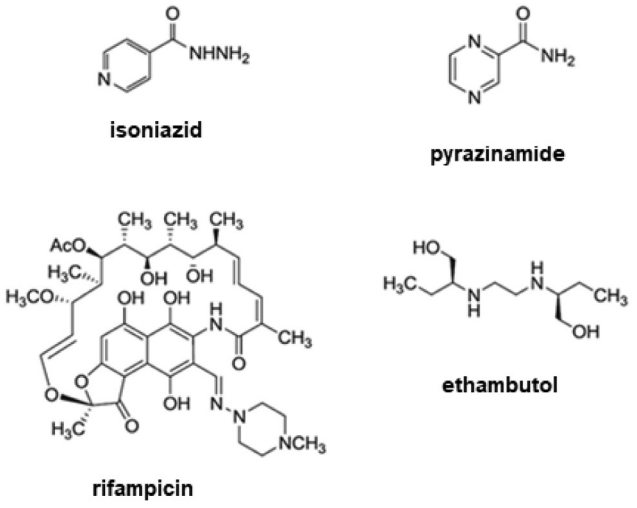

Figure 1. *Structural formulas of the most used substances for TB treatment*

The second-line drugs (Table 1) are used for the treatment of rifampicin-resistant TB and MDR-TB and can be classified as fluoroquinolones (Group A), aminoglycosides (Group B), other main agents (Group C) and additional agents (Group D).[5]

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Table 1. Classes of second line anti-TB drugs

Group	Classification	Drugs
Group A	fluoroquinolones	levofloxacin, moxifloxacin, gatifloxacin
Group B	aminoglycosides	amikacin, capreomycin, kanamycin, streptomycin
Group C	other important second-line agents	ethionamide / protionamide, cycloserine / terizidone, linezolid, clofazimine
Group D	additional agents	**D1:** pyrazinamide, ethambutol, high dose of isoniazid **D2:** bedaquiline, delamanid **D3:** para-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, thioketone

Drug resistance

The rapid emergence of resistant bacteria has jeopardized the effectiveness of antibiotics for TB treatment. The crisis of antibiotic resistance has been attributed to the excessive and inappropriate use of these drugs, as well as to the lack of development of new drugs by the pharmaceutical industry, due to the reduction of economic incentives and challenging regulatory requirements.[6]

Bacterial genes can be inherited or can be acquired from plasmids. Such horizontal gene transfer may allow the transfer of antibiotic resistance among different types of bacteria. Resistance can also appear through mutation. Antibiotics can remove drug-sensitive competitors, permitting resistant bacteria to reproduce as a result of a natural selection.[6]

Mycobacteria have some strategies for developing drug resistance. The main ones are: decreased permeability of the cell wall, increased efflux of the drug, degradation or inactivation of the drugs through enzymes and genetic modifications in the target of the drug. In *M. tuberculosis*, resistance is acquired only by chromosomal mutations and multiresistance occurs due to the accumulation of mutations in independent genes, which are each responsible for resistance to a particular antibiotic.[7]

Mycobacterium tuberculosis resistance types are classified as natural, initial, primary and acquired (or secondary). Natural resistance occurs with spontaneous mutation of bacilli; the initial one is observed in patients with some form of resistance to one or more drugs whose history of treatment is unknown; primary resistance occurs in patients infected with a resistant *M. tuberculosis* strain and the acquired or secondary occurs due to inadequate use of prescription drugs.[7]

Multidrug resistance

Treatment of multidrug-resistant TB is one of the greatest global challenges for TB control, especially rifampicin-resistant, isolated or combined with other drugs, as it is the most effective drug against *M. tuberculosis* bacillus. Schemes without rifampicin in its composition, either by resistance or intolerance, require the use of second-line drugs, which results in treatment with a longer duration, with great potential for toxicity and bad prognosis.[8]

As for drug-sensitive TB cases, the therapeutic regimen for MDR-TB should use at least four effective drugs (never used before or with a high likelihood of being sensitive), according to the rational drug classification, containing at least two essential drugs (bactericidal and sterilizing), plus two accompanying drugs (protective action against essential acquired resistance).[8]

In patients with rifampicin-resistant tuberculosis or MDR-TB, therapy with at least five anti-TB drugs during the intensive phase, including pyrazinamide and four second-line drugs (one from Group A, one from Group B and at least two from Group C) is recommended. If the minimum number of drugs against TB cannot be included in the treatment dose as indicated above, one agent of Group D2 and other agents of Group D3 can be added to reach the total of five (Table 2).[5]

SILVER USES

Silver and its silver(I) salts are considered toxic for humans as well to lower organisms. Many formulations included silver(I) compounds as drugs for certain medical treatments as antimicrobial and anticancer agents were used in the past century.[9]

The metal does not have biological role. On the contrary, it is considered highly toxic for living organisms depending on its concentration. Nevertheless, it is not a cumulative poison in the body, in a different way of other heavy metals. For some time now, Ag(I) complexes have been regarded as possible metallopharmaceuticals due to their biological properties. Several studies show the activities of silver against bacteria, fungi, parasites, cancers, and malaria.[9]

According to Medici *et al.*,[9] the efficacy of Ag(I) complexes against bacteria, primarily (the focus of this short review), depends on a number of factors: lipophilicity, redox propensity, water solubility and stability, and release rate of the Ag(I) ions. However, the authors comment that even if an Ag(I) complex is well-designed for medical use, its efficacy may decrease considerably when used *in vivo* because of formation of insoluble AgCl or binding of the complex to cellular enzymes.

A common approach for the syntheses of metal complexes—including Ag(I) complexes—is to associate the action of the metal center with that of a drug that is already in use or has already exhibited therapeutic properties against a certain disease. The intention is that the combination of metal and ligand will enhance the performance of the resulting complex, as is the case a number of Ag(I) silver complexes discussed in this article.

METHODOLOGY

This work is an integrative review of the literature, elaborated from the delimitation of the theme and the guiding question, formulation of objectives, definition of inclusion and exclusion criteria, identification, selection, categorization and evaluation of studies, interpretation of results and presentation of the known syntheses.[10]

Data collection occurred in December 2020 and was redone between 4th and 8th May 2021. Searches were performed on SciELO, PubMed, Google Scholar and Capes Portal de Periódicos, using the descriptors: “silver”, “tuberculosis”, “ethambutol”, “pyrazinamide”, “rifampicin”, “isoniazid” and “silver complex”.

As inclusion criteria for the selection of the studies of this integrative review, articles published between 2010 and 2020, in national and international journals, written in English, addressing the synthesis, characterization and *in vitro* biological analysis of Ag(I) complexes were reviewed. The following texts were excluded from the study: editorials, theses, dissertations, books, congress abstracts, review studies, articles that did not fit into the time frame or did not meet the proposed objective. Articles found in more than one database were considered only once.

The time frame from 2010 to 2020 is justified by the need to seek updated evidence on the subject in question. Systematic reviews found during the search procedure were not included in the presentation of results but were used to deepen the discussion of this study. Table 2

Table 2. Bibliographic search strategy

Search string	Databases	Search results
"silver" AND "tuberculosis" AND "ethambutol" "silver" AND "tuberculosis" AND "pyrazinamide" "silver" AND "tuberculosis" AND "rifampicin" "silver" AND "tuberculosis" AND "isoniazid" "silver complex" AND "tuberculosis"	PubMed	38 articles
	SciELO	8 articles
	Google Scholar	14,148 articles
	Capes Portal de Periódicos	1,661 articles
TOTAL		15,855 articles

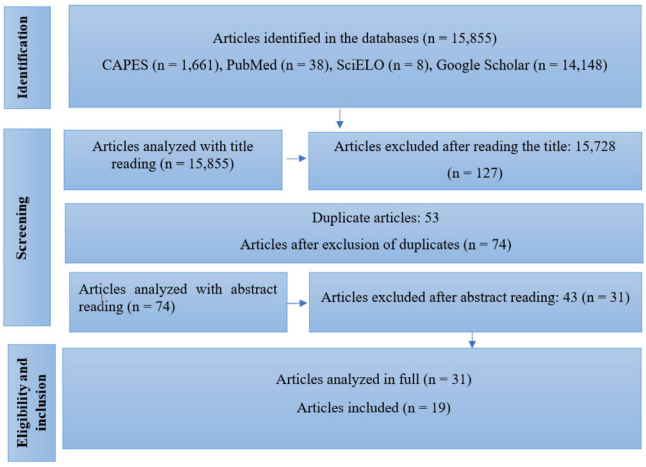

Figure 2. *Flowchart illustrating the study selection process according to the PRISMA recommendation*

shows bibliographic search strategy and Figure 2 shows flowchart illustrating the study selection process according to the PRISMA recommendation.[11]

The analysis process began with evaluation of the title, followed by the reading of the summaries of the publications in order to verify if they contemplated the research question and if they met the established inclusion criteria. After the preselection, the studies were read in their entirety in order to avoid selection bias. The final sample consisted of 19 selected articles.

To collect information relevant to the study, a literature review protocol was used, and an Excel software database was prepared with the information: author(s), year of publication, journal of publication, database, ligands and metal complexes.

The synthesis and critical analysis of the results are presented in the next section.

RESULTS AND DISCUSSION

The results of the search were analyzed and arranged in Table 3.

In a general way all 55 complexes described in the 19 articles are relatively easy to prepare, since experimental conditions are not special.

There are complexes where Ag(I) is coordinated to only one type of ligand (molecule or anion)[12–14,16,18–20,22,23,25,27–29] and complexes with mixed ligands.[15,17,21,24,26,30]

Ag(I) is coordinated preferentially to N-[12,14–20,22,23,26–28,30] and

Table 3. Results of the search

Title of the articles, authors, year of publication and reference	Ligands	Silver(I) complex	Anti-TB activity, MIC_{90} μg mL^{-1} (μmol L^{-1})
Pt(II) and Ag(I) complexes with acesulfame: crystal structure and a study of their antitumoral, antimicrobial and antiviral activities, Cavicchioli *et al.* (2010)[12]	acesulfame (ace), $C_4H_4KNO_4S$	$[Ag(C_4H_4NO_4S)]_n$	n/s (3.1)†
6-Mercaptopurine complexes with silver and gold ions: Anti-tuberculosis and anti-cancer activities, Cuin *et al.* (2011)[13]	6-mercaptopurine, $C_5H_4N_4S$	$(Ag[C_5H_3N_4S])\cdot H_2O$	25.0 (93.2)
A broad study of two new promising antimycobacterial drugs: Ag(I) and Au(I) complexes with 2-(2-thienyl) benzothiazole, Pereira *et al.* (2012)[14]	2-(2-thienyl)benzothiazole, $C_{11}H_7NS_2$	$[Ag(C_{11}H_7NS_2)_2NO_3]$	12.5 (20.7)
Synthesis, crystal structures, antimicrobial, antifungal and antituberculosis activities of mixed ligand silver(I) complexes, Altaf *et al.* (2013)[15]	(P1): triphenyl phosphine (P2): tricyclohexyl phosphine (P3): phenyldicyclohexyl phosphine (P4): diphenylcyclohexyl phosphine (P5): diphenyl(p-tolyl) phosphine (L1): thiosemicarbazide (L2): 2-(propan-2-ylidene) hydrazinecarbothioamide (L3): 4,5-dihydrothiazole-2-thiol (A) or thiazolidine-2-thione (B)	1 = $[Ag_2(P1)_2(L1)_4](NO_3)\cdot 2H_2O$ 2 = $[Ag_2(P1)_2(L3)_4](NO_3)_2$ 3 = $[Ag(P2)(L3)_2](NO_3)$ 4 = $[Ag(P2)(L1)_2]PF_6$ 5 = $[Ag(P3)_2(L2)]_2(NO_3)\}NO_3$ 6 = $[Ag_2(P2)_2(L3)_2](PF6)_2$ 7 = $[Ag_2(P4)_2(L2)_2](ClO_4)_2$ 8 = $[Ag(P5)_2(L2)(Br)]$ 9 = $[Ag_2(P1)_2(L2)_2](NO_3)_2$	1 = 10.2 (8.1) 2 = 15.6 (11.6) 3 = 10.6 (14.7) 4 = 10.6 (14.2) 5 = 12.5 (7.35) 6 = 7.8 (6.0) 7 = 12.5 (10.3) 8 = 12.5 (14.3) 9 = 10.2 (9.0)
Silver(I) complexes with symmetrical Schiff bases: Synthesis, structural characterization, DFT studies and antimycobacterial assays, Paiva *et al.* (2013)[16]	MBDA = *N*,*N*'-bis[(4-methoxyphenyl) methylidene]ethane-1,2-diamine, $C_{18}H_{20}N_2O_2$ MBDB = *N*,*N*'-bis[(4-methoxyphenyl) methylidene]propane-1,3-diamine, $C_{19}H_{22}N_2O_2$	AgMBDA = $[Ag(C_{18}H_{20}N_2O_2)_2]NO_3$ AgMBDB = $[Ag(C_{19}H_{22}N_2O_2)NO_3]\cdot ½H_2O$	AgMBDA = 21.2 (27.8) AgMBDB = 11.3 (23.5)
Synthesis and biological evaluation of ternary silver compounds bearing N,N-chelating ligands and thiourea: X-ray structure of $[\{Ag(bpy)(\mu\text{-tu})\}_2](NO_3)_2$ (bpy = 2,2′-bipyridine; tu = thiourea), Segura *et al.* (2014)[17]	phen = 1,10-phenanthroline bpy = 2,20-bipyridine tu = thiourea	1 = $[\{Ag(phen)(\mu\text{-tu})\}_2](NO_3)_2$ $C_{26}H_{24}Ag_2N_{10}O_6S_2$ 2 = $[\{Ag(phen)(\mu\text{-tu})\}_2](CF_3SO_3)_2$ $C_{28}H_{24}Ag_2F_6N_8O_6S_4$ 3 = $[\{Ag(bpy)(\mu\text{-tu})\}_2](NO_3)_2$ $C_{22}H_{24}Ag_2N_{10}O_6S2$	1 = 4.7 ± 0.4 (11.0 ± 1.0) 2 = 7.3 ± 1.4 (14.2 ± 2.8) 3 > 25

Table 3. Results of the search (cont.)

Title of the articles, authors, year of publication and reference	Ligands	Silver(I) complex	Anti-TB activity, MIC_{90} $\mu g\ mL^{-1}$ ($\mu mol\ L^{-1}$)
Coordinative versatility of a Schiff base containing thiophene: Synthesis, characterization and biological activity of zinc (II) and silver (I) complexes, Silva *et al.* (2014)[18]	ThioEn = *N*,*N*′-bis(thiophen-2-ylmethylene)ethane-1,2-diamine	1 = $[Ag(ThioEn)]NO_3$ 2 = $[Ag(ThioEn)_2]NO_3$	1 = 12.2 (29.2) 2 = 24.5 (36.7)
A silver complex with cycloserine: synthesis, spectroscopic characterization, crystal structure and *in vitro* biological studies, Ciol *et al.* (2018)[19]	cycloserine, $C_3H_6N_2O_2$	$[AgC_3H_5N_2O_2]$	16.5 ± 0.6 (79.1)
Silver(I) and zinc(II) complexes with symmetrical cinnamaldehyde Schiff base derivative: Spectroscopic, powder diffraction characterization, and antimycobacterial studies, Amaral *et al.* (2018)[20]	*N*,*N*′-bis(*trans*-cinnamaldehyde)ethane-1,2-diamine $C_{20}H_{20}N_2$	$[C_{20}H_{20}AgN_3O_3]$	10.4 (22.7)
Enhancement in anti-tubercular activity of indole based thiosemicarbazones on complexation with copper(I) and silver(I) halides: Structure elucidation, evaluation and molecular modelling, Khan *et al.* (2018)[21]	thiosemicarbazones (H^1L, H^2L, H^3L) + phosphine	13 = $[AgCl(\eta1\text{-}S\text{-}HIntsc)(Ph_3P)_2]$ 14 = $[AgBr(\eta1\text{-}S\text{-}HIntsc)(Ph_3P)_2]$ 15 = $[AgCl(\eta1\text{-}S\text{-}HIntsc\text{-}N1\text{-}Me)(Ph_3P)_2]$ 16 = $[AgBr(\eta1\text{-}S\text{-}HIntsc\text{-}N1\text{-}Me)(Ph_3P)_2]$ 17 = $[AgCl(\eta1\text{-}S\text{-}5\text{-}MeOHIntsc)(Ph_3P)_2]$ 18 = $[AgBr(\eta1\text{-}S\text{-}5\text{-}MeOHIntsc)(Ph_3P)_2]$	13 = 1.6 (n/s)†† 14 = 6.3 (n/s) 15 = 1.6 (n/s) 16 = 1.6 (n/s) 17 = 1.6 (n/s) 18 = 1.6 (n/s)
Synthesis and antimicrobial activity of a phenanthroline-isoniazid hybrid ligand and its Ag^+ and Mn^{2+} complexes, Ahmed *et al.* (2019)[22]	**L** = (Z)-*N*′-(6-oxo-1,10-phenanthrolin-5(6H)-ylidene)isonicotinohydrazide	1 = $[Ag(\mathbf{L})_2]NO_3{\cdot}2H_2O$ $[Ag(C_{18}H_{11}N_5O_2)_2]NO_3{\cdot}2H_2O$ 2 = $[Ag(\mathbf{L})_2]BF_4$ $[Ag(C_{18}H_{11}N_5O_2)_2]BF_4$	1 = 2.5 (2.9) 2 = 2.5 (2.9)
Silver complexes with fluoroanthranilic acid isomers: spectroscopic characterization, antimycobacterial activity and cytotoxic studies over a panel of tumor cells, Manzano *et al.* (2019)[23]	fluoroanthranilic acid $C_7H_6FNO_2$	$[Ag(C_7H_6FNO_2)_2]^+$ isomers (4fa, 5fa and 6fa)	Ag4fa = 2.6 ± 0.1 (9.8 ± 0.5) Ag5fa = 4.2 ± 2.2 (15.9 ± 8.6) Ag6fa = 2.6 ± 3.1 (9.8 ± 11.9)
Cytotoxic and apoptotic effects of ternary silver (I) complexes bearing 2-formylpyridine thiosemicarbazones and 1,10-phenanthroline, Silva *et al.* (2020)[24]	2-formylpyridine-N(4)-R-thiosemicarbazones (L) and 1,10-phenanthroline (phen)	1 = $[Ag(phen)(PHTSC)](NO_3){\cdot}HCl{\cdot}2H_2O$ $C_{19}H_{21}AgClN_7O_5S$ 2 = $[Ag(phen)(PMTSC)](NO_3){\cdot}HCl{\cdot}CH_3OH$ $C_{21}H_{23}AgClN_7O_4S$ 3 = $[Ag(phen)(PETSC)](NO_3){\cdot}HCl{\cdot}2H_2O$ $C_{21}H_{25}AgClN_7O_5S$	1 = 2.4 ± 0.4 (4.0 ± 0.6) 2 = 2.3 ± 0.3 (3.8 ± 0.5) 3 = 2.6 ± 0.2 (4.0 ± 0.4)
Copper(I) and silver(I) complexes of anthraldehyde thiosemicarbazone: Synthesis, structure elucidation, *in vitro* anti-tuberculosis/cytotoxicity activity and interactions with DNA/HSA, Khan *et al.* (2020)[25]	9-anthraldehyde thiosemicarbazone and phosphine	4 = $Ag_2(\mu_2\text{-}Cl)_2(\eta^1\text{-}S\text{-}9\text{-}Hanttsc)_2(Ph_3P)_2]$ $C_{68}H_{56}Cl_2Ag_2N_6P_2S_2$ 5 = $[Ag_2(\mu_2\text{-}Br)_2(\eta^1\text{-}S\text{-}9\text{-}Hanttsc)_2(Ph_3P)_2]$ $C_{68}H_{56}Br_2Ag_2N_6P_2S_2$ 9 = $[Ag_2Cl_2(\mu_2\text{-}S\text{-}9\text{-}Hanttsc\text{-}N^1\text{-}Me)_2(Ph_3P)_2]$ $C_{70}H_{60}Cl_2Ag_2N_6P_2S_2$ 10 = $Ag_2Br_2(\mu_2\text{-}S\text{-}9\text{-}Hanttsc\text{-}N^1\text{-}Me)_2(Ph_3P)_2]$ $C_{70}H_{60}Br_2Ag_2N_6P_2S_2$	4 = 1.6 (n/s)†† 5 = 1.6 (n/s) 9 = 12.5 (n/s) 10 = 12.5 (n/s)
(Amino)cyclophosphazenes as multisite ligands for the synthesis of antitumoral and antibacterial silver(I) complexes, Gascón *et al.* (2020)[26]	(amino)cyclophosphazenes and phosphine	2 = $[N_3P_3(NHCy)_6\{AgPPh_3\}_2](TfO)_2$ 3 = $[N_3P_3(NHCy)_6\{AgPPh3\}_3](TfO)_3$ 4 = $[N_3P_3(NHCy)_6\{AgPPh2Me\}_2](TfO)_2$ 5 = $[N_3P_3(NHCy)_6\{AgPPh2Me\}_3](TfO)_3$ 6 = $[N_3P_3(NHCy)_6\{AgTPA\}_3](TfO)_3$ 9 = $[N_3P_3(NHCy)_3(NMe_2)_3\{AgPPh_2Me\}_2](TfO)_2$ 10 = $[N_3P_3(NHCy)_3(NMe_2)_3\{AgPPh_2Me\}_3](TfO)_3$	2 = n/s (3.9)† 3 = n/s (0.97) 4 = n/s (3.9) 5 = n/s (3.9) 6 = n/s (3.9) 9 = n/s (3.9) 10 = n/s (3.9)
Antibacterial activities and antiproliferative assays over a tumor cells panel of a silver complex with 4-amino-benzoic acid: Studies *in vitro* of sustained release using bacterial cellulose membranes as support, Aquaroni *et al.* (2020)[27]	4-aminobenzoic acid, $C_7H_7NO_2$	$[Ag(C_7H_7NO_2)_2(NO_3)]$	12.7 (28.5 ± 6.6)
Synthesis, characterization, DFT modeling and *in vitro* antimycobacterial activity assays of a silver(I)-isoniazid complex, Paris Junior *et al.* (2021)[28]	isoniazid, $C_6H_7N_3O$	$[AgC_6H_7N_3O]NO_3$.	0.8 + 0.5 (2.6)
Chemical, spectroscopic characterization, molecular modeling and antibacterial activity assays of a silver (I) complex with succinic acid, Paris Junior *et al.* (2021)[29]	succinic acid, $C_4H_6O_4$	$Ag_2C_4H_4O_4$	n/s (23.9)†
Promising Ag(I) complexes with *N*-acylhydrazones from aromatic aldehydes and isoniazid against multidrug resistance in tuberculosis, Santos *et al.* (2021)[30]	*N*-acylhydrazones + isoniazid *	1 = AgIZSAL $[Ag(C_{13}H_{11}N_3O_2)_2(H_2O)]NO_3$ 2 = AgIZoVA $[Ag(C_{14}H_{13}N_3O_3)_2NO_3]{\cdot}H_2O$ 3 = AgIZmVA $[Ag(C_{14}H_{13}N_3O_3)]NO_3$ 4 = AgIZVAN $[Ag(C_{14}H_{13}N_3O_3)_2]NO_3$	1 = 11.56 ± 0.90 (17.24) 2 > 25 (> 34.23) 3 > 25 (> 56.67) 4 > 25 (> 35.09)

† The MIC_{90} values for these complexes were not specified in $\mu g\ mL^{-1}$ but in $\mu mol\ L^{-1}$ only. †† The MIC_{90} values for these complexes were not specified in $\mu mol\ L^{-1}$ but in $\mu g\ mL^{-1}$ only. n/s = not shown. * IZSAL = isoniazid with salicylaldehyde; IZoVA = isoniazid with o-vanillin; IZmVA = isoniazid with m-vanillin; IZVAN = isoniazid with vanillin. Antitubercular assays were performed against *M. tuberculosis* H37Rv strain.

O-atoms[12,18–20,23,24,29] of the ligands, and in a number of complexes to S-[13,15,17,21,24,25] and P-atoms[15,21,25,26] in the case of mixed ligands. In some cases, Ag(I) is coordinated to the halides Cl^- and Br^- [21,25] or NO_3^-.[14,22,27] This means that Ag(I) is an intermediate type of acid according to the Pearson acid-base concepts.

It is important to register that the majority of the substances used as ligands without activity against *M. tuberculosis* became active when complexed to Ag(I).[14,16–18,20–27,29] Four works show higher MIC_{90} values for the Ag-complexes than their respective ligands. This is the case for 6-mercaptopurine,[13] and the already

commercial drugs against TB: isoniazid[28] (and N-acylhydrazones + isoniazid)[30] and the second-line drug cycloserine.[19] Two works did not give the MIC_{90} values for the free ligands acesulfame[12] and tautomeric thiazolidine-2-thione.[15]

The first-line drug isoniazid appears as a ligand in one work but the MIC_{90} value of the complex is higher than the free drug.[28] In another work, isoniazid appears associated to phenanthroline forming a ligand that is a Schiff base.[12] A work published in 2021 presents four complexes containing isoniazid associated to *N*-acylhydrazones derivatives.[30]

Mechanisms of action of Ag(I) complexes related to *M. tuberculosis* are not well described in the literature but there are some evidences of interaction of some Ag(I) complexes with DNA. There are four possible mechanisms proposed for inhibition of bacteria growth by aqueous Ag(I) ions: (i) interference with the electron transport system, (ii) DNA-binding, (iii) interaction with the cell membrane,[12,13] and (iv) interaction with the thiol group in the vital enzymes to inactivate them.[15]

Considering the MIC_{90}, it can be concluded that a number of complexes have values that recommended them as antimicrobial agents in the future, because these Ag-complexes present lower MIC_{90} values than the second-line drugs such as ofloxacin, levofloxacin, and moxifloxacin.[30–32]

Table 4 highlights the MIC_{90} against *M. tuberculosis* of the drugs most commonly used in the fight against TB.

Table 4. Selected MIC_{90} of first- and second-line drugs against *M. tuberculosis* H37Rv strain

Substance	Average MIC_{90} and standard deviation (μg mL^{-1})	MIC_{90} (μmol L^{-1})
First line		
Isoniazid	< 0.098	0.715
Rifampicin	< 0.098	0.119
Ethambutol	1–2	n/s
Pyrazinamide	6–50	n/s
Second line		
Streptomycin	0.276 ± 0.091	0.475
Ofloxacin	0.382 ± 0.169	1.057
Amikacin	0.561 ± 0.165	0.958
Moxifloxacin	0.625 ± 0.024	1.557
Amoxicilin	16–32	n/s

MIC_{90} = Minimum concentration that inhibits 90% of bacterial growth. n/s = not shown. Adapted from Santos *et al.* (2021, p. 4),[30] Horita *et al.* (2014, p. 7011)[31] and Pyrazinamide (2008, p. 141-142).[32]

It is possible to list as the most effective Ag(I) complexes against *M. tuberculosis* the ones with two ligands, one of them being phosphine (PPh_3), in three works: Khan *et al.* (2018)[21] (5 complexes with MIC_{90} value 1.6 μg mL^{-1}), Khan *et al.*[25] (2 complexes with 1.6 μg mL^{-1}), and Gascón *et al.* [26] (1 complex with 2.2 μg mL^{-1}, 0.97 μmol L^{-1}). The complexes described by Silva *et al.*,[24] on the other hand, were synthesized with phenantroline and thiosemicarbazones (0.97–3.9 μmol L^{-1}). Exception to the complex by Massabni *et al.*[28] (0.8 μg mL^{-1}, 2.6 μmol L^{-1}) that used isoniazid as ligand but shows less effective results than the free ligand.

This review did not present articles that show research on silver nanoparticles against *M. tuberculosis* although the bactericidal effect of Ag nanoparticles has been well known.

CONCLUSIONS

Tuberculosis has been one of the deadliest diseases worldwide for ages. Anti-TB treatments have been efficient, but new drugs and alternative treatments are needed to reduce the number of people infected by this disease mainly because of the occurrence of multidrug resistant TB strains bacteria. The standard treatments basically use four first-line drugs: isoniazid, rifampicin, pyrazinamide and ethambutol. Despite the efficiency of these drugs, used since 1960, or their combination with other drugs, the cases of TB deaths continue to grow. Second-line drugs have also been used for the same reasons. This line includes drugs of the fluoroquinolones and aminoglycosides classes.

Metal complexes are presented as alternatives/options for anti-TB treatments. There are no cases of TB treatments using metal complexes but research in this area shows that they could be important and used in the future as adjuvants in eradicating the bacteria that contaminate environments and many surgical materials and objects. Silver is not considered an essential metal for living organisms. On the contrary, it is considered toxic, but many new complexes have been prepared and tested for use against diseases such as tuberculosis, cancer, leishmaniasis and others, and also to prevent contamination by bacteria in cases of severe burns.

In the present work, 19 articles were selected and 55 Ag-complexes that have proven to be efficient against the TB bacillus were analyzed. Many of them described synthesis and structural features involving Ag-complexes with various types of ligands. In general, the complexes showed greater efficiency than the organic molecules used as ligands.

There are suggestions for Ag(I) complex action by comparison with other metal ions, including Pt(II). The mechanisms of action are not well elucidated, but there are good prospects for further biological studies of the action of the complexes. So they can be used as drugs in the future for the treatment of TB, cancer and other diseases.

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