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REVIEW ARTICLE

A Review on Phytoconstituents and Metal Complexes for the Treatment of Tuberculosis

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Abstract

Tuberculosis (TB) is an infectious lung disease. Tiny droplets discharged into the air during cough and sneezes by an individual can transmit the bacteria that cause tuberculosis from one person to another. More than one million people die each year as a result of the communicable disease tuberculosis. Anti-TB allopathic drugs have been administered to treat the disease's symptoms; however, they can produce negative side effects such as hepatitis, hypersensitivity reactions, nausea, vomiting, etc. As a result of the toxicity and side effects of allopathic medicines, the use of herbal medicine is growing in popularity. Since ancient times, medicinal plants have been used to treat illnesses. Alkaloids, coumarins, flavonoids, polyphenols, terpenoids, quinines, and other secondary metabolites that have antibacterial activity are produced by plants and may be helpful in the treatment of tuberculosis. This review aims to explore the possible uses of medicinal herbs and metal complexes with antitubercular capabilities.

Keywords: Iron Complex, Metal Complex, Terpenes, Tuberculosis

1. Introduction

A type of bacteria called *Mycobacterium tuberculosis* (Mtb) is the cause of the contagious disease tuberculosis (TB). The lungs are typically the target of these bacteria's attacks, although they can also harm the kidney, spine, and brain. Through the air, TB can be transmitted from one person to another. The TB bacteria are released into the air when a patient with pulmonary TB coughs, sneezes, or spits. The majority of healthy people have an immune system that can get rid of the bacteria that cause TB[1]. Treatment for active TB has become extremely challenging due to the advent of Multi-Drug Resistant (MDR), Extended Drug-Resistant (XDR), and even completely Total Drug-Resistant (TDR) strains, which require meticulous and committed multi-drug therapy over a period of 6 to 30 months. Although it is improbable that a single stand-alone medicine would be effective against resistant TB strains, new medications and pharmacological combinations with novel mechanisms of action are urgently required. Researchers are looking for new antibacterial drugs to combat the spread of antibiotic resistance and the rise in infectious diseases caused by various pathogenic bacteria. New antimicrobial medications and nanotechnological materials need to be developed in order to treat infections caused by resistant bacteria. Metal- or metalloid-based medications have historically been prevalent in medicinal inorganic chemistry. Metal complexes are now a commonly utilised medicinal substance to treat a variety of ailments, having emerged as a new drug development strategy[2].

The structural organisation and enzyme activation, which take part in genetic information transmission from DNA are important functions of biological metal ions. Because of its numerous uses in fields ranging from biological to material sciences, complexes of transition metals have drawn the interest of comprising

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Metallo-organic, bio-inorganic, and inorganic chemists. For metal intoxication, some chelating agents have been created, such as technetium, rhenium, platinum, and gold, which can all be chelated with the help of water-soluble phosphine chelating agents. A large number of organic substances used in medicine do not work only in an organic manner; some are activated or bio-transformed by metal ions, such as metalloenzymes, while others have a direct or indirect impact on the metabolism of metal ions. These metal compounds' pharmacological properties are influenced by the metal ion, its ligands, and their structural characteristics. It is well known that some metal ions enter bacteria and deactivate their enzymes, while others produce hydrogen peroxide, which kills bacteria. For a physiologically active metal complex to transfer the metal to the active site, it must first possess a high enough degree of thermodynamic stability. It's crucial to consider the kinetics of any metal ion's ligation or delegation reactions[3]. Low-molecular-weight molecules that have a neutral charge and a small number of water-soluble substances are soluble in practically all media and can pass through cellular membranes passively. Due to a number of crucial factors, drug combinations have generally been shown to be a crucial component of antimicrobial therapy: (i) they increase activity by using substances with synergistic efficacy; (ii) they prevent medication resistance; (iii) they lower the dosages needed, lowering expense and the danger of harmful side effects; and (iv) they widen the range of activity. The iron porphyrin complex found in haemoglobin present in red blood cells is used by the body to transport and store oxygen. Magnesium porphyrins in chlorophyll make the photosynthetic activity possible in green plants. In biological systems, the transfer of alkyl groups from one molecule to another is accomplished by the cobalt-containing B12 coenzyme. Catalytic proteins (the metalloenzymes) are integrated with metals including copper, zinc, iron, and manganese, promoting a variety of chemical reactions necessary for life[4].

The simplicity of cleaving the connection between the ligand and the metal ion is solely responsible for a number of biological characteristics of metal-based drugs/ligands. It is known that a number of metal complexes speed up the drug's action and the effectiveness of the organic medicinal agent. Different ligands have various biological characteristics; the composition of the metal ions and the donor sequence of the ligands have a significant impact on the pharmacological action of metal complexes. The necessity of finding novel chemicals with antibacterial properties is widely acknowledged[5]. Compared to well-known classes of antibacterial medicines, the newly created compounds could be more potent and perhaps have a different mode of action for TB. Isonicotinic acid hydrazide (INH), a primary anti-TB medication with the increased therapeutic potential, has been evaluated for metal complexes of INH as antituberculosis agents have resulted in increased activity compared to the parent organic compound. The development of medicine has the potential to improve therapeutic outcomes and contribute to bacterial drug resistance. The imine group in Schiff bases has been employed for a wide range of biological activities. Schiff bases are created by reacting INH with a number of alkanols. These Schiff bases react with subsequent metal salts to produce Schiff base metal complexes. The medicinal efficacy of the compounds is anticipated to increase with increased lipophilicity of INH Schiff bases and their metal complexes. It suppresses immune function by reducing oxidative stress, and because the chemicals' therapeutic potential is increased by the Schiff bases metal complex, many clinically significant infections are now resistant to them[6,7].

2. Potential Anti-Tuberculosis Drugs from Nature

Due to the development of drug-resistant *Mycobacterium tuberculosis* strains and the association between tuberculosis and the human immunodeficiency virus, new antimycobacterial medications are being researched from nature-based sources to reduce the global burden of TB (AIDS). Plant species from Canada, South America, Europe, Africa, and Asia are supposedly said to have anti-TB properties. The following substances have been identified: ellagic acid, punicalagin, allicin, anthraquinone glycosides, iridoids, phenylpropanoids, beta-sitosterol, galanthamine, crinine, friedelin, ellagic acids, taraxerol, termilignan B, glucopyranosides, and 1-epicatechol.

Catechins also decrease the symptoms of TB found in green tea. Higher levels of catechins are found in patients with superoxide dismutase (SOD), an enzyme that prevents the dismutation process from producing hydrogen peroxide. Catechins work to prevent the generation of superoxide using superoxide anion as a scavenger. These

results imply that unprocessed extracts from green tea catechins may definitely be useful as adjuvant treatments for people with pulmonary TB. 1,7-bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione, also known as curcumin, is a phenolic substance. People have employed curcumin as a traditional treatment for many ailments for millennia. Curcumin has been shown in studies to have antimycobacterial properties. Although curcumin possesses anti-inflammatory, anticancer, and antioxidant properties, it is not lethal to healthy human cells. Despite being highly unstable and suffering from low bioavailability, these characteristics make curcumin a very alluring chemical compound to treat TB. Because it can cause macrophage cell death, curcumin has an anti-TB effect.

The phyto ingredient plume ricin, which comes from Bicolor P. known as Champa in India, is another antimycobacterial agent. Additionally, Bicolor P. farms in South Africa, the Philippines and Indonesia are also good anti-TB agents. With a MIC range of 1.3 to 2 µg/ml, plumericin outperformed the conventional medications rifampicin and isoniazid for MDR strains of *M. tuberculosis*. *Adoensis Vernonia Bip. Sch* is reportedly used as a natural treatment for tuberculosis by Indian traditional healers and in several African countries. *Vernonia saligna DC, Vernonia kotschyana Sch.Bip. ex Walp. and Vernonia cinerea (L.)* are the three *Vernonia* species that are used to treat tuberculosis. In Thailand, propolis and honey are common natural remedies for coughs and other ailments. Indian plants with *in vitro* antimycobacterial activity have been reported, include *Aegle marmelos* (L.) Correa, *A. paniculata* and *Ailanthus excelsa* Roxb, *Acacia catechu* (L.f.) Willd., and *Datura metel* L[8].

2.1 South American Anti-TB Plants

The largest South American source of natural anti-TB remedies is Brazil. Brazilian open-air markets sell the plants *Struthanthus marginatus Blume* and *Struthanthus concinnus Mart*, which are used to treat TB infections, 48 ethanolic crude extracts and fractions (hexane, dichloromethane, ethyl acetate, and n-butanol) from 10 Brazilian plants (Leguminosae, Monimiaceae, and Verbenaceae), one from Costa Rica, and one from Argentina were tested for anti-mycobacterial activity against *Mycobacterium tuberculosis*. Seven of the forty-eight plants tested were active, including *Lantana trifolia* (leaf extracts in hexane and dichloromethane), *Vitex cooperi* (bark extracts in methanol:water, 1:1), *Lippia lacunosa* (leaf extracts in hexane and dichloromethane), and *Lippia rotundifolia* (leaf extracts in hexane and dichloromethane)[9,10].

2.2 Anti-Tubercular Plants in Canada

The *Juniperus communis* and *Common juniper* are the most widely utilised medicinal herb by indigenous peoples in North America. Carpenter, *et al.,* reported mostly employing juniper as a tonic, in infusions, and to treat tuberculosis. Isolated from juniper's aerial portions, communic acid, isocupressic acid, and deoxy podophyllotoxin were all effective for *M. tuberculosis*. The antimycobacterial action of *J. communis* to two diterpenes called trans-communic acid and totarol as well as the sesquiterpene longifolene. The drug with the best *M. tuberculosis* activity was totarol. Totarol was also most effective against the 17 TB strains that were resistant to isoniazid, streptomycin, and moxifloxacin. The most effective drugs against rifampicin-resistant TB strains were longifolene and totarol. The *J. communis* plant's antimycobacterial terpenoids support its ethnomedicinal use as a traditional treatment for tuberculosis. Potentially effective natural remedies for TB and their antimycobacterial properties have been employed in various parts of the world and are discussed below. It might be possible to lessen or terminate the worldwide TB pandemic by transforming natural materials into new and more powerful TB medications and developing novel drugs[11].

2.3 Asia's Natural Anti-TB Medicines

One of the biggest tropical rainforests on earth is found in Indonesia. The Sundaland and Wallacea regions of Indonesia contain two of the top 25 biodiversity hotspots in the world. Most often known as Jamu, traditional herbal medicines are made from 10% of plant species that are thought to have some therapeutic properties. The following Indonesian Jamu plants have been used to treat TB symptoms: *Argyrospermum paniculatum* Nees, *Centella asiatica* (L.) Urb., *Caesalpinia sappan* L., *Brucea javanica* (L.) Merr., *Pluchea indica* Less., *Nasturtium indicum* DC., *Morinda citrifolia* L., *Lantana camara* L., *Hibiscus tiliaceus* L., *Vitex trifolia* L., *R. communis* and *Rhoeo spathacea* (Sw.) Stearn.

An anti-TB substance called ethyl p-methoxycinnamate was discovered in the rhizomes of *Kaempferia galanga L.,* which produces the essential oil. Clinical isolates of *M. tuberculosis* that are both drug-resistant and sensitive are inhibited by ethyl p-methoxycinnamate (MIC = 0.242-0.485 mM). The H37Rv and H37Ra strains of *M. tuberculosis* are inhibited by the *Vetiveria zizanioides Stapf* roots, a plant generally known in India as *Khas Khas, Khas, or Khus grass*. The strong antimycobacterial activity was generated by the ethanolic extract of roots; the MIC was 500 µg/ml. Additionally, the *M. tuberculosis* growth index was consistently decreased by the hexane fraction, MIC = 50 µg/ml.

A plant (L.) Schrad *Citrullus colocynthis* (Family Cucurbitaceae) is a traditional Indian herbal treatment for tuberculosis. Seven drug-resistant strains, eight MDRs and a single XDR among the 16 clinical *M. tuberculosis* isolates, were suppressed by fractions of *C. colocynthis*. Cucurbitacin E2-0-D-glucopyranoside and Ursolic acid, with MIC values of 50 and 25 µg/ml, respectively, were the two most active indicators against *M. tuberculosis* H37Rv, according to Mehta and co-workers. Other Indian plants with *in vitro* antimycobacterial activity were have been found, including *Ailanthus excelsa Roxb, A. paniculata, Aegle marmelos (L.) Correa, Acacia catechu (L.f.) Willd., and Datura metel L*[12].

3. Terpenes

The antimycobacterial activity of first-line tuberculosis medications was enhanced with terpenes, as reported by Sieniawska E., *et al.,* in 2018. Myrcene, sabinene, -pinene, (R)-limonene, (S)-limonene, and β-elemene natural terpenes were few to mention. Strong synergistic effects between the (S)- limonene and all of the antibiotics that were tested were seen (MICs for rifampicin were lowered from 16 µg/ml to 0.237 µg/ml, ethambutol was lowered from 16 µg/ml to 0.475 µg/ml, and isoniazid was lowered from 32 µg/ml to 0.475 µg/ml). Myrcene, (R)-limonene, -elemene, and sabinene combinations with TB led to lowered MIC values for ethambutol and rifampicin (ethambutol: from 3.9 µg/ml to 0.475 µg/ml; isoniazid: from 15 µg/ml to 0.475 µg/ml; and rifampicin). The entire investigation demonstrated that terpenes boosted the activity of anti-tuberculosis drugs[13,14].

4. Antitubercular Activity of Kaurene Derivative

A novel derivative of kaurene called caspicaiene was isolated by Ashaimaa Y. Moussa, *et al.,* in 2021 from a fungus culture of the strain Aspergillus N830 (Figure 1). Using the Alamar Blue Assay (MABA), the molecule demonstrated a promising anti-tubercular action in a dose-dependent manner, with a MIC value of 124.5 µM. In comparison to the positive control isoniazid MIC value was 0.24 µg/mL, six isolated known compounds demonstrated significant MIC values against *Mycobacterium tuberculosis*, ranging from 15.63 µg/mL to 125 µg/mL[15].

5. Review of Current Advances in the Development of Anti-tubercular Drugs

Although tuberculosis can be cured, the chances of this happening decrease as the disease develops multidrug resistance, and the situation worsens as the disease

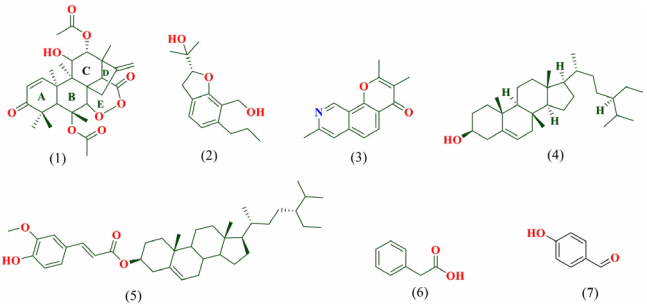


Figure 1. Chemical constituents of Aspergillus N8 30 isolate

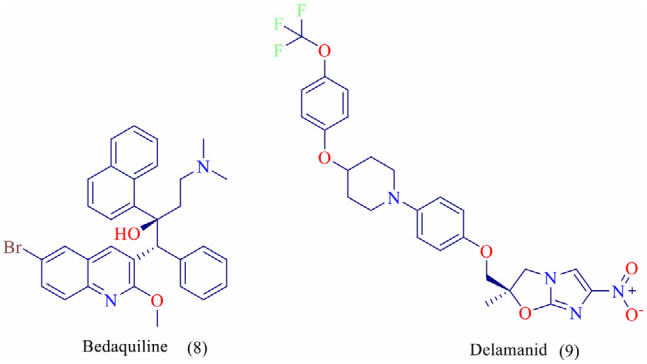


FIgure 2. Novel Anti-tubercular drugs

develops widespread drug resistance. There has been some encouraging news recently with the discovery of new treatments like bedaquiline and delamanid (Figure 2), as well as the discovery of new classes of anti-tubercular drugs, after almost five decades without any new TB drugs in the pipeline. Many older drugs that were not originally given for tuberculosis have been repurposed for the disease and are working effectively, including clofazimine, linezolid, and many more[16].

6. Flavones as Important Scaffolds for Anti-tubercular Activity

Flavones are benzo-γ-pyrone containing polyphenolic compounds that are mostly found in plants. The pigments that give flowers, fruits, and leaves their colours have been identified as flavonoids and they engage in a variety of biological processes. These flavonoids are secondary metabolites found in plants, and they can be divided into several groups according to their chemical structure, including flavanols, flavones, flavanones, isoflavones, anthocyanidins, aurones, and chalcones (Figure 3). Due to their extensive biological value and possible clinical applications, flavones are one of those that are becoming increasingly important. These flavones are frequently found in a wide range of herbs, fruits, and vegetables. Flavones continue to exhibit superb biological activity and play a significant role in drug discovery[17].

7. Metal-Based Drugs Used in the Market

Due to their widespread usage in the treatment and diagnosis of various illnesses, metal-based drugs and imaging substances have a significant function in medicine[18–22]. Before clinical evaluation, a known mode of action is currently essential, although during the initial stages of the development of metal-based drugs, these mechanisms are frequently disregarded[23–26]. The most well-known metal-based medications that have been approved for use in clinics, including cisplatin, oxaliplatin, carboplatin, and other anticancer Pt (II) complexes like auranofin, a gold-based arthritis medication, have extensive ligand exchange chemistry as one of their key characteristics. In short, the metal ion covalently bonds to vital macromolecules including proteins, enzymes, DNA, etc., blocking their function and causing cell death via several cellular pathways (e.g., apoptosis and necrosis). Because of the high concentration of chloride in blood following intravenous administration of cisplatin, the complex largely remains intact (i.e., with the formation of only trace amounts of the equivalent aqua ion). The complex goes through a process called aquation after entering

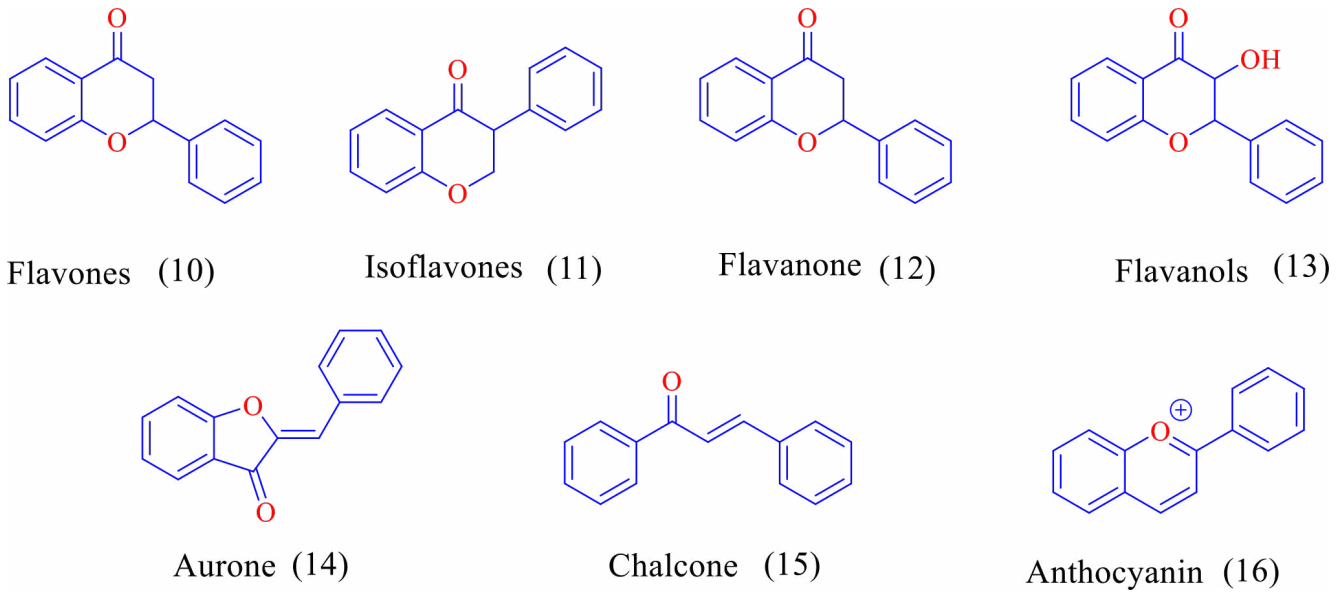


Figure 3. Various types of flavonoids

a cell, during which one or more of the chloroligands are switched out for molecules in water (as the chloride concentration inside a cell is much lower than in the blood)[27–31]. In order to prefer to bind to nuclear DNA at guanine's N7 position and cause primarily crosslinks within the strand, the newly produced Pt (II) species must first be activated. These crosslinks prevent DNA processing, which prevents replication and cell division[32,33]. The clinically approved drugs (cisplatin, carboplatin, oxaliplatin, auranofin, pentecostal), clinical trial-stage drug candidates (BMOV, staraplatin, NAMI-A, KP1339, ferroquine etc.)[34–36].

7.1 Copper Complex

Copper helps to neutralise free radicals, which can severely harm cells and boost the immune system to fight infections, prevent blood clotting, mend damaged tissues, and promote healing. Directly, as cofactors like cobalamins, the porphyrins or in groups that are furthermore bound to proteins[37]. Iron and copper proteins take part in many of the same biological processes.

- Dioxygen is bound reversibly by substances such as hemerythrin (Fe), haemoglobin (Fe), and hemocyanin (Cu);
- Dioxygen activation, such as hydroxylase dopamine (Cu), tyrosinases (Cu), and catechol dioxygenases (Fe) (essential in the synthesis of the hormone adrenaline);
- Electron transport, as demonstrated by c-type cytochromes (Fe), ferredoxins, and plastocyanin's (Cu);

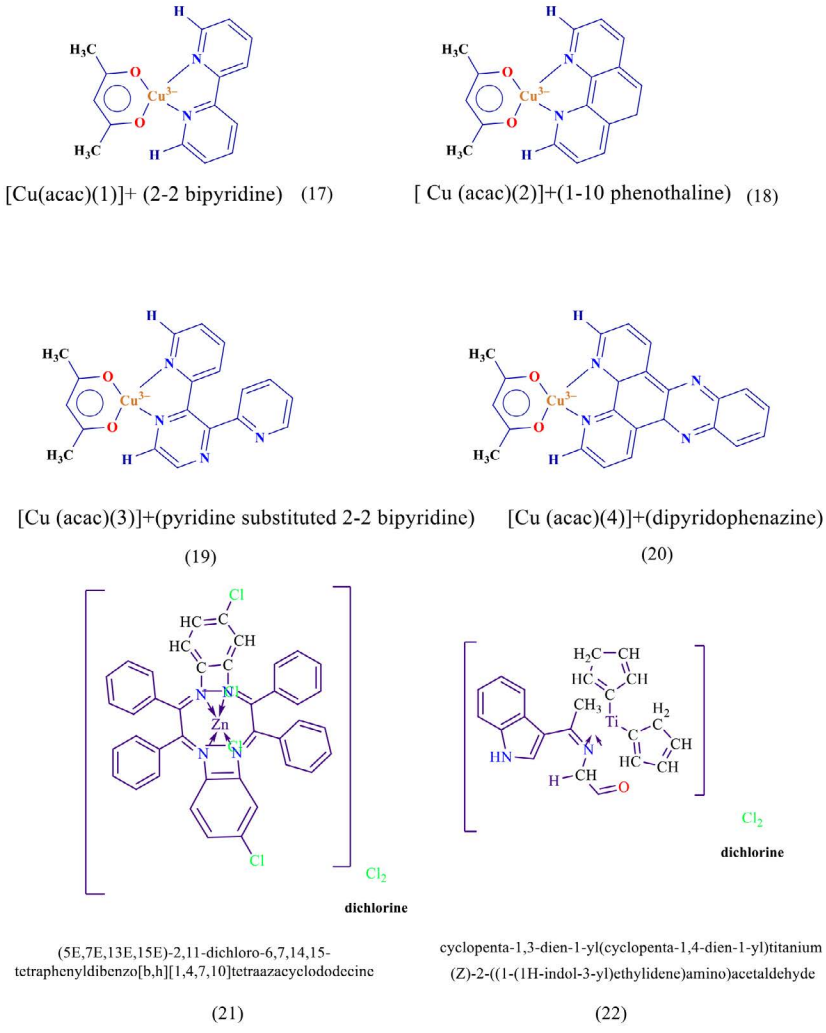


Figure 4. Metal complex structures possessing anti TB activity

- Superoxide dismutation by the redox-active metals Cu or Fe (superoxide dismutase)[38–40].

In 2016, Barbosa, *et al.,* assessed the *in vitro* effectiveness of copper-based drugs against resistant and susceptible *Mycobacterium tuberculosis,* whether used alone or in combination with isoniazid (INH), rifampicin, or ethambutol (EMB). 17 clinical *M. tuberculosis* isolates were tested for minimal inhibitory concentration using the resazurin microtiter assay and combination evaluation using the resazurin drug combination microtiter assay (5 multi-drug resistances and 2 resistants to EMB and/or INH). MIC values ranging between 0.78 to 12.50 µg/mL, casiopenas (Figure 4) had a strong impact against resistant isolates. Furthermore, both resistant and susceptible clinical isolates exhibit a synergistic impact, primarily with EMB[41].

7.2 Titanium Complex

Belwal S. in 2019 reported a titanium complex using an aqueous extract of horse gram and green chemistry to reduce macro-sized titanium and zinc compounds to nano-sized ones. The nanoparticles of biosynthesized metal nanoparticles were characterised using Ultraviolet-Visible (UV-Vis) and Fourier-Transform Infrared (FTIR) spectrophotometers. The reduced nanoparticles of the metals Ti and Zn were examined using Transmission Electron Microscopy (TEM). To ascertain *in vitro* characteristics, such as the impact of nanocomplex antimicrobials on the *Mycobacterium tuberculosis* (MTB) $H_{37}R_V$ strain, microdilution was used. First-line medications were not effective against MTB strains isolated from multidrug-resistant tuberculosis patients (MDR-TB). The novel nanocomplexes that were created showed potential antituberculosis properties. In comparison to zinc nanocomplexes, titanium nanocomplexes showed the greatest Minimum Inhibitory Concentration (MIC). In addition, Ti and Zn nanocomplexes were shown to have an IC_{50} of 1000µg/mL in a cytotoxic investigation, compared to isoniazid, they are non-toxic. The antituberculosis activity of Zn and Ti nanocomplexes (Figure 4) against MTB, H37RV, and MDR-TB strains was assessed using MIC, Light Emitting Diode-Fluorescence Microscopy (LED-FM), staining with Ziehl-Neelsen (ZN) and biochemical assays. Compared to the Ti nanocomplex, the Zn nanocomplex has better anti-MTB performance[42].

7.3 Ruthenium Complex

One of the rarest metals on earth is ruthenium. Because of its low toxicity, ruthenium medications can be explored in the medical field. It is commonly found in the minerals pentlandite and pyroxenite, along with other platinum metals. The effectiveness of nine polypyridyl-ruthenium (II) complexes (Figure 5) to suppress *Mycobacterium tuberculosis* was examined. The N-ligands, which included 14 2,20-bipyridines, 2,20-60,20-terpyridines, and di-alkyloxy-2,20-6,2-bipyridine-3,30-dicarboxylates (MTB), demonstrated outstanding efficacy against MBT. Unlike other chloro and acetonitrile derivatives, the compound aquo ligand, appears to be crucial to the antitubercular effectiveness of this novel group of metal-based substances. Researchers described an effective metal-based antitubercular drug that has Ru-OH_2 coordination, highlighting the significant role that a metal moiety plays in the cooperation between bioactive molecules to metal. The National Cancer Institute (NCI) is conducting testing for HIV and antitumor antibodies on complex 11, which will aid us in clarifying the connections between redox potential and activity. These polypyridine ligands' *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv, as well as that of their ruthenium complexes, were less effective than isoniazid's. Additionally, the free N and N-ligands A–E exhibited either minimal or no action (0–39 % inhibition). However, none of the compounds demonstrated efficacy against *M. tuberculosis* H37Rv, indicating that the compounds lack any specific anti-tubercular activity. This may be a result of their limited absorption (MIC.6.25 mg/mL against *M. tuberculosis*)[43].

7.4 Iron Complex

Ribonucleotide reduction (DNA synthesis), oxygenation, nitrogen reduction, energy production (respiration), and energy conversion (photosynthesis) are only a few of the processes in which iron is involved in helping terrestrial organisms live. The maintenance of plant, animal, and human life spans depends on metal ions, an essential element. Most broad and important transition metals that have functional iron-containing proteins take part in two key processes in living systems: oxygen transport and electron transfer.

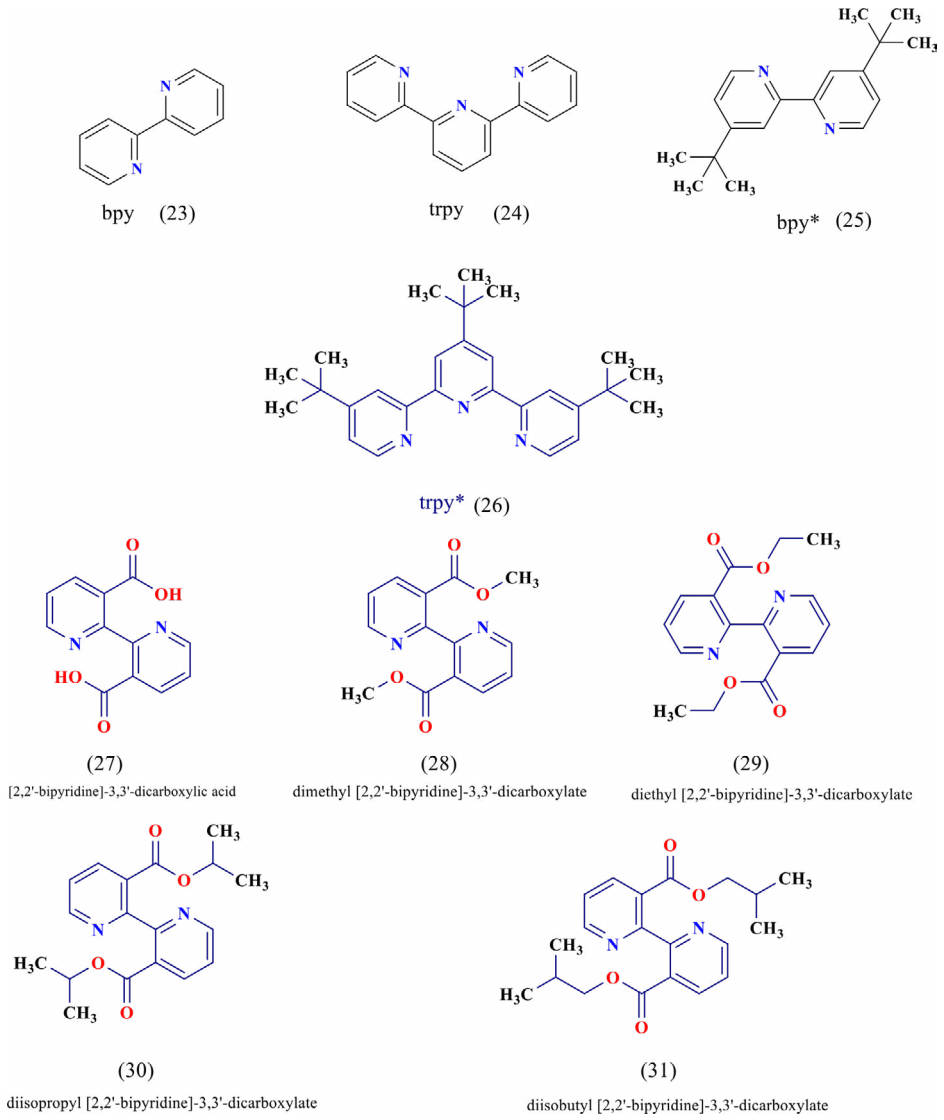
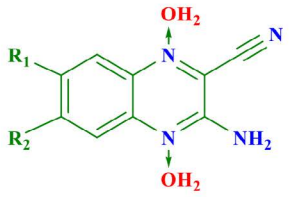


Figure 5. Structure of tested polypyridines compounds

In 2016, Singh, *et al.*,[44] reported testing *Mycobacterium tuberculosis* and *M. bovis* BCG with silver (AgNPs), gold (AuNPs), and gold-silver bimetallic (Au-AgNPs) nanoparticles made from medicinal plants such as *Barleria prionitis, Plumbago zeylanica, and Syzygium cumini*. AgNPs were the next most effective antitubercular agent, having a MIC of 2.56 µg /mL, after Au-AgNPs. It was discovered that the Au-AgNPs made from *S. cumini* were more selective for mycobacteria, with a selectivity index ranging from 94 to 108[45]. In 2010, Tarallo, *et al.*, reported two new iron complexes, [Fe(L-H)3], with 3-aminoquinoxaline-2-carbonitrile N1, N4-dioxide derivatives (L) as ligands (Figure 6). The new compounds exhibited *in vitro* growth inhibition efficacy against *Mycobacterium TB H37Rv* (ATCC 27294) as well as very modest unspecific cytotoxicity against eukaryotic cells (cultured murine cell line J774). Compared to the "second-line" treatment medicines, both complexes had greater inhibitory effects on *M. tuberculosis*[45].

7.5 Metal Hydroxyquinoline Complexes

In comparison to products based on metal salts, the novel metal complexes containing hydroxyquinoline (HQ) and its derivatives (Figures 7, 8 and 9) have superior therapeutic effects. Despite this, the complexes have poor water solubility, which results in reduced metal bioavailability following drug administration. HQ or its derivatives are frequently employed to change the physicochemical properties of metal complexes



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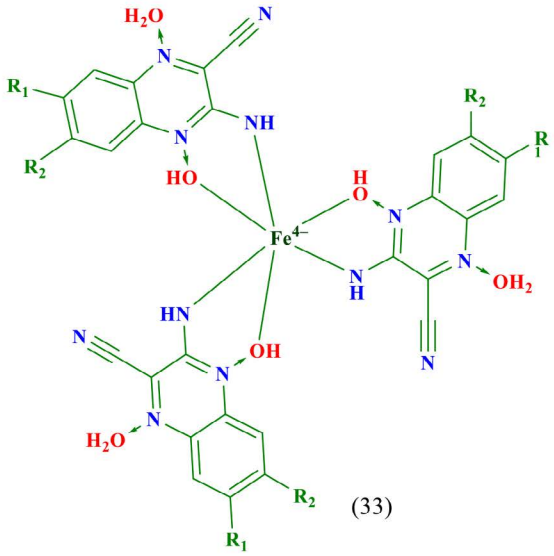
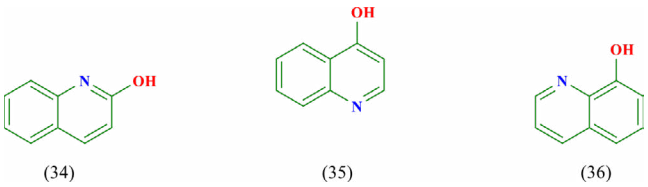


(33)

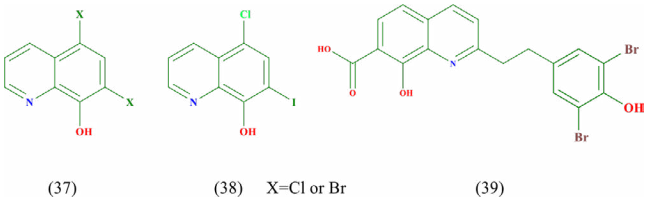
R_1=H R_2=H L1 R_1=H R_2=CH_3 L2 R_1=Cl R2=OCH_3 L3 R_1=H R2=CF3 L4

Figure 6. Scheme showing the structure of the selected ligands (L) and the proposed structure for the iron (III) complexed [Fe(L-H)3]. Selected ligands: L:L1=3-aminoquinoxaline-2-carbonitrile N1, N4-dioxide, L2=3-amino-6(7)-methylquinoxaline-2-carbonitrile N1, N4-dioxide, L3= 3-amino-6(7)-chloro-7(6)-methoxyquinoxaline-2-carbonitrile N1, N4-dioxide and L4= 3-amino-6(7)-trifluoromethylquinoxaline-2-carbonitrile N1, N4-dioxide.



(34) (35) (36)

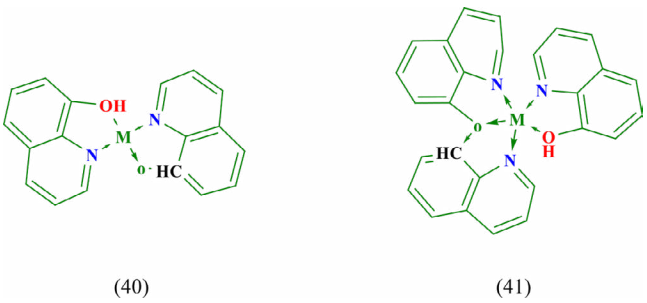
Figure 7. Structures of 2-hydroxy (34), 4-hydroxy(35), and 8-hydroxyquinoline(36)



(37) (38) X=Cl or Br (39)

Figure 8. Structures of halogen derivatives of 8-Hydroxyquinoline, clioquinol(38) and poly hydroxylatedstyrryl quinolones(39)

using liposome-based, polymeric, nanoparticle-based, and cyclodextrin-based carriers (CDs), etc. Compared to the medicines that are already on the market, the new products will be more effective and less toxic treatments for neurodegenerative, cancer, antioxidant, and bacterial diseases[46].



(40) (41)

Figure 9. Structures of four(40) and six covalent(41) complexed of 8-Hydroxyquinolines

8. Conclusions

In underdeveloped and developing nations, tuberculosis continues to be an international health issue. Though there has been a minor decline in trend over the past few years, TB still claims millions of lives worldwide despite systematic efforts and initiatives from international organisations and governments. Due to the rise of *M. tuberculosis* drug-resistant strains, several medicines that have been released onto the market have turned out to be ineffective. The majority of both first- and second-line TB drugs are ineffective in treating extensively drug-resistant (XDR), multidrug-resistant

(MDR), and Totally Drug Resistant (TDR) TB strains. As a result, these strains are particularly challenging to treat. Additionally, using synthetic medications too frequently can result in a variety of negative effects. As a result, there is a growing global interest in plant-based medications because they have less or no negative impacts on human health. In this review paper phytoconstituents and metal complexes with antimycobacterial properties have been chosen and assembled. This review's objective is to provide a scholarly overview of the use of medicinal plants and metal complexes in the treatment of tuberculosis.

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