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FRONTIERS IN CHEMICAL AND LIFE SCIENCES



ISSN: (3065- 4238)

<https://multisciajournals.com/journals/index.php/fcls>
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A Comparative Study of Antimicrobial Screening of Copper and Nickel Salophen Complexes

Dr.R.Jeevi Esther Rathnakumari

*Associate Professor of Chemistry,
Nazareth Margoschis College At Pillaiyanmanai,
Nazareth 628617, Tamil Nadu,
Affiliated to Manonmaniam Sundaranar University,
Tirunelveli, Tamil Nadu, India – 627 012.*

Article Info

Received: 1-03-2026

Revised:20-03-2026

Accepted:10-04-2026

Published:23-05-2026

Abstract

The emergence of multidrug-resistant microorganisms has created an urgent demand for the development of novel antimicrobial agents with enhanced biological efficacy. In the present investigation, Copper and Nickel salophen complexes derived from the Schiff base ligand N,N'-bis(salicylidene)-1,2-phenylenediamine were synthesized, characterized, and evaluated for their antimicrobial potential against selected pathogenic microorganisms. The salophen ligand was synthesized through the condensation of salicylaldehyde and 1,2-phenylenediamine in ethanolic medium, followed by complexation with Copper(II) sulfate and Nickel(II) sulfate to obtain the corresponding metal complexes. Structural characterization of the synthesized ligand and complexes was carried out using FT-IR and ESI-mass spectral analyses. FT-IR spectral data revealed characteristic azomethine $\nu(\text{C}=\text{N})$ stretching vibrations in the range of $1601\text{--}1620\text{ cm}^{-1}$, confirming Schiff base formation and coordination of azomethine nitrogen atoms with the metal ions. ESI-mass spectra further confirmed the molecular masses of the synthesized Copper and Nickel salophen complexes. The antimicrobial activity of the complexes was evaluated by agar well diffusion method against Gram-positive bacteria (*Staphylococcus* spp. and *Enterococcus* spp.), Gram-negative bacteria (*Klebsiella* spp. and *Escherichia coli*), and fungal species (*Aspergillus* spp.). The Copper salophen

complex demonstrated moderate antibacterial activity against *Enterococcus* spp. with a zone of inhibition of 15 mm, whereas the salophen ligand exhibited 12 mm inhibition. Nickel salophen complex did not show significant antibacterial activity against the tested microorganisms. Antifungal studies revealed slight inhibitory activity of Copper salophen complex against *Aspergillus* spp. with a 4 mm zone of inhibition.

The enhanced biological activity of the Copper complex was attributed to chelation effects, increased lipophilicity, and improved penetration through microbial cell membranes according to Overtones concept and Tweedy's chelation theory. The study concludes that Copper salophen complexes possess promising antimicrobial potential and may serve as effective candidates for the development of future metal-based therapeutic agents against resistant microbial pathogens.

Keywords: Salophen Complexes , Schiff Base Ligands , Antimicrobial Activity , Copper Complexes ,Metal Chelation Theory.

1. Introduction

Metal Salophen Complexes

N,N'-bis(salicylidene)-1,2-phenylenediamine (salophen), one of the most popular symmetrical tetradentate ligands analogue to salen, forms complex with transition and main group metals. These metal-salophen (salen) complexes find extensive applications in catalysis and used as sensor and drug [1,2]. Salophen ligands are regarded as privileged ligands, which readily combine with vanadium salts to form oxovanadium complexes which show binding properties with proteins. A special interest in this family of complex grew rapidly in the 1990s when the group of Jacobsen and Katsuki discovered the

enantioselective epoxidation of unfunctionalised alkenes by chiral Mn(salen) complexes. In continuation, interest in the chemistry of transition metal complexes incorporating Schiff base ligands particularly salen type ligand has been accelerated during the last two decades due to the discovery of their enzyme mimetic catalytic properties [3,4].

In their dianionic form, salophen/salen ligands possess two covalent and two coordinative binding sites located in a planar array. This arrangement allows the equatorial coordination of transition metals. Metal salen and salophen complexes display a square planar geometry with the metal ion in the plane formed by the N₂O₂-donor atoms. The

two axial positions are available for coordinating solvent molecules or other guests endowed with donating groups. Majority of metal-salophen complexes can be described as immobilized Lewis acid able to coordinate with Lewis bases by accommodating them in the apical positions. These features make them very similar to porphyrins, but it is obvious that their synthetic accessibility is much greater [5]. It is well known that salen/salophen ligands are able to stabilize many metals in various oxidation states, controlling the performance of the metals in a large variety of useful catalytic transformations. These include oxidation of hydrocarbons, alcohols, heteroatom containing organic compounds, aziridination of alkenes, Diels-Alder reactions, hydrolytic resolution of epoxides and alkylation of aldehydes.

Metal complexes of salen and salophen ligands have been used in medicinal studies. Lanthanide-salophen complexes have the capability to bind with neutral sugars and lipids and are used for the treatment of pathological conditions including ovarian cancer [6]. Recently, it has been shown that iron(III)-salophen is a potent growth suppressing agent *in vitro* for cell lines derived from

ovarian cancer and a potential therapeutic drug for the treatment of such tumors *in vivo* [7].

Antimicrobial Studies

In man, the highest concentration of nickel is found in the nucleic acids, especially in the RNA and DNA, and is thought to be somehow involved in protein structure or function. It activates enzymic reactions that lead to the breakdown or utilization of glucose. Nickel improves prolactin production, hence, it aids human breast milk production. Nickel improves iron absorption and bone strength, enhances adrenaline, glucose metabolism, hormones, lipid, cell membrane and may also be involved in production of red blood cells. It probably has a role in stabilizing RNA structure. Divalent nickel coordinates with Glyoxalase I enzyme and assist in the breakdown of to methylglycol lactate and water. Acireductone dioxygenase, an octahedral high spin Ni(II) complex catalyses the peroxo intermediate that decomposes to CO, formic acid and a carboxylic acid. Nickel superoxide dismutase (Ni-SOD) is a Metalloenzyme that protects cells from oxidative damage by catalyzing the disproportionation of the cytotoxic

superoxide radical to hydrogen peroxide and molecular oxygen.

Increase in death rate related to infectious diseases, is directly linked to the bacteria that have multiple resistances to antibiotics. The shortage of efficient antimicrobial agents is the main cause of this problem. Recent research focuses more on the synthesis of complexes of nickel with ligands, as a result of the biological properties. The synthesis of latest antibacterial agents, through various methods, is, for sure, an emergency medical issue. The discovery of latest nickel based drugs has been largely supported on ability of nickel to increase inhibitory potential of chemotherapy agents. Efficacy of some therapeutic agents has been reported to have increased upon coordination. The development of more potent nickel based drugs has been under investigations over the last three decades, and it has been discovered that chelates of nickel have enormous impact in medicine.

An antimicrobial agent is an agent that kills microorganisms or inhibits their growth [8]. The term antimicrobial is collective for antiviral, antibacterial, antifungal and antiprotozoal. Antimicrobial medicines can be grouped

according to the microorganism they primarily act against *viz.* antibiotics are used against bacteria and antifungals are used against fungi. Many antimicrobial agents exist, for use against a wide range of infectious diseases.

After the revolution in the golden era, when almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides) were discovered, these exciting compounds are now in danger of losing their efficacy because of the increase in microbial resistance [9]. Due to the rapid development of microorganism's resistance to antimicrobial agents, it is necessary to discover new antimicrobial agents, natural and synthetic to help in the battle against pathogenic microorganisms. In the recent years, there has been a growing interest in research for developing new antimicrobial agents from various sources to combat microbial resistance. Therefore, a greater attention has been paid to antimicrobial activity screening and evaluating methods. Antimicrobial susceptibility testing can be used for drug discovery, epidemiology and prediction of therapeutic outcome.

Transition metal complexes containing Schiff bases have been of

much interest over the past few years, largely because of their various applications in biological processes and potential applications in designing new therapeutic agents. They exhibit a broad range of biological activities such as antifungal, antibacterial, antimalarial, antiproliferative, antiinflammatory, antiviral and antipyretic properties [10]. The coordination chemistry of copper complexes has greater significance owing to their pronounced catalytic, industrial and immense pharmacological activities [11-19]. Literature reports show that metal salts do not exhibit antimicrobial activity but complexation leads to significant activity [20,21].

2. Scope and Objective

Microbial infection is a growing problem in contemporary medicine, and the use of antibiotics is inevitable. Development of resistance to antibiotics has become a major problem in recent years. Thus the treatment of bacterial infections remains a challenging therapeutic problem. As a biocompatible element, Copper and Nickel have a wide variety of biochemical and physiological functions. Biological activity of synthetic compounds for potential antimicrobial activity continues to be an important

strategy for the identification of new drugs. Hence, in this report the Copper and Nickel salophen complexes have been synthesized, characterized and the screening of these salophen complexes for its antimicrobial properties against human pathogens isolated from clinical specimens has been discussed.

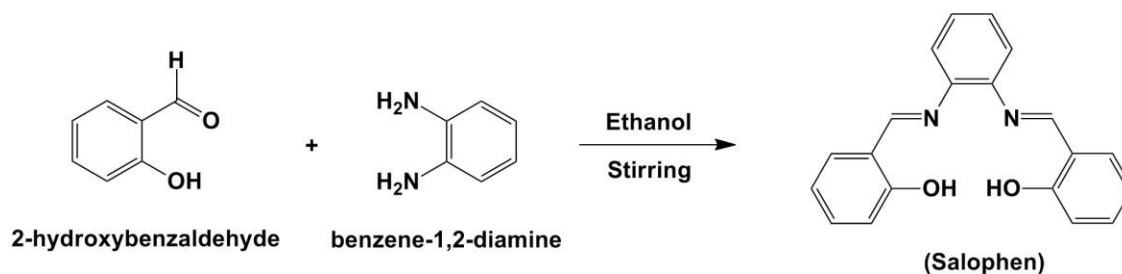
3. Synthesis of Copper and Nickel Salophen Complexes

3.1. Preparation of Salophen ligand

The salophen ligand required for the preparation of the Copper and Nickel salophen complexes were synthesized using established procedures with a slight modification [22]. The general procedure for the preparation of salophen ligand involves the condensation of salicylaldehyde and 1,2-benzenediamine in the ratio of 2:1 in an alcoholic medium.

Two equivalents of salicylaldehyde were dissolved in a minimum volume of boiling ethanol (20 mL) and it was added drop wise to one equivalent of 1,2-benzenediamine in 5 mL ethanol. The solution was stirred for one hour and then cooled to room temperature. The yellow solid thus obtained was filtered at the pump, washed with ethanol, diethyl ether and dried in air. The ligand was

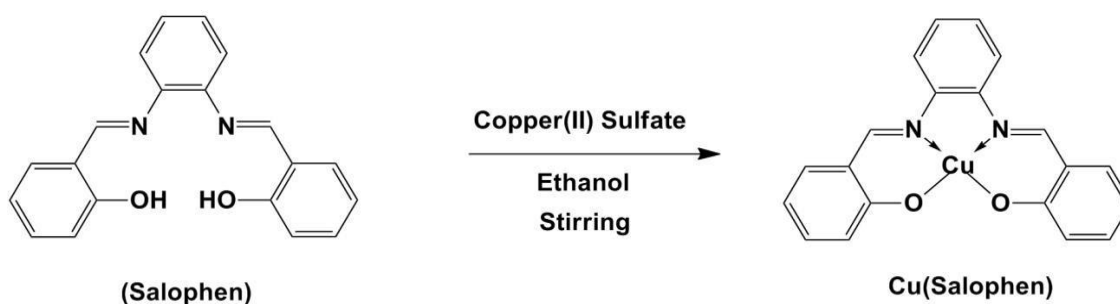
recrystallized from ethanol and chloroform in 1:3 ratio.

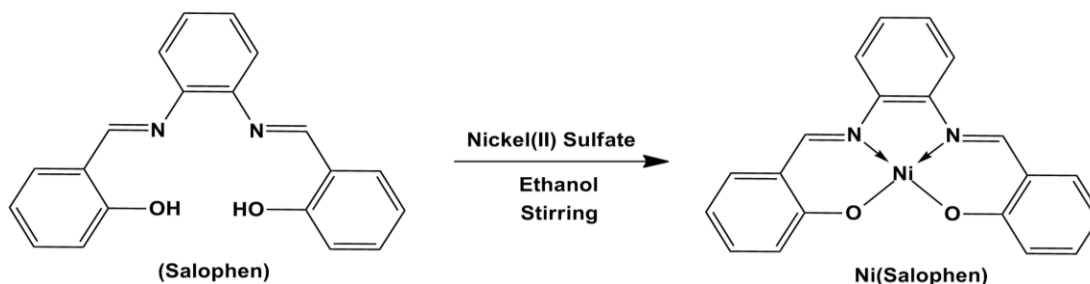


Scheme 1. Preparation of Salophen ligand.

3.2. Synthesis of Copper and Nickel Salophen Complexes

The synthesis of Copper and Nickel salophen complexes were accomplished by a procedure slightly different from that reported in the literature. To a hot ethanolic solution (50 mL) of each Copper sulfate and Nickel sulfate (CuSO_4 ; 0.250g, 1mM $\text{NiSO}_4 \cdot 5\text{H}_2\text{O}$; 0.263 g, 1 mM), the appropriate salophen ligand (0.316g, 1 mM) dissolved in ethanol was added with stirring. The mixture was subjected to heating with stirring for one hour and cooled to room temperature. The brown and maroon crystals separated were filtered, washed with diethyl ether and dried. Recrystallization was carried out in pure hot ethanol. The complexes were characterised by IR (Figure 1) and mass (Figure 2) spectra respectively. (**Table-1**)





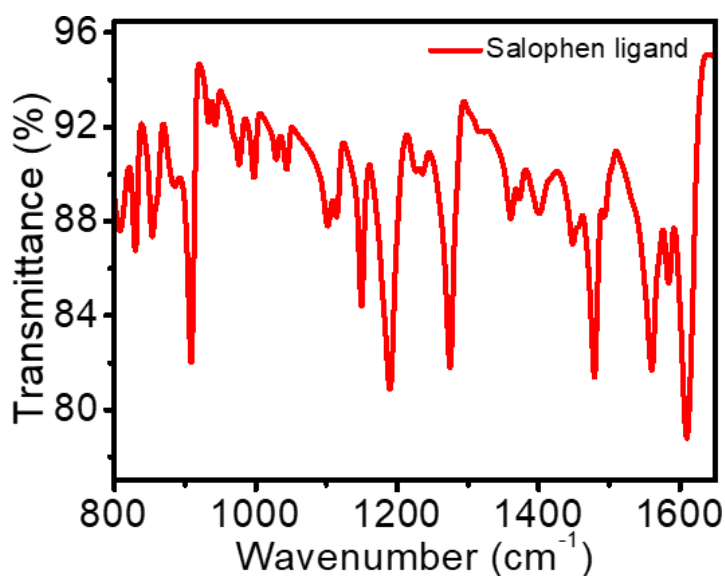
Scheme 2. Synthesis of Copper and Nickel Salophen Complex.

4. Characterization of Copper and Nickel Salophen Complexes

The Salophen ligand, Copper and Nickel salophen complexes were characterised by FT-IR and ESI-MS Studies.

Table 1. FT-IR (ν , cm^{-1}) and ESI-MS of Salophen ligand, Copper and Nickel salophen complexes

Salophen/ Complex	ν (cm^{-1})	ESI-MS
Salophen Ligand	1601-1620	316
Copper salophen	1590-1620	378
Nickel salophen	1585-1620	373



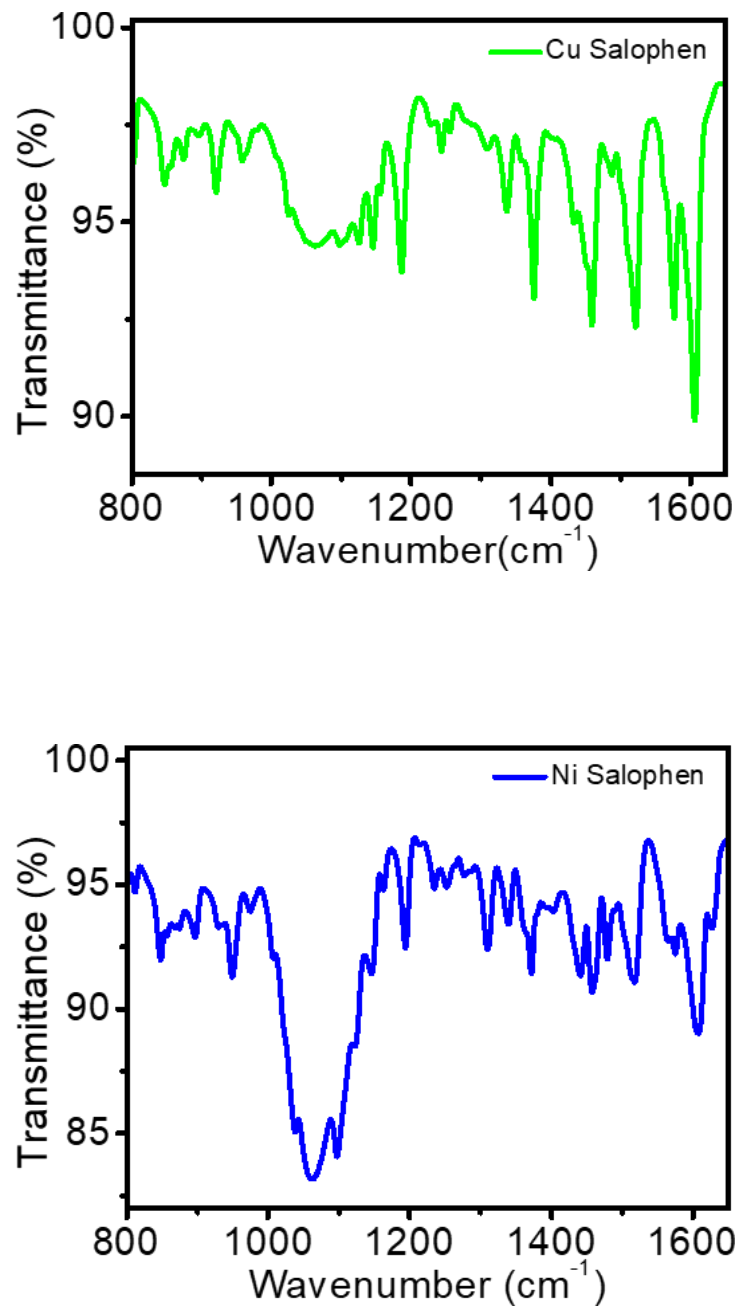


Figure 1. FT-IR spectra of Salophen ligand, Copper and Nickel salophen complex.

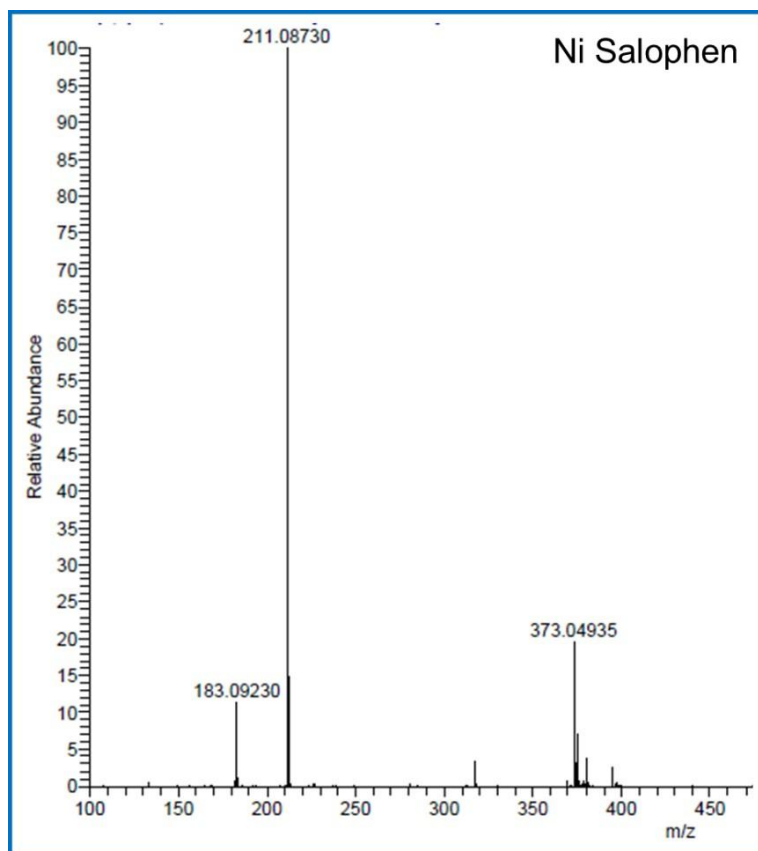
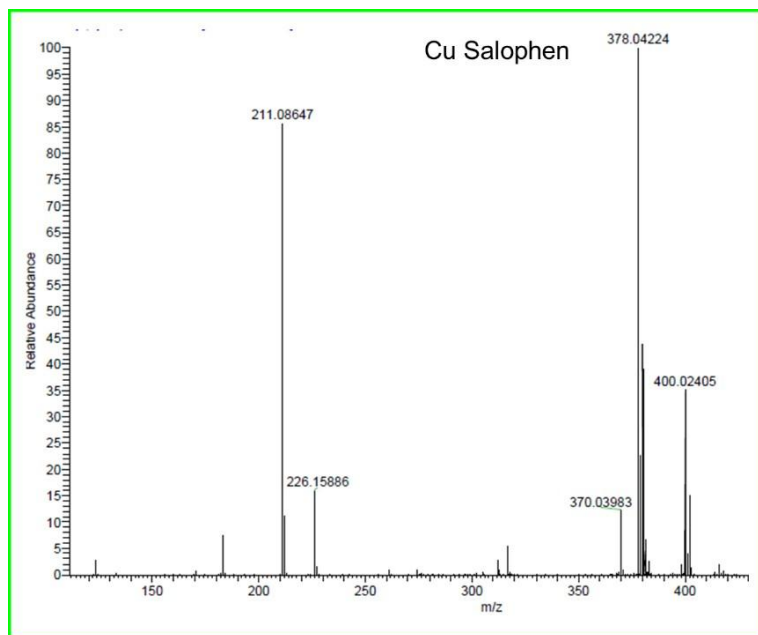


Figure 2. ESI-Mass spectra of Salophen ligand, Copper and Nickel salophen complex.

IR Prestige-21 FT IR-8400s (Shimadzu Corporation, Japan)

spectrometer was used to record the FT-IR spectral data of the ligand and the metal complex. Table-1 and Figure-1 reveals that the sharp and strong bands observed in the range of 1601 - 1620 cm^{-1} is due to $\nu_{\text{C=N}}$ of the azomethine group in the salophen ligand. The observed shift of ± 10 to 15cm^{-1} to a lower frequency of the $\nu_{\text{C=N}}$ in the complex indicates a decrease in the bond order of C=N due to the coordination of azomethine nitrogen to the metal ion. The ESI-MS spectra of the ligand and the complexes (Figure 2) were recorded on Thermo Scientific Extractive Mass Spectrometer and the m/z values obtained are similar to the formula weight (Table-1).

5. Antimicrobial Studies

5.1. Methodology

Agar Well Diffusion Test

The antibacterial screening of the Salophen Ligand, Copper salophen (Complex I) and Nickel salophen (Complex II) were carried out by determining the zone of inhibition using agar well diffusion method [23,24]. The drug extracts were tested against pathogenic bacteria (*Staphylococcus sps*, *Enterococcus sps*, *Klebsiella sps* and *Escherichia coli*).

Bacterial Inoculums Preparation

Inoculum of (*Staphylococcus sps*, *Enterococcus sps*, *Klebsiella sps* and *Escherichia coli*)

were prepared individually in a respective broth and kept for incubation at suitable temperature.

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Muller Hinton agar was used as the culture medium for this assay. The Muller Hinton agar was dispensed in pre-sterilized petridishes (25 ml each) and allowed to cool. These agar plates were homogenously inoculated with the test bacterium previously suspended in nutrient broth (10^3 cells/ml). The plates were allowed to solidify. After solidification holes/wells (cups) of 6 mm diameter were punched into agar with the help of flamed cork borer. Five wells were prepared for each plate. Of these five, three holes were filled with 50 μ l (5 mg) of the sample and the fourth hole was filled with 50 μ l of standard antibiotic solution (Streptomycin, 500 ug/ml) and the fifth hole was filled with blank (extracting solvent alone). The Petri dishes were incubated at 37 °C for 24 hr. After this incubation period the diameter of the inhibition zone formed around each hole (well/cup) was measured and the values were recorded. The antimicrobial activity was expressed as the ratio by the inhibition zone produced by the plant extract and the inhibition zone caused by the standard. Two sets of control were

used. One control was the organism control where standard antibiotic solution was used and the other control was the blank where only the extracting solvent was used. This was just to ensure the validity of the test.

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The test fungi used for antifungal analysis *Aspergillus sps* were isolated from the environment.

Assay for antifungal testing [25]

Potato Dextrose Agar was used to culture the fungal organism. The plates were inoculated with 24 hr culture of respective fungi. With the help of a flamed cork borer, 6 mm wells were cut out and to each of the well 50 μ l (5 mg) of sample were aseptically added with the help of sterile syringe. The plates were kept in cold for an hour to facilitate diffusion of the test solution (the extract). Later the plates were incubated at 27 °C. Inhibition was recorded by measuring the diameter of the inhibition zone after 72 hr. Fluconazole was used as a standard for

comparison of antifungal activity.

5.2. Microorganisms

Staphylococcus aureus is a gram positive organism and causes a broad range of infections. This variety is related to a number of virulence factors that allow it to adhere to surface, invade or avoid the immune system, and cause harmful toxic effects to the host. The toxins present in *Staphylococcus* sp., cause toxic shock syndrome and food poisoning. Nosocomial infections by *Staphylococcus epidermidis* have gained much attention because this skin colonizer has not apparently evolved to cause disease, but maintain the benign relationship with its host. Previously it was only regarded as an innocuous commensal microorganism on the human skin, but nowadays it is seen as an important opportunistic pathogen. Septicemia and endocarditis are also diseases associated with *S. epidermidis*. *Enterococcus sps.* is a gram positive bacteria. These bacteria, mainly *Enterococcus faecalis* and *Enterococcus faecium* are members of the normal flora of gastrointestinal tract but also are typical opportunistic pathogens. Enterococci are characterized by natural resistance to numerous antibiotics

(among them cephalosporins), and also by easy acquired resistance to antibiotics. Infections caused by multiresistant strains are difficult in treatment, chronic, recurrent and sometimes fatal are described. Enterococcal infections are caused often by *E. faecalis*, rarely by *E. faecium*. In the last years other species of enterococci have been isolated from different clinical materials (*E. casseliflavus*, *E. avium*, *E. durans*, *E. gallinarum*). Recently increase of enterococcal infections has been observed.

Klebsiella sps is a Gram-negative non-motile, encapsulated, lactose-fermenting, facultative anaerobic, rod-shaped bacterium. It appears as a mucoid lactose fermenter on MacConkey agar. Although found in the normal flora of the mouth, skin, and intestines, it can cause destructive changes to human and animal lungs if aspirated, specifically to the alveoli resulting in bloody, brownish or yellow colored jelly like sputum. In the clinical setting, it is the most significant member of the genus *Klebsiella* of the Enterobacteriaceae. *K. oxytoca* and *K. rhinoscleromatis* have also been demonstrated in human clinical specimens. In recent years, *Klebsiella* species have become important

pathogens in nosocomial infections.

Escherichia coli is a gram negative rod shaped bacteria. Most *E.coli* are commensals and as per Centre for Disease Control, *E. coli* bacteria normally live in the intestines of people and animals. Some *E. coli* are pathogenic, that cause either diarrhea or illness outside the intestinal tract. The types of *E. coli* that cause diarrhea can be transmitted through contaminated water or food, or through contact with animals or persons.

Aspergillosis is the group of diseases caused by *Aspergillus* sp. The symptoms include fever, cough, chest pain or breathlessness. The most common pathogenic species are *Aspergillus fumigatus* and *Aspergillus flavus*. *Aspergillus flavus* produces aflatoxin which is both a toxin and a carcinogen and which can potentially contaminate foods such as nuts. *Aspergillus fumigatus* and *Aspergillus clavatus* can cause allergic disease. Usually, only patients with weakened immune systems or with other lung conditions are susceptible. Acute invasive aspergillosis occurs when the immune system fails to prevent *Aspergillus* spores from entering the bloodstream *via* the lungs. Without the body mounting an effective immune

response, fungal cells are free to disseminate throughout the body and can infect major organs such as the heart and kidneys. The most frequently identified pathogen is *Aspergillus fumigates* - a ubiquitous organism that is capable of living under extensive environmental stress. It is estimated that most humans inhale thousands of *Aspergillus* spores daily, but they do not impact on most people's health due to effective immune responses. The major chronic, invasive and allergic forms of aspergillosis account for around 600,000 deaths annually worldwide.

6. Results and Discussion

As reported by Rosua *et al.* [26] the metal complexes of Schiff base ligands, especially copper(II) and vanadium(VI) complexes, exhibit higher antibacterial activity as compared to the free ligand and metal salts. Sobha *et al.* [27] explored the activity of Cu(II), Ni(II) and Zn(II) Schiff base complexes against various bacteria like *S. aureus*, *P. aeruginosa*, *E. coli*, *S. epidermidis* and *Klebsiella pneumonia* by the diffusion agar technique and reported that the complexes were more potent bactericides than the free Schiff bases. The higher

antimicrobial activity of the Schiff bases is attributed to the changes in structure due to coordination and chelation tends to make metal complexes act as more powerful and potent bacteriostatic agents, thus inhibiting the growth of the microorganisms.

A series of oxovanadium(IV) complexes with a class of triazole Schiff bases have been subjected to *in vitro* antibacterial and antifungal studies. It has been found that the simple Schiff bases showed weaker to significant activity against one or more bacterial and fungal strains and in most of the cases higher activity was exhibited upon coordination with vanadium(IV) metal complexes [28].

Prasad *et al.* [29] have shown that oxovanadium Schiff base complexes have enhanced antimicrobial activity over their parent ligands by disc diffusion method. It has been proposed that the higher activity of the metal complexes may be owing to the effect of metal ions on chelation. The polarity of the metal ions will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups and thus it enhances the penetration of the

complexes into lipid members and blocking the metal binding sites in the enzymes of microorganisms.

Antimicrobial studies carried out by Patil *et al.* [30] revealed that the activity of the ligand enhanced on complexation but to a lesser extent when compared to the standard used. The higher antibacterial activity of the VO(IV) complexes is attributed to the chelation effect, which further increases the delocalization of π -electrons over the whole chelate ring and enhances the lipophilicity of the complexes which again enhances the penetration of complexes into lipid membrane and blocks the metal binding sites on enzymes of microorganisms.

The antimicrobial studies of Cu(II), Co(II), Ni(II), Zn(II) and VO(II) azo Schiff base complexes and the ligands have been carried out by Anitha *et al.* [31]. It has been suggested, the higher activity of the metal complexes may be due to the effect of metal ions on the normal cell membrane [32]. Metal chelates bear polar and non polar properties together, which make them permeable to the cells and tissues. In addition, chelation may enhance or suppress the biochemical potential of

bioactive organic species. Further lipophilicity, which controls the rate of entry of molecules into the cell, is modified by coordination and the metal complexes become more active than the free ligand which in fact is in agreement with the literature [33].

Sharma *et al.* [34] compared the antimicrobial activity of ligands, nitrogenous bases- imidazole and benzimidazole, oxovanadium complexes and their coordination compounds with nitrogenous bases and proposed the variation in the effectiveness of the complexes against different organisms which may be due to either the difference in permeability of the cells of the microbes or on difference in ribosomes of the microorganisms [35,36]. The increase in activity of complexes was explained on the basis of chelation theory [37,38]. The mechanism of action is generally considered to be the disturbance of the cytoplasmic membrane, disrupting the proton motive force, electron flow, active transport and coagulation of cell contents [39,40].

Raman *et al.* [41] investigated the *in vitro* antimicrobial activity of Schiff base ligands of 4- aminoantipyrine derivatives of N₂O₂ type and the corresponding

copper, vanadyl, nickel and zinc complexes against different bacteria and fungi species. The minimum inhibitory concentration (MIC) values indicated that the metal complexes exhibit higher antimicrobial activity than the free ligand. The increased activity of the complexes was explained on the basis of Overtones concept and Tweedy's chelation theory. According to Overtones concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only the lipid soluble materials whose lipo solubility is an important factor, which controls the antimicrobial activity. On chelation, the increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocks the metal binding sites in the enzymes of micro organisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism [42]. Furthermore, the mode of action of the compounds may involve formation of a hydrogen bond through the azomethine group with the active centres of cell constituents, resulting in interference with the normal cell process.

In the present study, the *in vitro* antimicrobial activity of the synthesized

Copper and Nickel salophen complexes against various microorganisms were assessed by agar well diffusion method. The antibacterial activity of the complexes were examined against different gram positive (*Staphylococcus aureus* and *Enterococcus sps*) and gram negative bacteriae (*Klebsiella sps* and *E. coli.*) microorganisms and antifungal activity against fungal microorganism (*Aspergillus sp.*) by measuring the zone of inhibition. The *in vitro* antimicrobial screening results are given in Table 2 and Table 3. On the basis of the observed zone of inhibition given in Figure 3 and Figure 4, it was found that Copper salophen complex was moderately active towards *Enterococcus* microorganisms. The increased activity of the complex was found to be in accordance with the Overtones concept and Tweedy's chelation theory.

Table 2. Anti-bacterial potential of Copper salophen (Complex I), Nickel salophen (Complex II) and Ligand Salophen (Ligand – III) in acetonitrile solvent

Bacteria Name	Sample Zone of inhibition(mm)				
	Complex - I 5 mg	Complex - II 5 mg	Ligand – III 5 mg	Positive Control	Negative Control
<i>Staphylococcus sps (G+)</i>	Nil	Nil	Nil	22mm	Nil
<i>Enterococcus sps (G+)</i>	15mm	Nil	12mm	28mm	Nil
<i>Klebsiella sps (G-)</i>	Nil	Nil	Nil	23mm	Nil
<i>E. coli (G-)</i>	Nil	Nil	Nil	21mm	Nil

Keywords: Positive control (*Streptomycin*), Negative control, “**Nil**” No Zone, **mm** (Millimetre), **G+** (Gram Positive Organism), **G-** (Gram Negative Organism),

Figure 3. Anti-bacterial potential of Copper salophen (Complex I), Nickel salophen (Complex II) and Ligand Salophen (Ligand – III) in acetonitrile solvent.

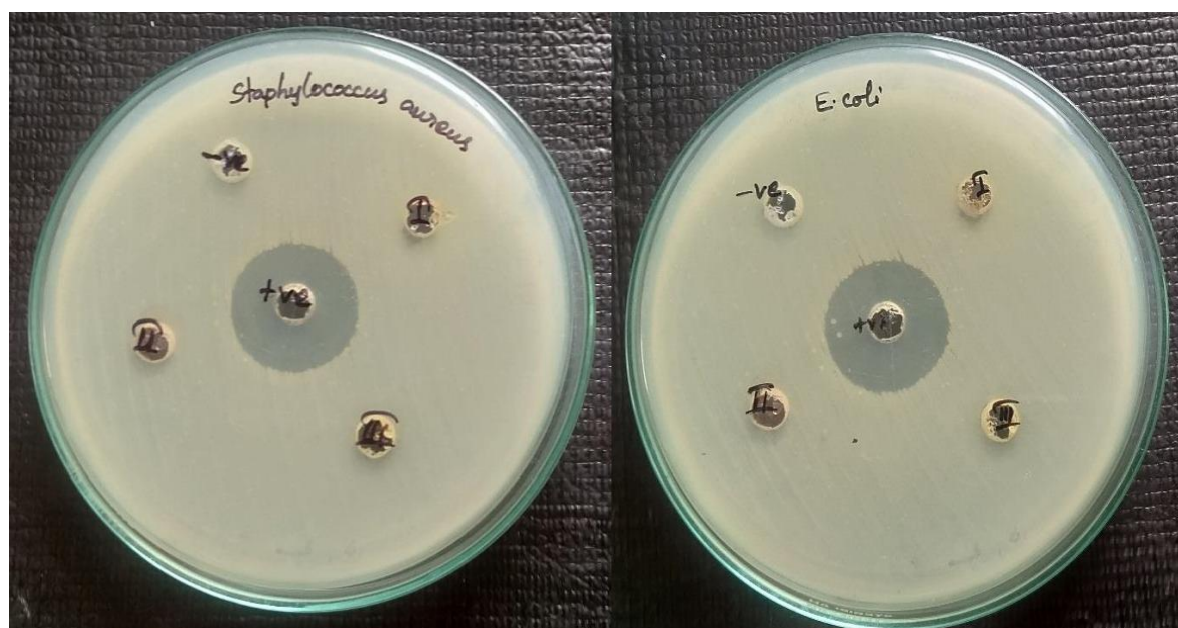
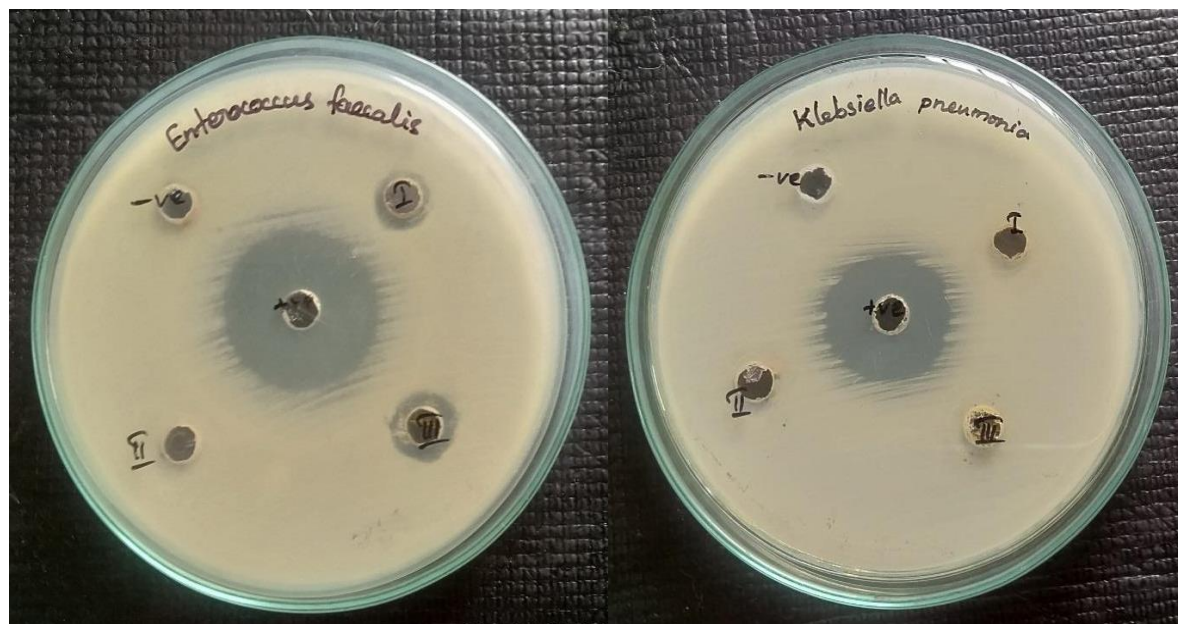
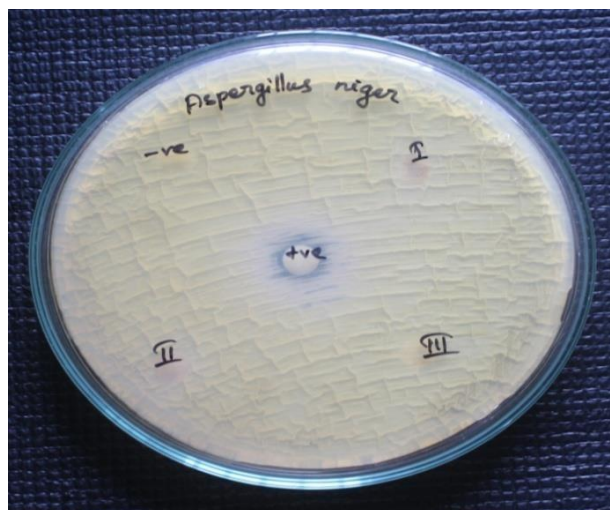


Table 3. Anti-Fungal potential of Copper salophen (Complex I), Nickel salophen (Complex II) and Ligand Salophen (Ligand - III) in acetonitrile solvent

Fungai Name	Sample Zone of inhibition(mm)				
	Complex - I 5 mg	Complex - II 5 mg	Ligand – III 5 mg	Positive Control	Negative Control
<i>Aspergillus sps</i>	4	Nil	2	11mm	Nil

Figure 4. Anti-Fungal potential of Copper salophen (Complex I), Nickel salophen (Complex II) and Ligand Salophen (Ligand – III) in acetonitrile solvent



complex shows significant effect of antimicrobial activity (15 mm zone of inhibition) against the bacteria *Enterococcus sps* which potentially causes the gastrointestinal tract infections. The Salophen ligand also showed moderate anti bacterial activity (12 mm zone of inhibition) against the enterococcus sps. Nickel complex did not show activity against the gram positive and gram negative bacteria. Copper complex exhibited slight anti- fungal activity towards the *Aspergillus sps*.

Conclusion

The synthesized Schiff base Salophen

ligand acts as a tetradentate ligand through the coordination of azomethine nitrogen and phenolic oxygen atoms to the metal ion Copper and Nickel. The bonding of ligand to metal ion was confirmed by the IR and mass spectral studies. Among the Copper and Nickel Salophen complexes, Copper Salophen showed moderate antimicrobial activity towards the *Enterococcus sps* and slight antifungal activity towards *Aspergillus sps*.

7. References

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