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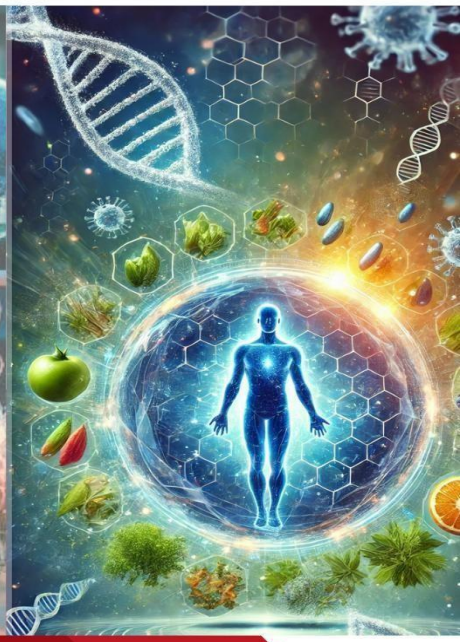

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Synthesis, Characterization and Antimicrobial Studies of Copper Salophen Complex

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Abstract

The continuous emergence of antimicrobial-resistant pathogens has intensified the search for novel metal-based therapeutic compounds with improved biological activity and pharmacological efficiency. In this study, a Schiff base Salophen ligand and its Copper(II) salophen complex were synthesized, structurally characterized, and evaluated for their antimicrobial potential against selected pathogenic microorganisms. The Salophen ligand was prepared through the condensation reaction of salicylaldehyde and 1,2-benzenediamine in ethanolic medium, followed by complexation with Copper sulfate to obtain the corresponding Copper salophen complex. The synthesized ligand and metal complex were characterized using Fourier Transform Infrared (FT-IR) spectroscopy and Electrospray Ionization Mass Spectrometry (ESI-MS). Spectral analysis confirmed the formation of the Schiff base and coordination of azomethine nitrogen and phenolic oxygen atoms with the Copper ion. The FT-IR spectra exhibited characteristic ν(C=N) stretching vibrations within the range of 1601–1620 cm^{-1}, while mass spectral data validated the molecular composition of the synthesized compounds. The antimicrobial activity of the synthesized compounds was investigated by agar well diffusion technique against Gram-positive bacteria (Staphylococcus spp. and Enterococcus spp.), Gram-negative bacteria (Klebsiella spp. and Escherichia coli), and fungal species (Aspergillus spp.). Experimental results demonstrated that the Copper salophen complex exhibited enhanced antimicrobial activity compared with the free ligand.

The Copper complex showed moderate antibacterial activity against Enterococcus spp. with a zone of inhibition of 15 mm, whereas the Salophen ligand exhibited 12 mm inhibition. Antifungal studies also revealed slight inhibitory activity of the Copper complex against Aspergillus spp. with a 4 mm zone of inhibition.

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

Keywords: Schiff Base Complex ,Copper Salophen Complex , FT-IR Spectroscopy , Antimicrobial Activity, Chelation Theory

1. Introduction

Metal complexes of Schiff base derived from aromatic carbonyl compounds have been widely studied because of the versatility of their steric and electronic properties, which can be modified by selecting the suitable amine precursors and ring substituent. Transition metal complexes with oxygen and nitrogen donor Schiff bases are of particular interest for their ability to possess unusual configurations, structural lability and their sensitivity to molecular environments. Amongst them, tetradentate Schiff bases with N2O2 donor atoms are well known to coordinate with various metal ions and have attracted great deal of interest due to their rich co-ordination chemistry. Many symmetrical tetradentate bis-type Schiff base ligands, usually obtained by the condensation of 1, 2-diamines with o-hydroxy aldehyde/ketone have been prepared and studied intensively.

Since the discovery of antibiotics by Alexander Fleming in the 1920s, most of the current compounds developed by medicinal chemists around the world are almost exclusively purely organic. Although metals and their complexes have been employed since ancient times, they were generally used for their applications as catalysts or materials, and their properties were often associated with toxicity. However, the use of structurally defined metal complexes in medicine mostly appeared at the beginning of the 20th century with the discovery of the arsenic- containing organometallic complex as the first effective treatment of syphilis (Salvarsan). Since then, many other metal complexes have been found to be useful in

medicinal chemistry, like the development of a famous mercuric-based antiseptic agent (Mercurochrome) or the treatment of rheumatoid arthritis by a gold complex agent (Auranofin). Nevertheless, the most relevant examples in the field of medicinal chemistry are undoubtedly the platinum-based anticancer drugs cisplatin, oxaliplatin and carboplatin. These complexes are still currently used in nearly 50% of all cancer treatments.

The search for new active antimicrobial compounds is of growing interest since the current clinical pipeline remains insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance. In the United States, each year more than 2.8 million people suffer from an antibiotic-resistant infection, resulting in more than 35,000 deaths. In Europe, antibioticresistance is responsible for an estimated 33,000 deaths annually. According to the World Health Organization (WHO), the newly approved products have limited clinical benefits over existing treatments and almost 75% of the antimicrobials under clinical development are simply derivatives of already known and used molecules existing on the market, and for which multiple resistance mechanisms are well established. Therefore, there is an urgent need for the development of new antimicrobial agents.

The global sales of antibiotics are generally higher when compared to other drugs which are prescribed. A continuous increase in the number of infections caused by bacterial resistance to one or multiple class of antibiotics poses a significant threat as it may lead to treatment failure and some associated complications [1]. Thus the treatment of bacterial infections remains a challenging therapeutic problem. Despite many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic resistant bacterial strains in the last decade constitutes a substantial need for the development of new classes of antibacterial agents [2].

Schiff base-metal complexes are an area of increasing interest due to their biological activity. These Schiff base complexes have numerous applications such as, in the treatment of cancer, antibacterial agents, antivirus agents, antifungal agents and for other biological properties [3]. Schiff bases can coordinate a wide variety of transition metal ions in different oxidation states forming complexes with interesting properties, architectures and applications [4,5]. The wide variety of Schiff base ligands and their metal complexes play an important role due to their easy synthesis and structural

diversity as well as to the possibility of fine tuning of steric and electronic properties, which has made it possible to identify several factors affecting their activities. This has led to the development of new industrially important catalysts and novel antibacterial agents relevant to global issues such as bacterial resistance [6].

As a biocompatible element, copper has a wide variety of biochemical and physiological functions. Many of these functions are due to the inhibition or stimulation of enzymes that participate in phosphate metabolism. Furthermore, copper is able to replace other transition metal ions in enzymes due to its biocompatibility with a variety of potential ligand systems. In addition, copper complexes are well documented to have therapeutic application and have been used as model compounds to clarify the mechanism of several biochemical processes.

One of the most interesting properties of metal complexes including those of copper is their antimicrobial activity. Various methods have been reported to evaluate their activity. Glucosamine-6-phosphate synthase (GlcN-6-P synthase) has been recently considered as a new target in antimicrobial studies because the GlcN-6-P produced by this enzyme is crucial for the survival of the cell [7,8]. It has been demonstrated that inactivation of GlcN-6-P synthase even for a short time, results in morphological changes like agglutination and lysis and is therefore lethal for pathogenic microorganisms [9]. Any compound that can inhibit the action of this enzyme is a potential antimicrobial agent.

Based on the global concern to public health, discovery of new antibiotics has become an important objective. Biological activity of synthetic compounds for potential antimicrobial activity continues to be an important strategy for the identification of new drugs with possible clinical values.

2. Scope and Objective

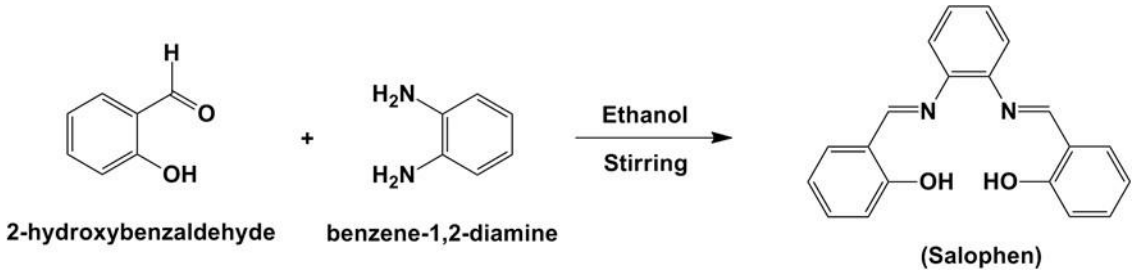
Microbial infection is a growing problem in contemporary medicine, and the use of antibiotics is inevitable. Development of resistance to antibiotics has become a major problem in recent years. Thus the treatment of bacterial infections remains a challenging therapeutic problem. As a biocompatible element, Copper has 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 Salophen ligand and Copper salophen complex have been synthezised, characterized and the screening of these

salophen ligand and complex for its antimicrobial properties against human pathogens isolated from clinical specimens has been discussed.

3. Synthesis of Copper Salophen Complex

3.1 Preparation of Salophen ligand

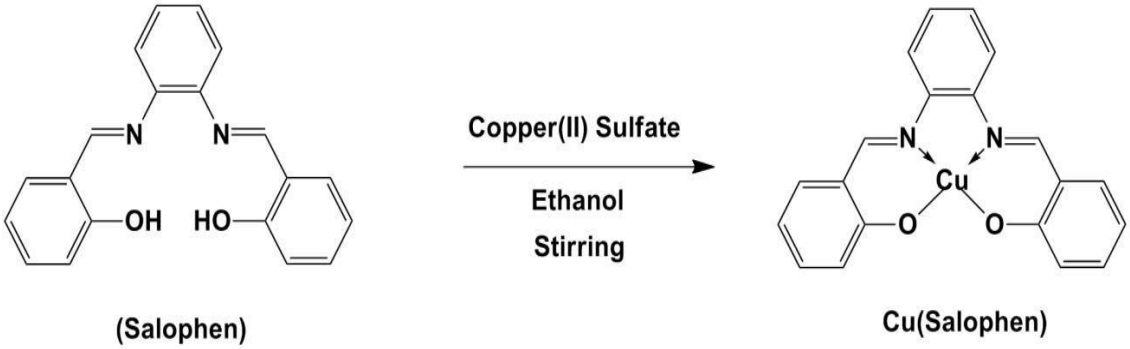
The salophen ligand required for the preparation of the Copper salophen complex was synthesized using established procedure [10]. The general procedure for the preparation of salophen ligand involves the condensation of salicylaldehyde and 1,2-benzenediamine in the ratio of 2:1 in an alcoholic medium. 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 Salophen complex

The synthesis of Copper salophen complex was accomplished by a procedure slightly different from that reported in the literature. To a hot ethanolic solution (50 mL) of Copper sulfate ($CuSO_4$; 0.25g, 1mM), the appropriate salophen ligand (1 mM) dissolved in ethanol was added with stirring. The mixture was subjected to stirring with heating for one hour and cooled to room temperature. The brown crystals separated were filtered, washed with diethyl ether and dried. Recrystallization was carried out in pure hot ethanol. The complex was characterized by IR (Figure 1) and mass (Figure 2) spectra respectively.



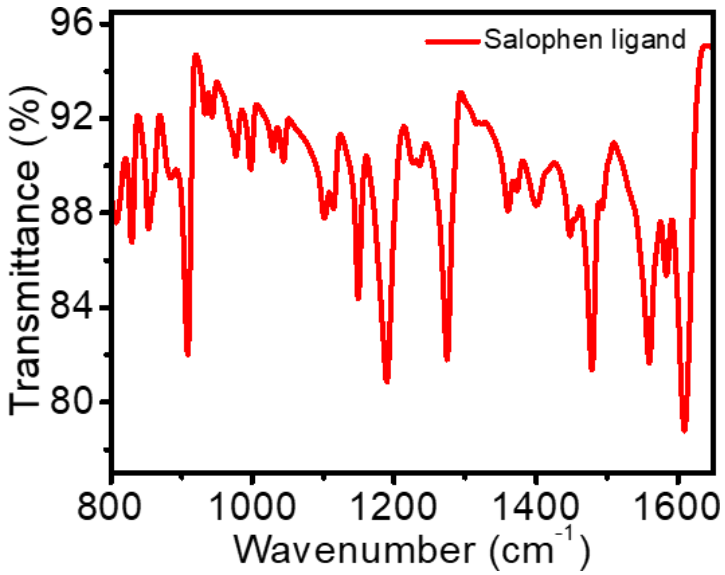
Scheme 2. Synthesis of Copper salophen complex.

4. Characterization of Salophen Ligand and Copper Salophen Complex

The Salophen ligand and copper salophen complex were characterized by FT-IR and ESI-MS Studies.

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

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



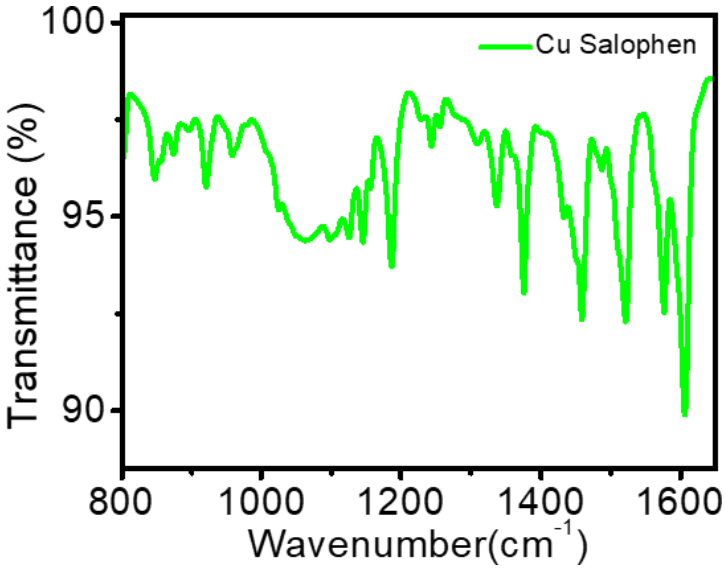
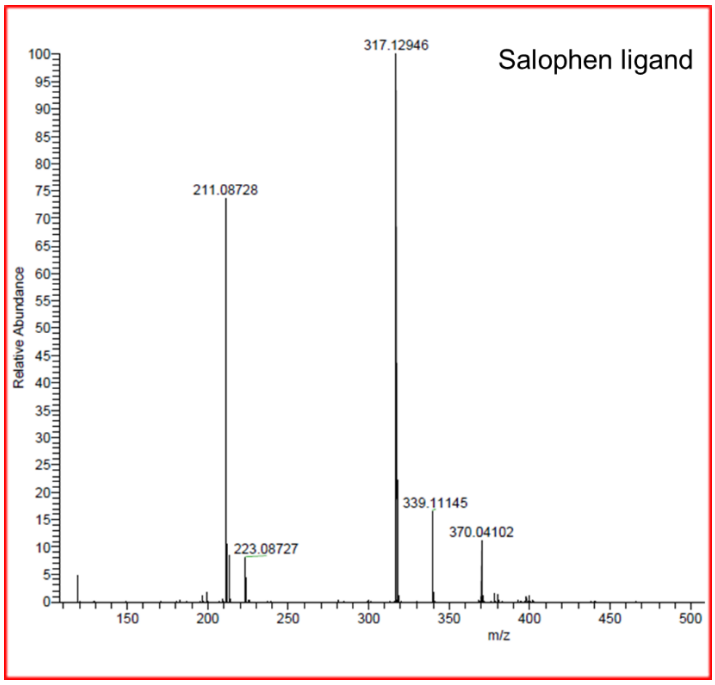


Figure 1. FT-IR spectra of Salophen ligand and Copper salophen complex.



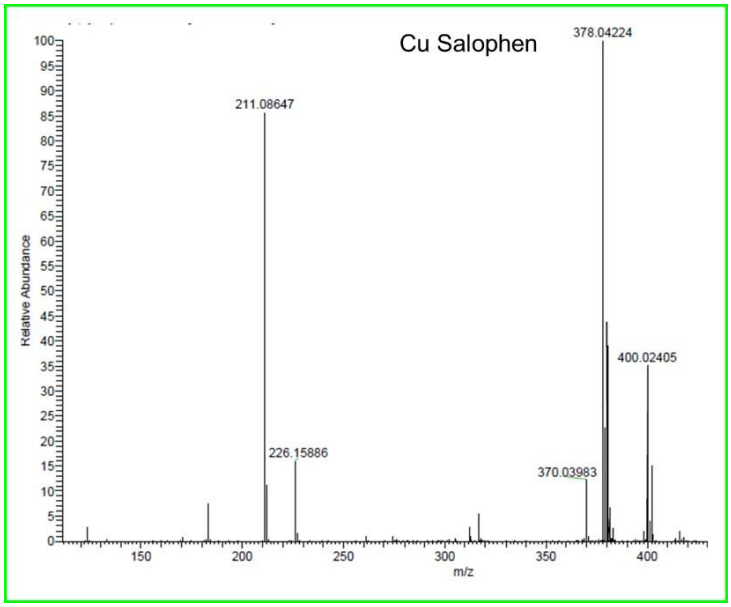


Figure 2. ESI-Mass spectra of Salophen ligand and Copper salophen complex.

IR Prestige-21 FT IR-8400s (Shimadzu Corporation, Japan) spectrometer was used to record the FT-IR spectral data of the ligand and 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 $\nu_{(C=N)}$ of the azomethine group in the salophen ligand. The observed shift of ± 10 to 15cm^{-1} to a lower frequency of the $\nu_{(C=N)}$ 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 complex (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

(i) Agar Well Diffusion Test

The antibacterial screening of the Salophen Ligand and Copper salophen complex were carried out by determining the zone of inhibition using agar well diffusion method [11,12]. 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.

Assay for antibacterial testing Agar well diffusion method

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 corkborer. Five wells were prepared for each plate. Of these five, three holes were filled with 50µl (5 mg) of the sample and the fourth hole was filled with 50µlof standard antibiotic solution (Streptomycin, 500ug/ml) and the fifth hole was filled with blank (extracting solvent alone). The Petri dishes were incubated at 37 º 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.

(ii) Antifungal Activity

Test Organism

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

Assay for antifungal testing[13]

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 50µl (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 ºC. 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,[1] 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.* [14] 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.* [15] 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 [16].

Prasad *et al.* [17] 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.* [18] 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.* [19]. 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 [20]. 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 entity 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 [21].

Sharma *et al.* [22] 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 organism which may be due to either the difference in permeability of the cells of the microbes or on difference in ribosomes of the microorganisms [23,24]. The increase in activity of complexes was explained on the basis of chelation theory [25,26]. 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 [27,28].

Raman *et al.* [29] investigated the *in vitro* antimicrobial activity of Schiff base ligands

of 4- aminoantipyrine derivatives of N_2O_2 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 microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism [30]. 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 Salophen ligand and Copper salophen complex against various microorganisms were assessed by agar well diffusion method. The antibacterial activity of the ligand and the complex 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* antibacterial and antifungal screening results are given in Table-2 and Table-3. On the basis of the observed zone of inhibition, it was found that Copper salophen complex was moderately active towards Enterococcus microorganisms. The antibacterial activity of the complex was a little higher than the salophen ligand. 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 and Salophen ligand in acetonitrile solvent.

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

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

Table 3. Anti-Fungal potential of Copper salophen complex and Salophen ligand in acetonitrile solvent

Fungai Name	Sample Zone of inhibition(mm)			
	Complex 5 mg	Ligand 5 mg	Positive Control	Negative Control
Aspergillus sps	4	2	11mm	Nil

Copper 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 antibacterial activity (12 mm zone of inhibition) against the enterococcus sps. The salophen ligand and 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. The bonding of ligand to metal ion was confirmed by the IR and mass spectral studies . It was found out that the salophen ligand and Copper Salophen complex showed moderate antibacterial activity towards the Enterococcus sps.and slight antifungal activity towards Aspergillus sps.

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