



Synthesis, characterization and anti-microbial activities of Ni (II) and Mn (II) of barbitone in water medium

¹Olagboye, S. A.*, ²Adebawore, A. A., ¹Adebawore, A. A. (Jnr), ²Akinyeye, R. O., ¹Akinnawo, A. S., ¹Omotoso, E. O., ³Iyiola, F. B. and ⁴Adediji, P. O.

¹Department of Chemistry, Ekiti State University, Ado-Ekiti, Nigeria.

²Department of Industrial Chemistry, Ekiti State University, Ado-Ekiti, Nigeria.

³Department of Microbiology, Ekiti State University, Ado-Ekiti, Nigeria.

⁴Nigeria Centre for Disease Control, Prevention, Abuja, Nigeria.

Abstract

The newly synthesized metal chelate of sodium barbitone with the Ni (II) and Mn (II) ions was examined and characterized by elemental analysis, colors and melting points/thermal decomposition, and the Infra-red (IR), UV-visible spectroscopic methods to predict the sites for metals coordination. The antimicrobial studies of sodium barbitone ligand (free ligand) together with its metal chelates serve as references for the following pathogenic bacterial isolates; *Salmonella typhi*, *Ralstonia solanacearum*, *Streptococcus faecalis*, *Erwinia carotovora*, and *Pseudomonas glycinea*, and the following pathogenic fungal isolates (*Serpula lacrymans*, *Epidermophyton floccosum*, and *Trichophyton verrucosum*). The activity data show that the metals chelate have pronounced activity with a promising biological activity compared to sodium barbitone parent-free ligand against microorganisms that are significant to human health.

Keywords: Spectroscopic techniques; anti-microbial activities; barbitone; metal ions.

Introduction

Overcoming the alarming problem of microbial resistance to antibiotics is a matter of urgency, then the discovery of novel active compounds against new targets is needed. Some crude drugs, sources for medicinal preparations, are originated from wild growing material. However, some popular known plant-based drugs have shortened the life span of the sourced material. There is a continuous search for more potent and cheaper raw materials to feed the industry. So, nowadays, pharmaceutical industries are looking for synthesizing alternative compounds which act as a drug (Chohan *et al.*, 2006; Fasina *et al.*, 2017).

Complexes or coordination compounds are molecules entrusted to possess a metal center, bond to ligands that donate electrons to the metal. Complex ions can form many compounds by binding with other complex ions in multiple ratios and could invariably lead to many combinations of coordination compounds; then, the structures of certain coordination compounds can also have isomers, which can change their interactions with other chemical agents. The bonding between metal and its ligands can be structured to fit in terms of metals, tetrahedral, and octahedral structures (Emara *et al.*, 2011).

Hamouda *et al.* (2014) reported the crystal structure of $[\text{Pd}(\text{en})\text{barb}](\text{H}_2\text{O})_4$, prepared from a solution originally containing $[\text{enPd}(\text{H}_2\text{O})_2]\text{SO}_4$, barbituric acid, and hydroxide ion in a 1:2:2 molar ratio. In the complex, Pd (II) formed bonds to both deprotonated amide nitrogen and a deprotonated tetrahedral carbon.

Giwa *et al.* (2013) reported that the Cu (II) complex of sodium barbitone coordinated in bidentate fashion through one carbonyl and Na^+O^- oxygen atoms together with the carbonyl oxygen of acetate to give tentatively octahedral geometry for Cu (II).

Antimicrobial resistance is becoming a global concern with rapid increases in multidrug-resistant bacteria. Some previously treatable pathogens are now becoming untreatable, for example, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). MRSA (resistant to methicillin, cephalosporins, all beta-lactams, and occasionally in gentamicin, erythromycin, and trimethoprim/sulfamethoxazole) VRE (resistant to vancomycin, ampicillin, and gentamicin). Apart from this also includes *Enterococcus faecalis* and *Enterococcus faecium*. Besides, this organism and some other organisms showed drug resistance (M. tuberculosis (Strain no: H37Rv ATCC 27294, susceptible to rifampicin, isoniazid, streptomycin, and ethambutol); there are two more other clinical strains multidrug-resistant such as M. tuberculosis drug (MDRTB) are not susceptible to isoniazid and rifampicin, and the second one is *Klebsiella pneumoniae* drug, which is resistant to bacteria. The resistant microorganisms list also extends to other gram-negative organisms like *Escherichia coli*, *Shigella flexneri*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and Gram-positive *Bacillus subtilis* bacterial strains. Birinchi *et al.* (2006) stated in their research that some fungal pathogens showed the resistance feature against drugs like *Candida albicans*, *Aspergillus flavus*, *Fusarium solani*, and *Candida glabrata* and can serve as a repellent.

The biological activity of complexes of 2-hydroxy-3, 5-dimethylacetophenoneoxine (HDMAOX) with Ni (II) has been culture against (*Alternaria alternata*; *Aspergillus flavus*; *Aspergillus nidulus*; *Aspergillus niger*) fungi and (*Streptococcus typhi*; *Escherichia Coli*) bacteria. It is clear from the antifungal activity that the metal complexes are more fungi toxic than the chelating agent itself. The bacteria screening results revealed that the Nickel (II) complexes showed the minimum activity against staphylococcus bacteria (Singh *et al.*, 2006, Pandya *et al.*, 2009).

Materials and Methods

All chemicals and solvents used were of analytical grade, the chemical used was of the highest purity available, including Sodium barbitone, Cobalt chloride hexahydrate, and nickel chloride hexahydrate manganese, Silica gel, Barium Chloride, all used without further purification. The solvents such as absolute ethanol, methanol, acetone and DMSO, DMF, chloroform, toluene, n-hexane, ethyl acetate, distilled water, hydrogen peroxide, concentrated

hydrochloric acid (Anala R), and concentrated nitric acid purchased from a Bisolab Chemical Store at Ajilosun Ado-Ekiti, Ekiti State.

Instrumentation

Weight measurement was employed using Sensitive Analytical Balance [0.0001g, SCALTEC (Germany)]; stirring and heating using a magnetic stirrer thermostat hot plate (VELP Europe); Automatic pipette to take a small volume of solvents. Decomposition temperatures were detected using Harries Melting point apparatus; the infrared spectra using a Perkin Elmer FT-IR type in the wavenumber region 4000-400 cm^{-1} ; drying of precipitate using a Desiccator containing Silica gel, Oven drying method was adopted using dry-heat sterilization oven. Percentage %Cl and %S were obtained by gravimetric method (Argentometric) for % Cl using AgNO_3 solution and % S by Mohr method using BaCl_2 solution. While the % metals of Ni (II) and Mn (II) on the complexes were obtained by complexometric titration using EDTA.

$$\% \text{ Sulphur} = \frac{\text{Total Volume} \times \text{Volume of barium sulphate precipitate}}{\text{Volume of aliquot} \times \text{Volume of the Sample}} \times 0.1373 \times 100$$

$$\% \text{ Cl} = \frac{a \times 24.7}{b}$$

a = weight of AgCl

b = weight of sample (complex) used

The solubility test was determined using available transparent organic solvents.

Preparation of murexide indicator

The indicator was prepared by mixing thoroughly 50g (0.86mol) of NaCl and 0.1g of murexide in a crucible and finally transferred into a dry brown bottle.

Synthesis of metal complex of barbitone

Synthesis of divalent metal complexes with sodium barbitone at different ratio concentrations

Synthesis of Ni (II) barbitone at different ratio concentrations by direct mixing method. 0.469 (0.019mol) of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ carefully dissolved in distilled water and mixed with 0.51g (0.0025mol) of sodium 5,5-dimethylbarbiturate ligand solution made with distilled water. The reaction mixture was stirred vigorously on a magnetic stirrer for 3 hours, and a pale green precipitate obtained was filtered, washed in a mixture of water/ether through the sintered glass porosity number 4, and dried in a desiccator for five (5) days.

The concentration of Ni (II) ions complexed with 5,5-dimethylbarbiturate (1:2) is double by increasing the ligand by two. The processing of mixing, stirring, filtering, washing, and drying remains the same.

Barbiturate complexes are mixed with distilled water by a direct mixing method. 0.54g (0.021mol) of a colorless solution of MnSO_4 salt were prepared with distilled water and mixed with 0.51g (0.0025mol) 5,5-dimethylbarbiturate ligand, made to mark with distilled water in a 10 ml standard flask. The reacting mixture of Mn (II) barbiturate was stirred continuously for 3 hours. The resulting brown mixture was filtered, through the sintered glass porosity number 4, washed in water/ether, and dried in a desiccator for five (5) days. While Mn (II) (Barbitone) $_2$ complex in ratio 1:2 was prepared by increasing the concentration of the 5,5-dimethylbarbiturate to 2. A brown precipitate obtained was treated with Mn (II) barbiturate in a 1:1.

Physical measurement and characterization

Melting points/ decomposition temperature

A small quantity of the metal complexes was put into a one-end sealed capillary tube using the sample compartment of the Harries melting points apparatus with a 1000⁰C thermometer to conduct Thermal analysis.

Solubility Test

The solubility test of the metal complexes was determined using non-polar (DMSO, N, N-dimethyl formaldehyde) and polar solvents (n-Hexane, Ethylacetone, Acetone, water, Toluene, Ethylacetate, Ethanol, Methanol).

Digestion of Complexes for percentage metals

About 0.01g of metal complex was weighed into a digestion bottle using a weighing balance, followed by the addition of three drops of nitric/perchloric acid mixture. Then the complexes were placed on an electric heater and kept in a fume cupboard until the mixture was almost dried and the bottle became clear. The digested complexes were transferred into a 100ml standard flask and made the mark with distilled water.

Titration of the digested complexes solution

25ml of the sample was pipette into a 25ml conical flask. A pinch of murexide indicator was added to the solution, followed by two drops of Ammonia/Ammonium Chloride (NH₃/NH₄Cl) buffer solution (yellowish color), then titrated with Na₂EDTA solution, and the endpoint was reached, the color changed from yellow to pink.

Gravimetry analysis of the complexes

About 0.05g complexes were weighed into a digestion bottle using a weighing balance. Then, 20ml of 2% NaOH solution was added and followed by a few drops of 30% H₂O₂ on heating using a volumetric flask. The heating continued until the peroxide (H₂O₂) escaped. Then it was allowed to cool and transferred into 50ml of a standard flask and made to mark using distilled water.

Structural characterization

Various elucidating techniques have been adopted over the years to elucidate the bonding and geometry of the ligands and the prepared complexes. UV-Visible spectrometry, Fourier Transform- Infra-Red (FT-IR) spectrometry, and Percentage metal using Mohr complexometry titration are for the characterization.

UV-Visible spectrometry

The UV/Visible spectrum of the ligands and complexes was detected using the Solid infection method. 0.01g of the sample was robbed on 3cm by 0.5cm filter paper containing Paraffin oil. Then, the sample extract containing the paraffin sample was pore into a sample compartment of the UV-Visible Spectrometer, and the spectral band was measured by measuring the transmittance/solid reflectance.

Fourier Transform-Infra Red (FT-IR) spectrometry

The Fourier Transform-Infrared spectrum of the solid sample was determined in an IR spectrometer (model 3434), using a potassium bromide (KBr) disc prepared from a powdered sample mixed with dry KBr in a ratio of 1:200. Triplicate measurements were selected, and the spectrum with the clearest peaks was chosen and selected.

Antimicrobial

Evaluation of antibacterial activities of the samples

The bacteria used for this experiment were cultured aerobically at 37°C for 24hrs peptone water and antibacterial testing using Mueller Hinte Agar (MHA). The Agar diffusion method of Murray (2004), modified by Olurinola (2004), was employed for the experiment. Pure isolates of each bacterium were seeded using MHA plates for about 30 minutes, and a sterile cup borer of 10mm diameter was isolated to make wells on the solidified into which were filled with 0.5ml of the extract concentration 0.05g/ml of distilled water and allowed to diffuse for 45 minutes, after which the plates were subjected to incubation at 39°C for 24hrs. The zone of inhibition around the wells was measured in radii (mm) using digital vernier calipers (DVC). Ciprofloxacin (500mg) 2 micro-gram concentration was used as a standard for positive control.

Evaluation of anti-fungal activities of the samples

The selected fungi of choice used for this investigation were as indicated in the table provided.

The Poisoned Food Techniques (PFT) method by Shukui *et al.* (2008) was developed and modified in this study. 5ml of reconstituted extracts containing 0.05g/ml of their contents blended with 20ml of molten Potato Dextrose agar (PDA). The molten PDA was allowed to cool to about 45°C before pouring plinked and allowed to solidify.

72hours old cultured fungal was cultured in the center of the plates with the aid of a 4mm cup borer. Ketoconazole and carbendazim (12%) + mancozeb 63% w.p. was employed as a positive control at the recommended rate. Negative control plates (NTR) without any treatment, each incubated at 27°C for 72hrs, and mycelia growth present in each incubation was measured and calculated.

Mycelia growth inhibition was estimated in percentage using the formula below:

$$\text{Mycelia growth inhibition} = \frac{NTR-TR}{NTR} \times 100$$

Where NTR = diameter of fungi colony in negative plates (plates without any treatment) and TR = diameter of fungi colony in the trended plate.

Results and discussion

The physical characteristics data of the metal complexes of Ni (II) and Mn (II) with barbitone while varying the ratio of metal to the ligand ratios (1:1; 1:2) are shown in the Tables below. Table 1 reported the results of the elemental analysis and some physical characteristics of the metal complexes; Table 2 detailed the solubility properties of the complexes; Table 3 depicted the band peaks of FT-IR present in the metal complexes; Table 4 pictured the antibacterial properties; Table 5 shown the antifungal properties of the metal complexes.

Table 1: Physical Analysis of Barbitone Metals Complexes

COMPLEXES	RATIO	M/wt	% YIELD	COLOUR	M.Pt	% METAL	S	Cl
[NiLCl(H ₂ O)].5H ₂ O	1:01	385.2	43.61	Pale green	202	17.19	-	10.3
[NiL ₂ Cl(H ₂ O)].5H ₂ O	1:02	568.2	89.44	Pale green	156	15.88	-	9.91
[MnL(SO ₄)(H ₂ O)].5H ₂ O	1:01	441.9	33.33	Brown	248	14.7	11	-
[MnL ₂ (SO ₄)(H ₂ O)].5H ₂ O	1:02	624.9	90.08	Brown	154	13.64	13	-
Barbitone (C ₈ H ₁₁ N ₂ NaO ₃)	-	206	-	White	224	-	-	-

L = C₈H₁₁N₂NaO₃

The analysis of the metal complexes in Table 1 revealed that Ni (II) Barbitone complexes showed a very high proportion of percentage yields at different ratios in the ligand with 37.50% and 84.51%, with characteristic pale green residue thus, shows that the ligand has a dominant effect on the color of the metal Ni (II). Its melting point lies between 150-250°C to show the level of purity of the metal complexes (Hassan *et al.*, 2020).

Mn (II) Barbitone complex also has a high percentage yield when the ratio of metal to ligand varied by 1:2 with brown residue obtained, indicating that the ligand has a dominant effect on the color of the metal, also confirms the d-d electronic transition involving the promotion of an electron from one orbital level to another (Giwa *et al.*, 2013).

Solubility of barbitone metal complex Ni(II) and Mn(II)

The result of solubility of barbitone metal complexes of Ni (II) and Mn (II) is analyzed and shown in Table 2; the solubility of the complexes of Nickel (II) and Manganese (II) Barbiturate ligand in some organic solvents like water, DMSO, toluene, methanol, ethanol, ethyl acetone, this shows that metal complexes are non-polar in character.

Table 2: The Solubility Properties of the Complexes

SOLVENT	Ni(barbitone)	Ni(barbitone) ₂	Mn(barbitone)	Mn(barbitone) ₂
Water	Soluble	Soluble	Soluble	Soluble
DMSO	Insoluble	Insoluble	Insoluble	Insoluble
Toluene	Slightly soluble	Insoluble	Slightly soluble	Insoluble
Methanol	Slightly soluble	insoluble	Insoluble	Insoluble
Ethanol	Soluble	Soluble	Soluble	Slightly Soluble
Ethylacetone	Insoluble	Insoluble	Insoluble	Insoluble

3.2 FT-IR spectroscopy

The FT-IR examination of the free ligand and its corresponding metal complexes was discussed provincially in this study (Table 3). The IR displays various sharp bands in the mid-infrared region, clearly indicating the presence of barbital (Refat; Sharshar, 2012).

Table 3: The Band Peaks of FT-IR

COMPLEXES	RATIO	C=O	C-O	C-N	N-H	O-H	M-N	M-Cl	M-O
C ₈ H ₁₁ N ₂ O ₃ Na	-	1687	1315	-	3359	-	-	-	-
[NiLCl(H ₂ O)].5H ₂ O	1 : 1	-	1371	1095	-	-	755	382	454
[NiL ₂ Cl(H ₂ O)].5H ₂ O	1 : 2	1698	1391	1098	3241	3563	770	381	455
[MnL(SO ₄)(H ₂ O)].5H ₂ O	1 : 1	1678	1379	1240	3081	3211	760	-	496
[MnL ₂ (SO ₄)(H ₂ O)].5H ₂ O	1 : 2	1679	1380	1380	3081	3209	775	-	496

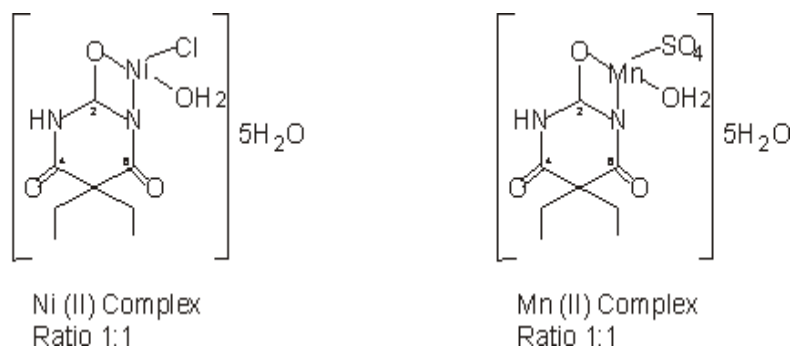
Sodium barbitalone = C₈H₁₁N₂O₃Na

There is a broad absorptions band at 3241.41 cm⁻¹ in the complex of Ni (II) (i. e. 1:2; metal: ligand) following the lattice water. Another strong narrow absorptions band at 3081.77 cm⁻¹ and 3081.74cm⁻¹ complex Mn (II) ratio 1:1 and Mn (II) ratio 1:2 respectively as compared to ligand (3321.63 cm⁻¹), while the prominent bands detected at 3563.49 cm⁻¹, 3211 cm⁻¹, and 3209 cm⁻¹ in the metal complexes of Ni (II) and Mn (II) but not found in the ligand in an indication of the presence of O-H bond or probably due to the formation of hydrogen bond perhaps due to the water of crystallization detected at 3563.49 cm⁻¹ (Ni) is due to the formation of hydrogen bonds. The ligand 3321.63 cm⁻¹ has a significant shift of $\nu(\text{NH})$ in complex Mn (II) at ratio 1:1 and 1:2 and are detected at 3211.76 cm⁻¹ and 3209.53 cm⁻¹ simultaneously, and then the attribute of O-H in the complexes in the form of water of crystallization and an unbounded or non-coordinated water molecule had resulted and affected the bandwidth. The frequency range of 1604-1698 cm⁻¹ has mastery over every strong IR and Raman band arising from carbonyls. The change was observed for carbonyl vibrations $\nu\text{C}=\text{O}$ in positions 4, 6, and $\nu\text{C}-\text{O}$ in position 2 (Figure 1), diagnostic for its participation in coordination (Hassan *et al.*, 2020). The $\nu\text{C}=\text{O}$ in complexes Mn (II) peak are observed at two distinct absorptions, (1604 - 1698 cm⁻¹), while complex Ni (II) absorptions bands at 1698 cm⁻¹. The $\nu\text{C}=\text{O}$ in positions at 4 and 6 do not correlate predictably with the coordination modes of this group. It might grossly come from intra or intermolecular hydrogen bonding interactions (Yilmaz *et al.*, 2009), which affect the carbonyl bands, shifting them to lower frequencies.

The $\nu\text{C}-\text{O}$ in position in 2 also shifted to lower frequencies (1456 cm⁻¹, 1452 cm⁻¹); (1319 cm⁻¹, 1449 cm⁻¹); (1413.84 cm⁻¹, 1413.89 cm⁻¹) concerning the ratio 1:1 and 1:2 for complexes Co (II), Ni (II), Mn (II) respectively compared to that of the ligand (1461 cm⁻¹) This indicates that the barbital anions coordinated to the metal via the carbonyl oxygen O which in position 2. The appearance of a medium intensity band at 438-618 cm⁻¹ in spectra of the complexes was ascertained by assigned to the stretch of M-O (Table 3) (Timerbaev *et al.*, 2006). There are characteristic peaks at 382 and 381 cm⁻¹ in Ni (II) complexes $\nu(\text{M}-\text{Cl})$ vibration reported by Barros-Garcial *et al.* (2005); Olagboye (2012).

The results from the FT-IR examination for the free ligand and its corresponding metal chelates prove the proposed structure of the complexes (Figure 1).

Figure 1: The Proposed Structure for Metal Chelates



UV-spectroscopy

The UV visible spectroscopic data of Ni (II) and Mn (II) metal complex with barbitone showed a high absorption band in the visible region of the spectrum curve, showing the presence of the metal molecule in the ligand metal complex (Hassan *et al.*, 2020).

Table 4: The UV visible spectroscopic data of Ni (II) and Mn (II)

COMPLEX	UV Spectrum	Absorbance	UV Spectrum	Absorbance
	200-400nm	range	400-800	range
C ₈ H ₁₁ N ₂ O ₃ Na	256nm – 427nm	0.010 – 0.039	646nm – 763nm	0.114 – 0.159
[NiLCl(H ₂ O)].5H ₂ O	244nm – 395nm	0.008 – 0.028	433nm – 763nm	0.008 – 0.033
[NiL ₂ Cl(H ₂ O)].5H ₂ O	233nm – 368nm	0.009 – 0.013	421nm – 678nm	0.008 – 0.078
[MnL(SO ₄)(H ₂ O)].5H ₂ O	253nm – 293nm	0.037	572nm – 762nm	0.128 – 0.179
[MnL ₂ (SO ₄)(H ₂ O)].5H ₂ O	256nm – 351nm	0.010 – 0.032	401nm – 762nm	0.094 – 0.130

As a result, there is a kind of counter-intuitive relationship in the UV visible spectral of transition metal complexes, Ni (II) complex absorbance range of 0.009-0.078nm respectively compared to absorbance range of the ligand 0.01-0.159 which indicate d-d electronic transitions require very little energy which occurred relatively insignificant (Hassan *et al.*, 2020). Manganese complex shows the highest absorbance 0.037-0.179nm in the range between 572-562nm wavelength indicating metal to ligand charge transfer MLCT transitions require much more energy but occur relatively significantly, leading to a strong absorbance in the spectrum (Refat and Sharshar, 2012).

Antimicrobial activities

The microbial activities with the sodium barbitone and its corresponding metal complexes; the standards (Amoxicillin and Streptomycin sulfate for antibacterial) towards different microorganisms were examined and tabulated. The data recorded in Table 5 and Figure 2 represented antibacterial activities of the free ligand, and its metal chelates were cultured against *Salmonella typhi*, *Ralstonia solanacearum*, *Streptococcus faecalis*, *Erwinia carotovora*, and *Pseudomonas glcinea* to access their potential antimicrobial properties.

Table 5: The Antibacterial properties of the metal complexes

Complex	<i>S.typhi</i>	<i>R.olanacearum</i>	<i>S.faecalis</i>	<i>E.carotovora</i>	<i>P.glycinea</i>
NiL	15	11	11	15	10
NiL ₂	15	7	19	16	13
MnL	-	-	-	-	-
MnL ₂	-	-	-	13	7
Ligand	-	-	-	-	-
Amoxicillin	18.5	17	15.5	18.5	16.67
Control (streptomycin Sulphate 0.05mg/L)	19.5	21	21	21.5	18

Figure 2: Antibacterial Activities of the Complexes.

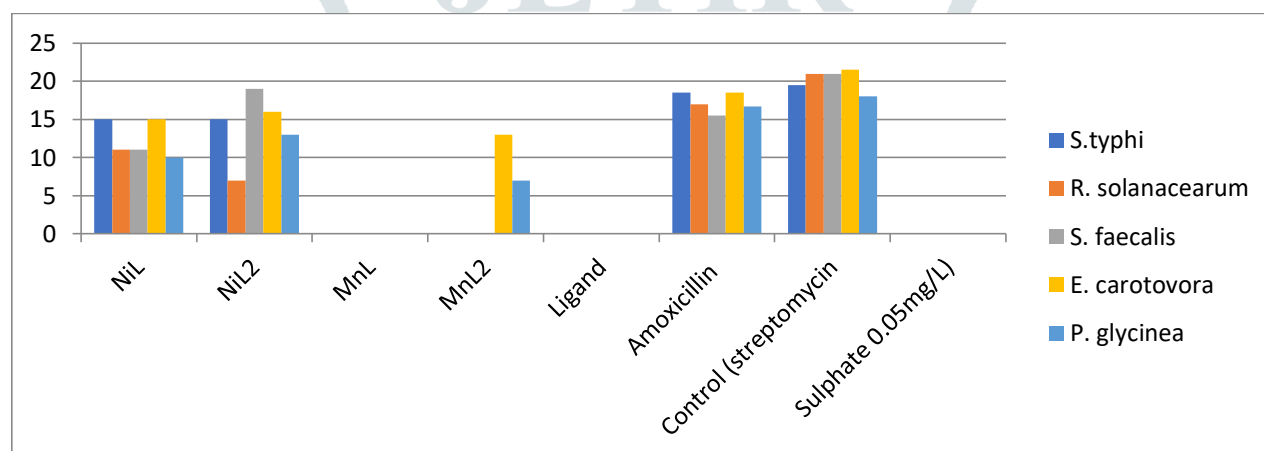


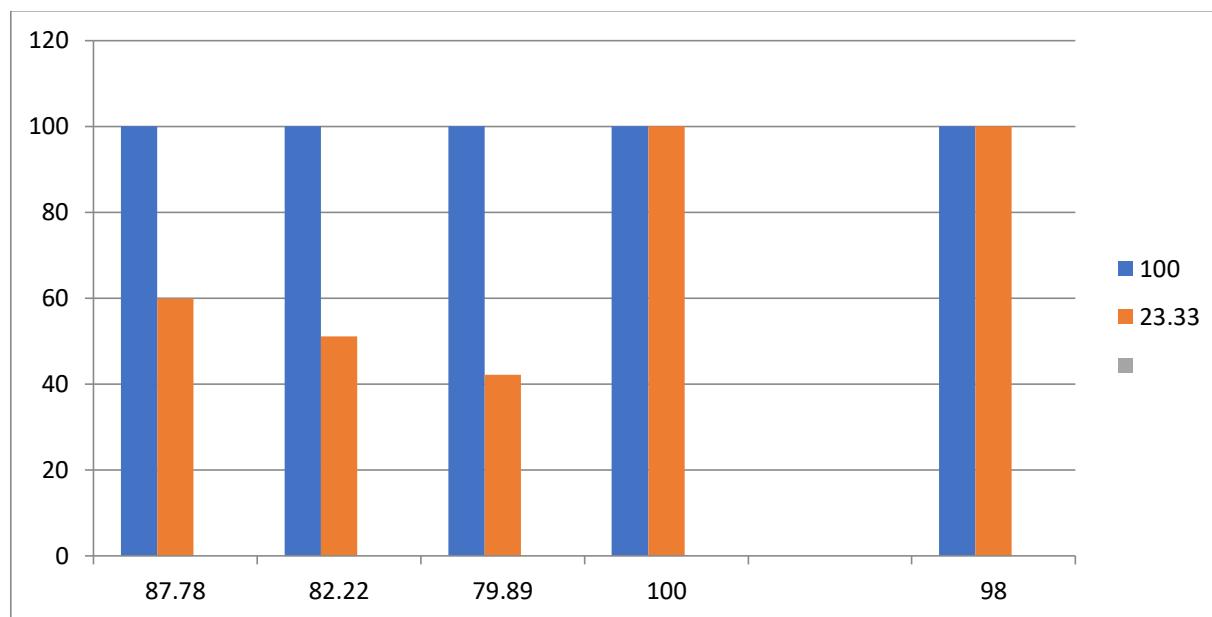
Table 6: Result showing antifungal activities of the compounds

Complex	<i>S. lacrymans</i>	<i>E. floccosum</i>	<i>T. verrucosum</i>
NiL	70	100	23.33
NiL ₂	87.78	100	60
MnL	82.22	100	51.11
MnL ₂	79.89	100	42.22
Carbendazin 12% + mancozeb	100	100	100
Ketokonazole	98	100	100

The results of the mycelial growth inhibition in percentage (%) after 72hrs of incubation at 25°C recorded 100% inhibitions against the selected fungi pathogens at 0.05% concentration.

The antimicrobial activities of the complexes in the case of *Epidermophyton floccosum*, Ni (II), and Mn (II) show the highest activity than Mn (II), and it has no innate against *Epidermophyton floccosum*.

Figure 3: Antifungal activities of the compounds.



The increase in the microbial activity of the metal complexes (Figure 3) inhibits the multiplication process of the microbes by blocking the activity sites of the enzymes (Murukan and Mohanan, 2007).

Conclusion

The free ligand sodium barbitone and its corresponding metals complexes (Ni (II) and Mn (II)) are elaborate and all other reagents used are prepared in the laboratory. The structures of free ligands and their metal chelates are proposed based on elemental analyses and spectroscopic measurements (FT-IR and UV visible Spectroscopy). Analytical data and square planer geometry for metal complexes are evident in the proposed structure. Also, the synthesized metal complexes with the free ligands are biologically active. The presence of metal complexes significantly enhanced both the antibacterial and antifungal activities against microbial strains compared to the free ligand.

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