METAL COMPLEXES OF AMINO ACID DERIVATIVES IN WATER AND ETHANOL MEDIA: (Synthesis, characterization and antimicrobial evaluations)

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Abstract: Glycine and tyrosine was used as a mixed ligand with transition metals in water methanol medium to form some complexes which was synthesized by direct mixing method and characterized by some physical properties such as percentage yields, colours, melting points and elemental analyses like chloride ions and Sulphur inform of sulphate and spectroscopic analyses like Uv – visible spectrophotometer scan through 200 – 800nm and infra-red spectrophotometer ranging between 300 – 3800cm-1. The results of metal complexes showed that they were pure and the percentage yields were moderately high and reproducible. UV-Visible spectroscopic studies revealed a change transfer bond which involves an electron promotion into an empty ligand orbital (metal to ligand charge transfer) from a metal-based orbital. Infra – red spectrophotometer results presumed the coordination sites of the complexes were probably from nitrogen of NH2 group and carboxylate ions of the carboxylic acid. The metal complexes were screened against some bacteria: Escherichia coli, Staphyococcusaureus, Shigelladysentriae, Klebsiella pneumonia, Salmonella typhii and fungi were Phythophthoria.megacourier, Fusariumvasinfactum and Chrysanthemum nigrumn. The results of antimicrobial studies alongside with the ligands and complexes formed, attested that metal complexes were extra proactive than the parent ligands used.

Keywords: Amino acid, metal complexes, antimicrobial and spectroscopic analysis.

INTRODUCTION

A lot of effort has been made to increase both reactivity and potency of some therapeutic agent by mixing them with some metals in which the cation and anions of some biomolecules to form metal complexes (Li-June, 2003). Spectacular colors in which transition metal complexes possessed are as a result of an electronic transitions which is either byd-d transitions or charge transfer bands (Harris, 1989). Glycine functions as a bidentate ligand for many metal ions. A distinctive complex of glycine with metal such as Cu(glycinate)$_2$, i.e. Cu(H $_2$NCH$_2$CO$_2$)$_2$,shows that it functions as a bidentate ligand that can exists as both cis and trans isomers and as a bifunctional molecule which includes N-centered and carboxylate-center reactions (Dunn,1991)..

There are 20 standard amino acids in which Tyrosine (4-hydroxyphenylalanine) is one of them that are used by cells to synthesize proteins. It is generally categorized as a hydrophobic amino acid, non-essential amino acid which have a polar side group, it is more hydrophilic than phenylalanine. (Douglas, 2001).

Due to high biological application, complex combinations of metal ions with amino acids are very important, however, synthesis of complexes of Ni(II) and Zn (II) with amino acids(D-Penicilamine and L-Cysteine) showed good therapeutically activities. (Rao, 1989). The therapeutically action of drugs are greatly influenced by existence of metal ions in the biological fluids. (Wong et al, 1999).

A lot of literatures revealed that tyrosine is found to be useful number of studies have found tyrosine to be useful in some certain situations like stress, cold, fatigue, sleep deprivation (Hao, 2001, Magill et al., 2003) decreases in stress hormone levels (Deijenet al., 1999), improve in reasoning and physical activities in human trials.(Mahoney et al., 2007). In 2010,Al-Mudhaffaret al, performed the antimicrobial activities after it was complexed with some metals such asCu(II), Co (II) or Ni (II) which shows high antibacterial activity towards E-coli and S.aureus than the corresponding ligands used.(Al-Mudhaffaret al., 2010).

Many researchers around the globe have developed interest in complexes of transition metals with amino acids which play an important role in biological systems.(Adkhiset al., 2000).Majority of microorganism have developed resistance to their corresponding antimicrobial which is a global concern. (Sara, 2010). This has led to continuous searching for innovative antimicrobial compounds, and also to synthesize complexes of high biologically important.(Farrell, 2003 and Johari, 2009).The synthesized complex have enhanced activity over their parent ligands due to the increase lipophilic character.(Chang et al., 2010).Antibacterial, antifungal, and anticancer properties have been displayed by some mixed ligand complexes of amino acid and its derivatives (Badar, 2012). The purpose of this research work is to synthesize, characterize and to evaluate the anti-microbial activities of the metal complexes of amino acids mixed ligand with transition metals in water- alcohol medium.

EXPERIMENTAL MATERIALS:

All the chemicals and solvents used were of analytical grade (Sigma – Aldrich) and used with no further purification. The metal salts used for the complexation are; Iron(III) sulphate, cobalt(II) chloride hexahydrate, manganese (II) chloride, nickel(II) chloride hexahydrate and copper chloride dihydrate were gotten from British Drug House Chemical Limited Co.Poole, England.

Measurement

The melting points of the complexes were recorded on a Gallenkamp melting point apparatus, Infrared spectral analyses were detailed using Shimadzu FTIR-8400S Fourier Transform Infrared Spectrophotometer in the range 4500-250cm^{-1}.Uv- visible spectrophotometer The solid reflectance were also determined using a double beam machine scan in the range 200 – 800nm. The percentage of chloride and sulphur in the metal complexes were determined by gravimetric methods, using silver nitrate (Argentiometric method) and barium chloride reagents respectively (Vogel, 1989 and Olagboye, 2015).

Antimicrobial Activity

The test microorganisms used for screening antimicrobial activity were standard pathogenic strains gotten from the culture collection unit of the Department of Microbiology, Ondo State University Teaching hospital, Akure, Nigeria. The laboratory tests were carried out at the Pest and Control Section of the Department of Crops and Protection, Federal University of Technology, Akure, Nigeria.

The synthesized compounds were tested for their antibacterial activities against Escherichia coli, Staphyococcusaureus, Shigelladysentriae, Klebsiella pneumonia, Salmonella typhii. Broth Dilution Method was used to investigate the antimicrobial activities of the compound which is one of the non-automated in vitro susceptibility tests (Jarrahpour, 2004). The control tube having no antibiotic is instantly sub cultured by scattering a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and was incubation at 37°C overnight. The accuracy of the drug concentrations was checked by reading the MIC (minimal inhibitory concentration) of the control organism (Joshi, 2009). The MIC is recorded as the lowest concentration inhibiting growth of the organism. Ampicillin and amoxicillin as a standard drugs was compared with the MIC value of the synthesized compounds.

The antifungal tests of newly synthesized complexes on the selected organismsPhythophthoria megacarrier, Fusariumvasinfectumand Collectotrichumnigrium, using Poisoned food techniques at 0.025g/ml concentration (Shukiaet al., 2008), the culture medium was a sterile molten potato dextrose (PDA) and the solvent used was water – dimethylsulphuroxide (DMSO). Mancozeb, a standard anti-fungal agent, as a positive control at 0.25g/ml concentration. A negative control plate (NTR) without any treatment was also set up. Mycelia growth inhibition was calculated in percentage. (Olagboye, 2013, Olagboye, et al, 2018 and Igwo-Ezikpeet. al., 2013)

RESULTS AND DISCUSSION

Reactions of the Glycine (L) and Tyrosine (L') ligands chemically with the metal (II) chlorides (Ni, Cu, Fe and Co) and Manganese (II) Sulphate gave reasonable yields with varying coloured complexes as shown below by chemical equations:

$MnCl_2.2H_2O + L + L' \rightarrow [Mn(L)(L')]Cl_2 + 2H_2O$……………………(1)
$NiCl_2.6H_2O + L + L' \rightarrow [Ni(L)(L')]Cl_2 + 6H_2O$………………...(2)
$CuCl_2.2H_2O + L + L \rightarrow [Cu(L)(L')]Cl_2 + 2H_2O$………………..…(3)

$Fe_2(SO4)_3.7H_2O$ + L + L' → [2Fe (L) L'] $(SO_4)_3$ + $7H_2O$………(4)
$CoCl_2.6H_2O$ + L +L' → [Co (L) L'] Cl_2 + $6H_2O$ ……………....…(5)

TABLE 1: PHYSICAL CHARACTERISTICS OF THE METAL COMPLEXES

Complex/compound	Ratio	Colour	% Yield	Melting Point (M.P)	% Cl	% S
[Mn(Tyr)(Gly)]SO_4	1:1:1	Milk colour	99.63	218	-	-
[Cu(Tyr)(Gly)]Cl_2	1:1:1	Blue colour	22.10	210-220	64.22	-
[Ni(Tyr)(Gly)]Cl_2	1:1:1	Green colour	72.42	220	19.76	-
[Fe(Tyr)(Gly)]SO_4	1:1:1	Brown colour	77.24	+250	-	10.93
[Co(Tyr)(Gly)]Cl_2	1:1:1	Pink colour	21.58	90-92	63.34	-

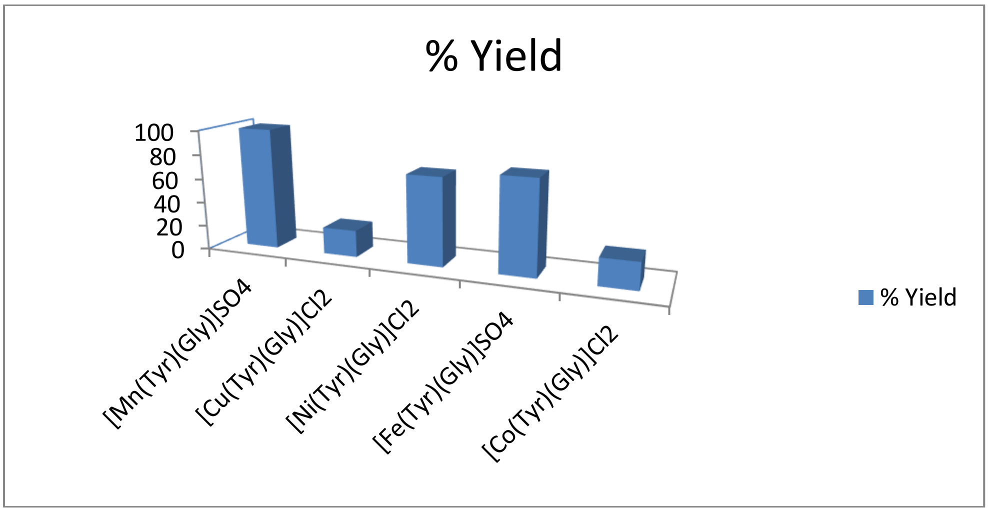

Figure1Chart showing the % yields of the metal complexes

TABLE 2: SOLUBILITY OF THE METAL COMPLEXES

Complex/Compound	Ratio	Solvents Used				
		Methanol	**Ethanol**	**Distilled water**	**Acetone**	**N-hexane**
[Mn(Tyr)(Gly)]SO_4	1:1:1	S	S	SS	S	SS
[Cu(Tyr)(Gly)]Cl_2	1:1:1	S	S	SS	S	S
[Ni(Tyr)(Gly)]Cl_2	1:1:1	S	SS	SS	SS	SS
[Fe(Tyr)(Gly)]SO_4	1:1:1	S	SS	S	SS	NS
[Co(Tyr)(Gly)]Cl_2	1:1:1	S	S	SS	SS	S
TYROSINE	-	S	SS	S	SS	S
GLYCINE	-	S	SS	SS	SS	S

S=Soluble, SS=Slightly Soluble, NS=Not Soluble

The physical parameters such as colours, percentage yields and melting points (M.Pt) or decomposition temperatures of the metal complexes are shown in Table 1. The complexes exhibited a wide range of colours that were in contract with those gotten for related coordination compounds. The different colours of the complexes obtained indicates that the ligands have dominant effects on the colours of the metal ions (i.e. Mn, Cu, Ni, Fe, Co) complexes (Olagboye, 2015)

The synthesized Mn(II), Cu(II), Ni(II), Co(II), Fe(II)and Zn(II) mixed ligand complexes of tyrosine and glycine were characterized in the Chemistry Department Ekiti State University, Ado-Ekiti. The metal complexes physical properties are presented in table 1. The metal complexes are of various colours. Mn(II) complex Mn(Tyr)(Gly)SO4 is milk in colour, Cu(II) complex Cu(Tyr)(Gly)Cl2 is blue in color, Ni(II) complex Ni(Tyr)(Gly)Cl2 is green in colour, Co(II) complex Co(Tyr) (Gly)Cl2 is pink, Fe(III) complex Fe(Tyr)(Gly)So4 is brown, showing that ligands have dominant effects on the metal salts (Wilkinson, 1998).It is also evident of coordination of metals to the ligand, The colour of the compounds is attributed to'd-d' orbital transition of electron between one energy level to another, by their magnitude of splitting, which in turn depends on the geometry of the complex, the nature of the ligand and charge transfer (Rodgers, 1994,). The pure substance always show higher melting point than the impure substance. The results of the elemental analysis for the experimental values are very close to the theoretical values. Argentiometric method was used to confirm the presence of chloride ion by the formation of white gelatinous precipitate of AgCl using AgNO3 solution outside coordination sphere as shown in equations 2 - 5. The % yields of the complexes are commendable. Cu(II) Complex Cu(Tyr)(Gly)Cl2 has the highest of 99.63% while Co(II) complex Co(Tyr)(Gly)SO4 has the lowest % yield of 21.58%. The complexes synthesized are non-hygroscopic, crystalline powder with diverse melting point varying from 90oC to 250oC. The melting points of the metal complexes are greater than their corresponding ligands (Olagboye, 2015). Fe(III) complex Fe(Tyr)(Gly)SO4 has the highest melting point of 250oC while Co(II) complex Co(Tyr)(Gly)Cl2 has the lowest melting point of 90oC as shown in figure 1.

The solubility of the synthesized metal complexes in several solvents in Table 2 confirmed the variety of the complexes with the ligands. In solvents like ethanol, methanol, acetone and n-hexane the complexes were found to be soluble. Mn(II), Cu(II) , Fe(III) and Ni(II) complexes were found to be soluble in methanol while Co(II) and Zn(II) complexes were found to be soluble in ethanol, suggesting that metal complexes are non- polar in nature. The solubility of the metal complexes in the common solvents indicated their low polarity which can be used to predict the suitable solvents that could be utilized for further spectroscopic studies (Jones and Fleming, 2010).

The UV-Visible spectrophotometer was used to examine and measure the level of unsaturation and conjugations of the metal complexes which were recorded in table 3 below.

TABLE 3: UV - VISIBLE SPECTROSCOPY RESULTS (nm)

COMPLEXES	RATIO	Band 1	Band II	Band III	Band IV	Absorbance
Mn(Try)(Gly)SO_4	1:1:1	760	680	350	250	
Cu(Try)(Gly)Cl	1:1:1	762	651	363	256	
Ni(Try)(Gly)Cl	1:1:1	678	644	361	253	
Fe(Try)(Gly)Cl	1:1:1	775	680	350	245	
Co(Try)(Gly)Cl	1:1:1	679	647	340	254	
Glycine	-			256	240	
Tyrosine	-			280	244	

TABLE 4: INFRA-RED ANALYSIS OF METAL COMPLEXES

COMPLEXES	RATIO							
P		V(O-H)	N-H	COO^-	H_2O	M-N	M-O	$-Cl^-$
Mn(Try)(Gly)SO_4	1:1:1	3408	3205,3040	1590,1609	739	,575	430	-
Cu(Try)(Gly)SO_4	1:1:1	3670,3864	3040,3129	1590,1608	739		432	373,384
Ni(Try)(Gly)SO_4	1:1:1	3626,3817	--	1585,	742	575	434	380, 387
Fe(Try)(Gly)SO_4	1:1:1	3438.3738	3119,3206	1590,1608	739	573	529	382
Co(Try)(Gly)SO_4	1:1:1	3658	3119,3208	1589,1609	740	575	528	380
Glycine		3438,	3171	1587,	-	500	-	-
Tyrosine		3710	3124	1589, 1514	-	-	-	-

The elevation of an electron from a metal-based orbital was revealed by UV-Visible spectroscopic studies into an empty ligand orbital (metal to ligand charge transfer) which show a change transfer bond. The intense adsorption in the UV-region around 240 – 280 nm is a feature of a metal-charge transfer (Kunkely and Voger, 2006) and allotted to charge transfer to the d orbitals of the metal, d-$\pi^*$from π orbital of the donor ligand and inter ligands to the d orbital of the metal, n-π^* transitions (Naemi and Moradian, 2009). The bands at 199 and 211 nm in the spectra of glycine and 210nm and 230nm in tryrosine (ligands) but with bands shift to higher wavelengths to the visible regions in the metal complexes shown in the table 3 suggests ligand coordination . The Uv - visble spectra of glycine and tyrosine display two different bands at 211 and 230nm absorption bands maxima allotted to n $\rightarrow\pi^*$ and $\pi \rightarrow \pi*$ transitions can be attributed to carbonyl and amino moiety in the ligands but with bands shifted in all the metal complexes(Aiyelabola*et al*,2012)

Maxima bands at 680 and 760nm assigned to $^2T_{2g}\rightarrow{}^2T_{1g}$ and $^2T_{2g}{}^2A_{1g}$ transitions which are traceable to octahedral geometry environment was showed by Mn(II) complex. Six coordinate tetragonal (octahedral) geometry shown by Cu(II) complex with two absorption band at 651 and 762nm and assigned to $^2B_{1g}\rightarrow$ $2B_{2g}$ and $^2B_{1g}\rightarrow{}^2E_g$. Absorption bands of Ni(II) Complex at 644 and 678nm indicate $^3A_{2g}\rightarrow{}^3T_{1g}$ and $^3A_{1g}\rightarrow{}^3B_{2g}$ transitions. These bands observed may be assigned to six coordinate low spin and high spin octahedral geometry.

The Fe(III) complex exhibited two absorption bands at 680 and 775nm , the highest in the group ,this may due it high spin electrons, d^5 configuration. $^3A_{2g}\rightarrow{}^3T_{1g}$ and $^3A_{2g}\rightarrow{}^3T_{2g}$, corresponding to an octahedral geometry. Cobalt (II) complex showed two absorption bands at 647 and 679nm assigned to $^2E_g\rightarrow{}^2T_{Ig}$ and $^2E_g\rightarrow{}^2T_{2g}$, these bands are assignable to low spin octahedral. However, all these bands featured in the Uv- visible spectra confirm octahedral geometry for all the mixed ligand complexes of glycine and tryrosine (Tella*at al.* ., Lever, 1968, Osowole*et al*, 2014 and Godwin, 2004). On the hand, effective coordination of the ligands is confirmed by the shift of the bands to higher wavelength in the metal complexes. d- d transition observed in the metal ions which could be d_{xz} or $d_{yz}\rightarrow d_{x^2-y^2}$ electronic transition can be attributed to the transition from ultraviolent region to visible region (Ogunniran, *et al*,2015)

The vibration bands at 3124 cm^{-1} and 3171 cm^{-1} assigned to $V(NH_2)$ group in the ligands (tyrosine and glycine) shifted to higher wave number in all the complexes 3129,3205,3206, 3208 cm^{-1} except $Ni(Try)(Gly)SO_4$; this is probably due to coordination of metal through or via nitrogen of NH_2 group. The vibration band found around 3710 cm^{-1} have been assigned to V(OH) stretching frequency in the tyrosine (ligand) but with both hypsochromic and bathochromic shifts in the metal complexes may due to hydroxyl groups of coordinated water(water of crystallization) in the metallic salts as glycine (ligand) has no hydroxyl group. The sharp bands found at 1587cm^{-1} in glycine and1589cm^{-1} in tyrosine but with higher band shift to 1609 cm^{-1} in the synthesized metal complexes are likely as a result of metals coordination through the coo-(carboxylate ions) (Pranay-Guru,2009 and Aiyelabola, 2012). Another prominent bands at 739,740 and 742 cm^{-1} occurred in every metal complexes are attributed to bonded water (inner water) in the coordination sphere but not found in the ligands spectra while bands found around 573 – 575cm^{-1} and 430 – 529cm^{-1} in the spectra of metal complexes may be attributed to M – L and M – O respectively, however, bands found around 373 – 383 cm^{-1} are due to chloride ions as confirmed from gravimetric method of chloride determination.(Ogunniran*et al* ,2008, Abdulsada, 2018 and Raman *et al*,2004)

ANTIMICROBIAL SCREENING

TABLE 5: ANTIBACTERIAL ACTIVITIES OF THE METAL COMPLEXES

	E.coli	S. aureus	S. dysentriae	K. pneumonia	S. typhii
[NI(Tyr)(Gly)]Cl2 1:1:1	11	15	12	12	10
[Fe(Tyr)(Gly)]SO4 (1:1:1)	15	16	5	7	
[Fe(Tyr)(Gly)]SO4 (1:1:1)	16	17	19	19	18

[Cu(Tyr)(Gly)]Cl2 (1:1:1)	18	8	17	6	5
[Mn(Tyr)(Gly)]So₄ (1:1.1)				18	
Amoxicillin	16	15	15	16	16
Ampicillin	20	25	16	15	16

TABLE 6: ANTIFUNGAL ACTIVITIES OF THE METAL COMPLEXES

	P.megacourier	F.vasinfactum	C.nigrumn
A	5	5	3
B	5	2	5
C	10	28	38
D	2	13	10
E	8	8	6
Monozeb	80	70	70

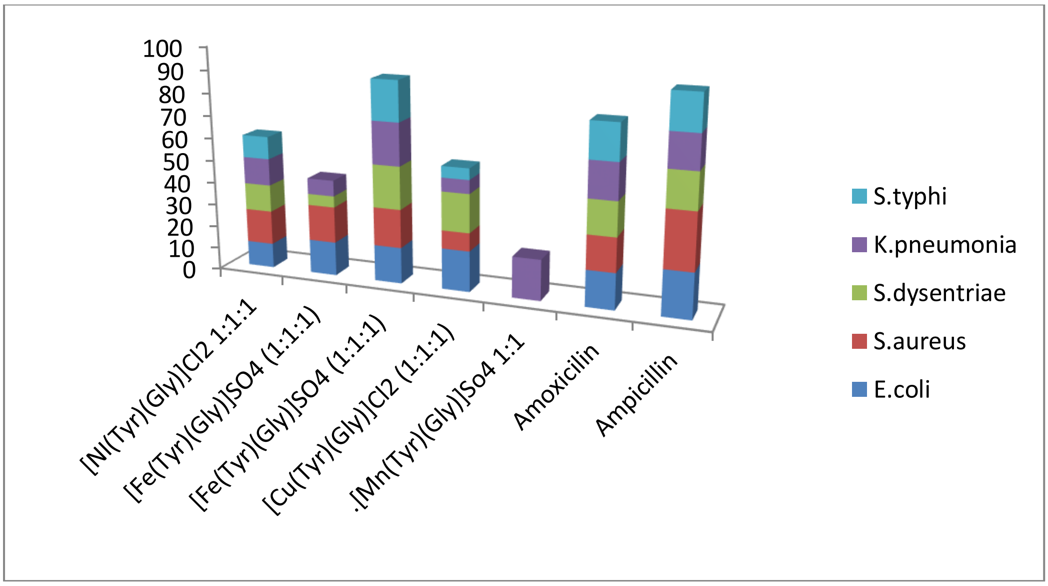

Figure 2: Chart showing Antibacterial screening of various metal complexes at 0.5% concentrations

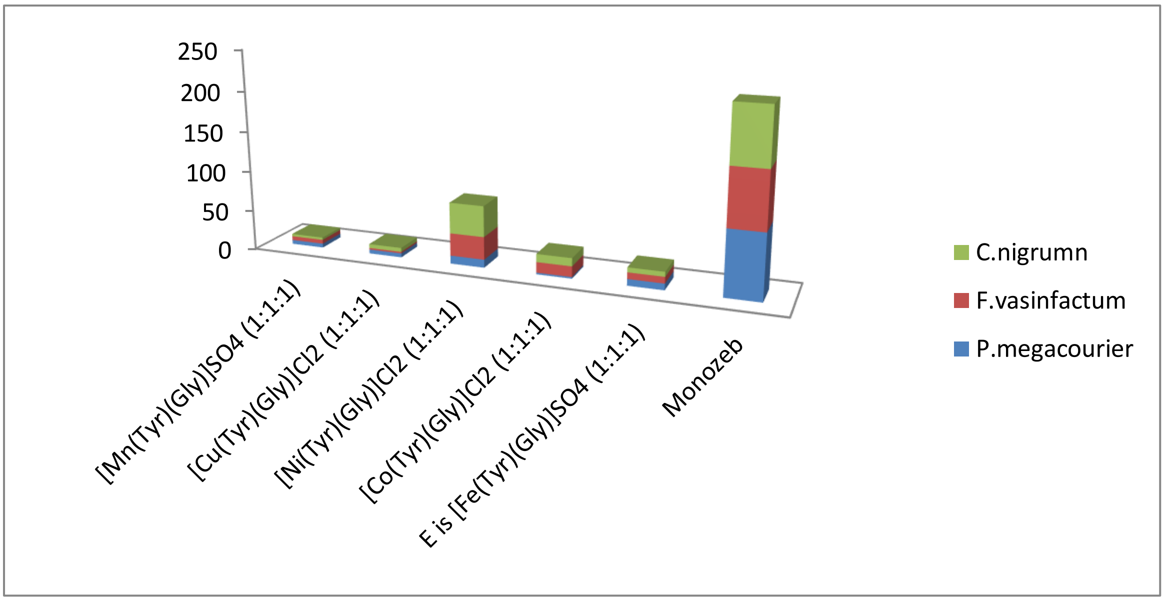

Figure 3 Chart showing the antifungal activities of the complexes

The antimicrobial activities of the synthesized compounds were tested. Their antibacterial activities against gram positive bacteria Escherichia coli, Staphyococcusaureus, Shigelladysentriae, Klebsiella pneumonia, Salmonella typhiiwas first tested.

The diagrams below showed the zones of inhibition after 24 hours of incubation at 37^{O}C of metal complexes at 0.5%. From antibacterial activity tests the significant results were obtained. The complex Fe(Tyr)(Gly)SO_4 and Ni(II) complex Ni(Tyr)(Gly)Cl_2 are effective on some microorganisms which include Escherichia coli, Salmonella Typhii, Shigelladysentriae, Klebsiella pneumonia and Staphylococcus aureuswhereas, the ligand (tyrosine and glycine) itself and Co(II) complex Cu(Tyr)(Gly)Cl_2 has no activity on the microorganisms. Fe (III) complex Fe(Tyr)(Gly)SO_4 is effective on Escherichia coli, Staphylococcus aureusand Klebsiela pneumonia but has no effect on Salmonella typhii. Ni (II) complex Ni(Tyr)(Gly)Cl_2 show an antibacterial activity on Klebsiella pneumonia. Klebsiella pneumonia and Escherichia coli was the most sensitive organism to the metal complexes. The diameter of inhibition of the metal complexes ranges from high to no zone of inhibition. Co (II) complex Co (Tyr)(Gly)Cl_2 has no effect on any of the five bacteria tested at any concentration. In addition, Mn(II) complex Mn(Tyr)(Gly)SO_4 if effective on Klebsiellapneuminiawith the minimum inhibitory concentration of 16.00µg/ml but has no effect on Shigelladysentriaeand Salmonella typhii.

The antimicrobial activity of the mixed complexes shows great potent against the five bacteria, the percentage inhibition displays that the mixed ligand is more potent than the parent ligand and be a better potential antibacterial drugs (Ogunniran et al, 2007).

Table 6 explained the results of antifungal screening of the metal complexes, mixed ligand complexes and Monozeb as the control. The biological activity of metal complex containing Sulphur increases on complexation. Liposolubility is one the factor that helps in controlling the antimicrobial activity by overtone concept which only permit the flow of lipids -soluble materials (Singh *et al., 2012*). Due to the ability to serve as principal cytotoxic, metal complexes is more active than the ligands (Al-Soud*et al.*, 2003).

CONCLUSION

In this study, Zn(II), Cu(II), Fe(III), Mn(II) and Co(II) complexes of Tyrosine and Glycine (mixed ligands) have been synthesized using direct mixing method which served as the secondary ligand and was characterized. The percentage yield for manganese complex was the highest followed by iron complex, then, nickel complex, whereas, copper complex and cobalt complex shown the least yield (i.e. Mn(II)>Fe(III)>Ni(II)>Cu(II)>Co). Different color transformations during the synthesis were showed by the metal complexes. The solubility of the complexes was tested and the complexes showed different solubility level. Coordination of metal to ligand occur at the v(NH_2)

group and COOH group. It is also an apparent that metals coordinate to the ligand bidentately through the v(NH_2) nitrogen atoms observed at the vibration bands 3171cm^{-1} and 3124cm^{-1}of ligands (glycine and tyrosine) and COOions of carboxylic group with sharp bands found at 1587cm^{-1}in glycine and 1589cm^{-1}in tyrosine but with higher band shift to 1609cm^{-1}. UV-Visible spectroscopic studies of the metal complexes revealed a change transfer bond which involves the elevation of an electron from metal-based orbital into an empty ligand orbital which is also known as metal to ligand charge transfer. The intense adsorption in the UV-region around 240 – 280 nm is a characteristics of a metal-charge transfer. The highest antibacterial effect on bacteria used: Escherichia coli, Staphylococcus aureus, Shigelladysentriae, Klebsiella pneumonia and Salmonella typhi was displaced by Cu(II) and Zn(II) complexes Whereas, the ligand itself and Co (II) complex had no effect. Escherichia coli and Klebsiella pneumonia was the most sensitive organism to the metal complexes. From the study, the viability and validation for the synthesis of mixed metal complexes was shown. The metal complexes shows great physical and chemotherapy properties than their corresponding parent ligand.

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