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SYNTHESIS, CHARACTERIZATION AND BIOCHEMICAL PROPERTIES OF NICKEL COMPLEXES OF AMINO ACIDS (HISTIDINE, METHIONINE)

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ABSTRACT

Ni(II)-amino acids coordination compound having octahedral stereochemistry, the general formula [NiL_2Cl_2] where L= Methionine, Histidine ratio(1:2) have been synthesized and characterized by element analysis, molar conductance and FTIR bonding pattern between metal ion and ligand show similar to each others. Electrochemical behaviour of the entire synthesized compound was studied using cyclic voltametry. Free radical scavenging activity (DPPH assay, ABTS assay) and anti-diabetic activity (α-glucosidase inhibition assay) was performed and found that both the activities showed moderate inhibition. The study will be helpful to provide an alternative remedy for the cure and treatment of targeted disease.

KEYWORDS: Synthesis, Amino acids, DPPH, Complexes.

1. INTRODUCTION

Amino acids are available in proteins and are categorized as essential elements for the prevention and protection from harmful ailments. From the chemical point of view, all the ligands are optically active and contain side chain groups to form a chelate ring with a metal ion bound at the α-β-amino nitrogen.[1] Transition metals having potential biological activity, play an essential role on metabolism and cellular signalling of drugs and as hydrogen storage media.[2] The transition metals like Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) are essential trace elements and used as nutritional supplement which act as co-factors in various enzyme systems such as metalloenzymes or as enzymatic activators.[3,4] Metal ions form different complexes with various biological macromolecules and with their synthetic derivatives which will be used as alternative for inhibiting the various ailments. Nickel is indispensable trace elements found in various biological systems. It is mostly found in nickel-based enzymes as an essential co-factor. It forms coordination complexes with amino acids within enzymes. It is also present in nucleic acids, but its role in DNA or RNA is still not clearly described.[5] Nickel (II) complexes have various biological potential have been reported it act as anticonvulsant and antiepileptic agents and is also described that it have antibacterial, antifungal, antimicrobial, antioxidant, and anticancer activities. Therefore, the research of Ni(II) complexes become important in the field of bioinorganic and coordination chemistry. This study were planned on some complexes which may have various aspects in the bio-coordination and bioinorganic chemistry.[6,7]

Amino acids are basic unit of protein which have a central carbon atom surrounded by a hydrogen atom, a carboxyl group (COOH), an amino group (NH_2), and an R-group. Meanwhile it has both amine (NH_2+R) and carboxyl (C=O) functional groups which is represented in general formula $H_2NCHRCOOH$, where R is one of many side groups.[8] It play a major role in regulating multiple processes related to gene expression, including modulation of the function of the proteins that mediate messenger RNA (mRNA) translation.[9]

Methionine is sulphur containing essential amino acid. It is used to as nutrition supplement and act as antioxidant in biological system.[10] Similarly, Histidine is a basic amino acid, essential for human development. It is also a precursor of histamine, which released by immune system cells during an allergic reaction. This research provide us new oppertunitities offered by the arising the medicinal chemistry and creating and exiting frame work for the development of a model generation of highly active drug with minimized side effects which could add significantly to be current critical research on practice. Therefore the attention have were synthesized the new Ni(II) complexes containing L-amino acids. The synthesized compound were characterised by elemental analysis, molar conductance CV, IR, UV- visible and also antidiabetic properties was evaluated. The study will provide a foundation for the development of remedy for the cure and treatment of targeted disease.

2. EXPERIMENTAL METHOD

2.1 Chemical and reagent

L- methionine, L- threonine, L- histidine, L- arginine, dinitrosalicylic acid, p-nitrophenyl-α -D-glucopyranoside, Sodium Chloride, Sodium Diphosphate, Disodium Phosphate were purchased from SRL, India. While $NiCl_2$, rat intestinal acetone powders were procured from Sigma-Aldrich, and DPPH, ABTS was brought from Alfa-Acer. All chemicals other chemicals i.e. ethanol, sodium hydroxide, water were synthetic grade and used without further purification.

2.2 Synthesis of Complexes at 6-7 pH

2 mM of amino acids (Arginine, Histidine, Methionine and Threonine) were dissolve in 30 ml water a transparent solution were obtained. In above solution of 1 mM of $NiCl_2$ were mixed drop by drop with continuous stirring, a blue/deep blue solution were obtained. The excess solvent was removed by evaporation to facilitate precipitation of the complex on cooling.[14] The General reaction for the preparation of complexes of nickel is as follows:

$NiCl_2$+ 2(L-amino acids)→ [Ni(L-amino acid)$_2$] + HCl

2.3 Conductivity measurement

Molar Conductivity of the complexes was measured by using an elico disital conductivity bride model CM-88 using freshly prepared solution of the complex in methanol.[15]

2.4 Electronic Spectra

Electronic (UV–Vis) spectra were recorded on a Shimadzu 1800 spectrophotometer using 10-mm quartz cells. All spectra of complexes were recorded in aqueous solution, with same concentration (0.03 mg/ml).[16]

2.5 IR Spectroscopy

Infrared (IR) spectra were obtained by the KBr pellet method using a Bruker Alfa-T model Fourier transform (FTIR) spectrometer (Bruker Instrument, Germany). The spectrometer was equipped with a Globar IR source, KBr beam splitter, and detector. For each spectrum, 16 scans were obtained with the resolution of 4 cm-1. The obtained IR spectra were processed by means of the program OPUS 7.0.[16]

2.5 Cyclic Voltammetric studies

The cyclic voltammetric measurements were carried out with a BAS Instrument having an electrochemical cell with a three-electrode system. The auxiliary electrode was an Ag /$AgCl_2$. Glassy carbon was used as a working electrode, while a platinum wire electrode used as a reference electrode. The concentration of complexes was taken 0.3 mg/ml, dissolved in supporting electrolyte 10 ml of 0.01 M solution of sodium perchlorate ($NaClO_4$) solution.[17]

3. Biochemical studies

3.1 *In-vitro* antioxidant assay

3.1.1 DPPH Assay

This assay is based on the measurement of the scavenging ability of antioxidant substances towards the stable radical. The free radical scavenging activity of the test samples of Ni (II) complexes and l-Arg, Meth, His and Thr examined by *in-vitro* method using DPPH radical as described by Sasikumar et al with slight modification. 125µl of various concentrations of test samples were mixed with 125µl of DPPH (4mg/100ml methanol) solution and 50 µl of tris HCl solution (pH 7.4). The mixture was incubated for 30 min and the absorbance was measured at 517 nm against a reagent blank in a micro titer plate reader (Bio-TEK, USA). Ascorbic acid was used as standards. All determinations were carried out in triplicate.[18]

% Inhibition = {[(AC - AS)/AC] ×100}

Where, AC is the absorbance of the control and AS is the absorbance of the tested sample. The concentration of inhibitor required to inhibit fifty percent of free radical activity under the mentioned assay conditions is defined as the IC_{50} value.

4. RESULTS AND DISCUSSION

Table 1: Analytical and physical data complexes.

S/N	Complex	Empirical formula	Colour	Formula weight	Yield (%)	Found value		
						C	H	N
2	[Ni(His)$_2$C l]	$C_6H_9N_3O_2Ni$	Off Blue	569.4	65%	21.04	1.7	24.6
4	[Ni(Met)$_2$C l]	$C_{10}H_{22}N_2O_4S_2Ni$	Palegreen	497.57	62%	24.1	2.0	28.1

4.1 Ultra violet- Visible (UV-VIS) and molar Conductance

The molar conductance of Ni(II) complexes of amino acids [[Ni(His)$_2$Cl$_2$], [Ni(Met)$_2$]Cl$_2$, was studied at 3×10-^{3}M concentration in room temperature. The values of conductivity are summarized in Table 2. All complexes were dissolved in Methanol. The molar conductance data varies Ni(II) complexes [Ni(His)$_2$Cl$_2$] and [Ni(Met)$_2$]Cl$_2$ are found 283, 234µs-1cm^{2}mol^{-1} indicating that the complexes were found 2:1 electrolyte nature. The molar conductance data revealed that metal to ligand molar ration is 1:2 for complexes.[15]

The electric absorbtion spectra of the amino acids Ni(II) complexes of amino acids in DMSO were recorded at room temperature band position of the absorbtion maxima and proposed geometry are listed in Table 2 and Fig 1.1 Electronic spectra of Ni(II) d-d transition band the in the regions 24390– 25000, 16528–16667, and 12987–13333 cm−1. These are assigned to the spin-allowed transitions $3A2g \rightarrow 3T_2g(I)$, $3A_2g \rightarrow 3T1g(II)$, and $3A_2g \rightarrow 3T1g(III)$, respectively, consistent with their well-defined octahedral configuration.[20] $[Ni(Met_2)Cl_2$ and $[Ni(His)_2Cl_2]$ complex found in two d-d band and one band found in π-π transition. Ni(II) and its complex found in one d-d band and other band found in L-M(LMCT) charge transfer transition or π-π, n – π transition.[21,22]

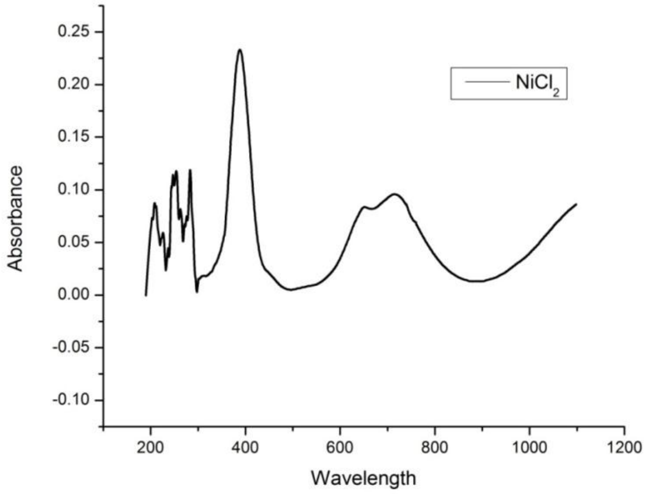

Fig. 1.1 Electronic Spectra of $NiCl_2$

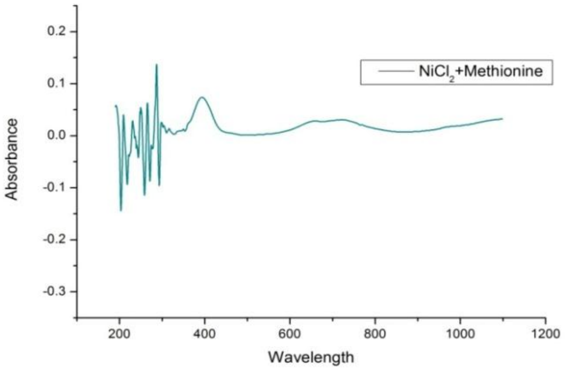

Fig.1.2 Electronic Spectra of $[Ni(Met)Cl_2]$

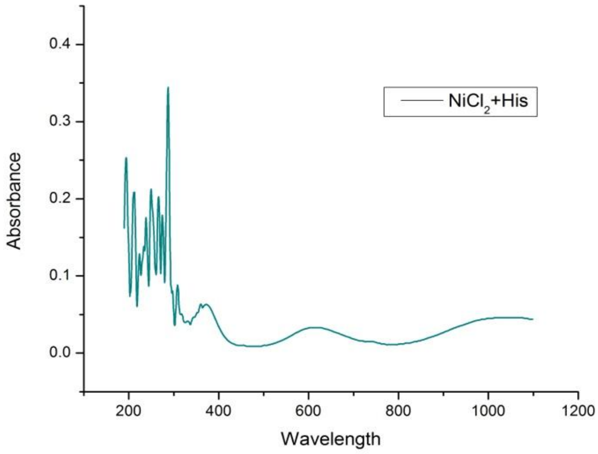

Fig.1.3 Electronic Spectra of [Ni(His)Cl$_2$]

Table 2: Band Assignment of UV-Vis. Spectra and molar conductance of Ni(II) and its complexes.

S.No.	Complex	Experimented Band (Transition)	Wave length Found (nm)	Wave number Found	Molar Conductance (electrolyte type)
2.	[Ni(His)$_2$Cl$_2$]	V_2 (${}^3A_2g$-${}^3T_1g$	620	16129	283(2:1)
		V_3(${}^3A_2g$-${}^3T_1g$	377	26525	
3	[Ni(Met)$_2$Cl$_2$]	V_1(${}^3A2g$-${}^3T_2g$)	721	13869	234(2:1)
		V_2 (${}^3A_2g$-${}^3T_1g$	655	15267	
		V_3(${}^3A_2g$-${}^3T_1g$	394	25380	

4.2 IR Spectra

Sophisticated Infra-Red spectroscopy instrument is used to dignose ionic and covalent bonds associated with coordination compounds. It is proposed that when metal ion combines with the ligand to form complex, its vibration spectra expected to be changed.

In our study, the IR spectra of Nickel complex, a sharp one peak at 3390-3330 which is due to symmetrical and asymmetrical stretching vibration of N-H in a primary group which demonstrated that the NH$_3$ group of zwitterions free ligand is depronated to –NH$_2$ and participated in the coordination with metal ion. The bending absorption band for NH$_3$ vibration is almost disappear [Ni(His)$_2$] complex in some reasons (Figure 2.1 and Figure-2.2 and Table 3). The –COO asymmetrical and symmetrical absorption band occur at between 1600-1450 in all complexes, respectively which are relatively lower frequency compare to those of free ligand. The reduction of absorption band frequency may be due to the formation of coordination bond through oxygen atom of -COO group with metal ion. Further more some band observed between 580-550cm-1 are attribute to (M-N=C) and those with the band of 645-655cm-1 are assigned to (M-O). FTIR data showed the coordination of the Amino acids with Ni (II) metal ions.[21,22]

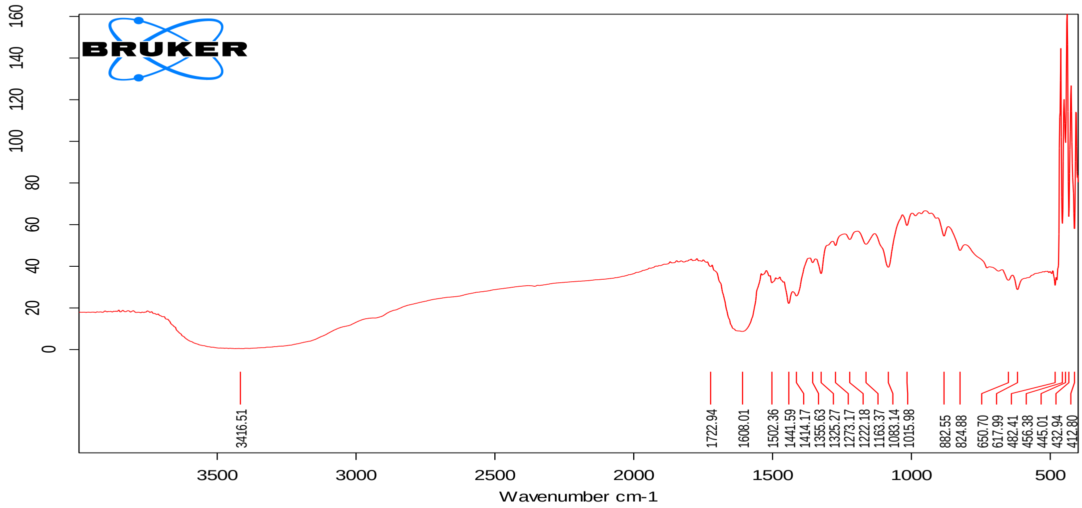

Fig. 2.1 FTIR spectra of [Ni(His)$_2$Cl$_2$] complex.

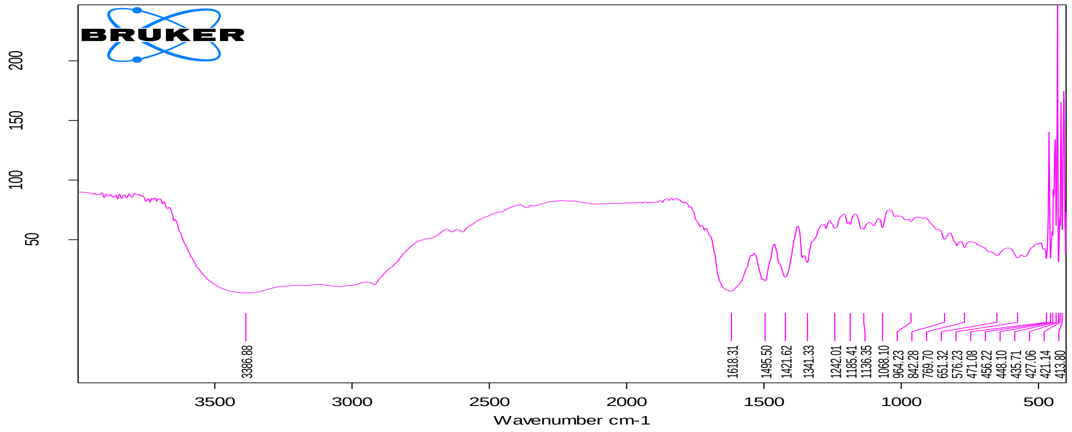

Fig. 2.2 FTIR spectra of [Ni(Met)$_2$Cl$_2$] comp.

Table 3: Most Significant FTIR band Spectra of the Ni(II) and its complexes.

S.N.	Complex	v(NH(str)	(C-H) Bending	v(COO) (asym str.)	v(COO) (sym str.)	v (M-N)	v (M-O)
2	[Ni(His)$_2$Cl$_2$]		1222	1608,1502	1441	-	650
4	[Ni(Met)$_2$Cl$_2$]	3386	1242	1618	1421	576	651

4.3 Cyclic Voltametry

Cyclic voltagramms of all complexes were recorded in 0.1M KCl electrolyte in solution. The current potential data, peak separation, peak current ratio of the voltagrrame at scan rate are recorded in table 4 and representative voltagrame of all complexes is shown in figure 6. In the all complexes (Ni(His)$_2$Cl$_2$], [Ni(Met)$_2$Cl2)] there is a cathodic peak at the -0.493, -0.417 and anodic peak at -0.017, -0.115 respectively. The cyclic voltagramme of the electro active species indicates that there is a two electron transfer process. The peak current for the anodic and cathodic peak in the voltagramme of the complex is remarkably lower than that of the metal salt. So the three complex [Ni(His)$_2$Cl$_2$] and [Ni(Met)$_2$Cl$_2$] electrochemical process is reversible.[23]

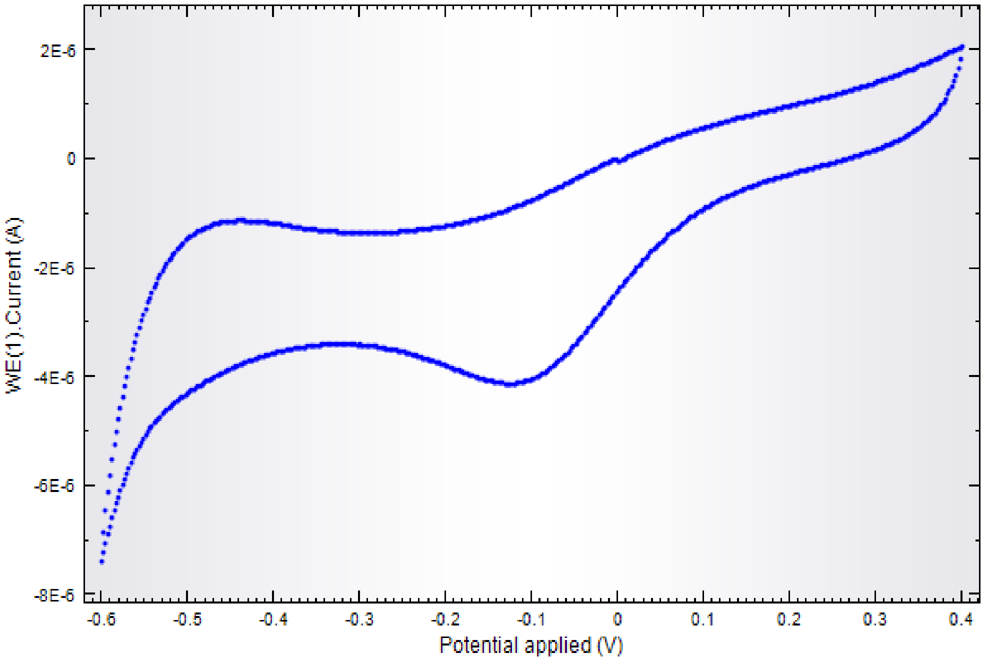

Fig 3.1 CV Spectra of [Ni(Met)$_2$Cl$_2$]

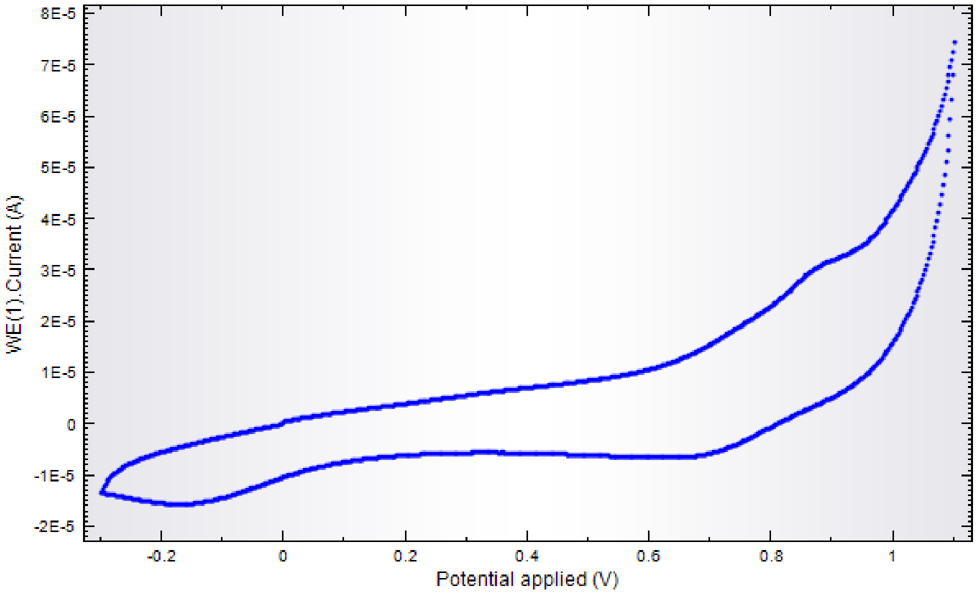

Fig 3.2 CV Spectra of [Ni(His)$_2$Cl$_2$]

Table 4: CV parameters analysis of all complexes.

S.No	Epc (mV)	Epa (mV)	Ep(mV)	$E_{1/2}$
2. $[Ni(His)_2Cl_2]$	-0.617	-0.869	0.252	-0.743
4. $[Ni(Met)_2Cl_2]$	-0.417	-0.115	0.586	-0.501

4.4 In-vitro antioxidant assay

4.4.1 DPPH scavenging assay

In the present study, *in-vitro* DPPH free radical scavenging activity of Ni(II) complexes of amino acids was evaluated and compared with standard i.e. ascorbic acid. DPPH showed concentration dependent activity on increasing the concentration of test samples more scavenging of free radical occurred. The results found from this study describe relation to the utilization of the synthesized compounds in the treatment of pathological diseases arising from oxidative stress. The IC_{50} values for DPPH scavenging activity was ranged from 818-2143 µg/ml. The $[Ni(His)_2]$ seen moderate activity among all the complexes with IC_{50} value 818.12 µg/ml while $[Ni(Met)_2]$ was cheapest scavenger with IC_{50} value 2143.06 µg/ml. IC_{50} values of compounds compared with IC_{50} value of standard ascorbic acid (IC_{50} = 215.02 µg/ml).

Pandeya et al examined DPPH scavenging activity of VO (IV) complexes of amino acids the results found that, VO - Histidine complex was showed potent scavenging activity with IC_{50} value 50.28 µg/ml among the other synthesize metal complexes.[24] Aarti Kamal examined DPPH scavenging activity of Cu(II) complexes of amino acids the results found that, $[Cu(His)_2]_2SO_4$ complex was showed potent scavenging activity with IC_{50} value 66.31 µg/ml and $[Cu(Gly)_2]_2SO_4$ was given lower scavenging activity with IC_{50} value 209.54 µg/ml among all synthesized metal complexes.[25]

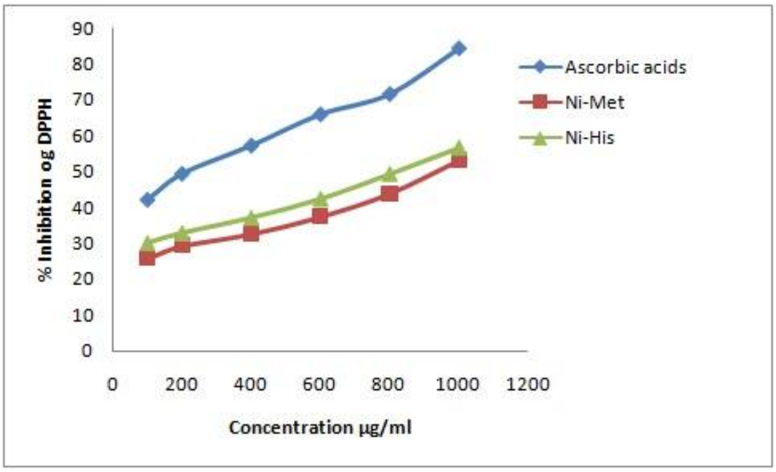

Fig. 4: Inhibition curve of Ascorbic acids, [Ni(Met)2] and [Ni(His)2] complexes.

Table 5 % Inhibition and IC50 value of DPPH assay for ascorbic acid and all complexes.

Con.	**% Inhibition of DPPH**		
	Ascorbic acid	**[Ni(Met)2]**	**[Ni(His)2]**
100	42.001	25.80065	29.9306
200	49.2341	29.21242	32.7205
400	57.1021	32.56536	37.0128
600	65.7841	37.32353	42.3073
800	71.4223	43.79412	49.3035
1000	84.1201	52.98093	56.6719
IC_{50} value	**215**	**991**	**818**

5. CONCLUSION

Transition metals have an essential role in biological system. In current work we have synthesized and characterized metal complexes via infrared and ultraviolet spectral properties. Sharp and intense peak between 1440-1618 cm-1 in IR spectrum represents metal-ligand bonding which represents that Ni(II) with amino acid complexes have synthesized. UV spectral bands in region of 394 -720 nm are showing d-d transition and 190-250 nm are showing π-π transition which is indicating involvement of imines nitrogen atom in synthesized metal complexes and assuring metal ligand coordination.

The electrochemical properties of the metal complexes reveal the reversible and irreversible redox process. All complexes possess antioxidant activity was found $[Ni(His)_2]$ most potent inhibition by DPPH. We have performed in-vitro antioxidant activity further work to be validating reliability.

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Conflict of Interest The authors declare that they have no conflict of interest.

REFERENCES

1. L. Lehinger, D. L. Nelson cox and M. M. Cox, W.H. Freeman CBS, New York USA, 3rd ed., 2005; 71- 95.
2. R. K. Andrews, R. L. Blakeley, B. Zerner, in: H. Sigel, A. Sigel (Eds.), Marcel Dekker inc., New York, 1988; 23.

3. A. Moester., Second ed. of the amino acid, vol.-I Acadmiv press Inc. New york, 1960; 19-21.
4. M. N. Hugnes, the Inorganic chemistry of biological process. John wiley and sons Newyork, 1981.
5. N. E Dixon, C. Gazzola, R. L. Blakeley and B. Zerner, J. Am. Chem. Soc., 1975; 97: 4131-41133.
6. L. N. Magner A History of Medicine, Taylor & Francis Group, LLC: Boca Raton, FL, USA. 2nd Ed. (2005).
7. Orvig, M. J. Abrams, Medicinal inorganic chemistry: introduction. Chem Rev., 1999; 99: 2201-2204.
8. G. Fraucher, E. Karnaukhova, A. Muehi, H. Hoeger, B. Lubec, Life Sci., 1995; 57: 813.
9. R. Scot and Leonard, American journal of clin Nutrition, 2006; 83(2): 500-507.
10. J. M. Berg, J. L. Thymoczcko, L. Stryer, Fifth ed.W.h Freeman and Company new York, 2001; 41.
11. Voet and J. Voet, Biochemistry, John Wiley and Sons, New York, 1993; 59.
12. L. Cheng, Y. Y. Sun, Y. W. Zhang, G. X. Tris, *Acta Crystallographica Section E*; 2008; E64: m1246.
13. W. J. Geary, *Coord. Chem Rev*., 1971; 7: 81 122.
14. IP. Tripathi, A. Kamal, A. Dwivedi, Ind. J. Appl. Res., 2014; 4(10): 262-264.
15. P. Tripathi, M. K. Mishra, R. Tripathi, C. Mishra, A. Kamal, L. Shastri, A. Dwivedi, U. K. Shukla , K. B. Pandeya. Res. J. Chem. Sci., 2014; 4(6): 13-1720(14).
16. V. Sasikumar and P. Kalaisezhiyen, Cogn., *Biochem Anal Biochem*, 2013; 3: 150. DOI: 10.4172/2161-1009.1000150.
17. R. Roberta, N. Pellegrini, A. Proteggente, A. Pannala, M. Yang, C. R. Evans, *Biology & Medicine*, 1999; 26: 1231–1237.
18. IP. Tripathi, A. Dwivedi, British J. Medic Med. Res., 2016; 16(6): 1-11.
19. A.B.P, lever, inorganic electronic spectroscopy, 1984; 507.
20. B. N. Figgis and J. Lewis, ‘Progress in Inorganic Chemistry, vol 6, 37, Wiley Inter science New York, (1964).
21. L. J. Bellamy, The infrared spectra of complex molecule, third ed. Wlley, new York, 1975; 266.
22. K. Nakamoto, Infrared spectra of inorganic and coordination compound, IV Ed. Wiley Interscience, new York, 1986; 288.

23. A. Calliste, P. Tortillas, D. P. Allais, A. Simon, J. L. Duroux, *Journal of agricultural and food chemistry*, 2001; 49(7): 3321-27.
24. K. B. Pandey, I. P. Tripathi, MK Mishra and N. Jaiswal, J. Bio. Sci. and Med, 2017; 2(4): 38-47.
25. A Kamal, Synthesis Characterization and Biochemical Studies of Copper complex, Department of Physical Sciences Faculty and environment, Mahatma Gandhi Chitrakoot Gramodaya Vishwavidyalaya, Chitrakoot, Distt. Satna (2017).