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Synthesis, Characterization and Antimicrobial Investigations of (Ag, Cu, Ni, Co,Mn andHg)Complexes With Schiff Base Derived From PVA andErythro-Ascorbic Acid Derivative

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Abstract
The aim of this work is the synthesis of new Schiff base derived from PVA and Erythro-ascorbic acid derivative (pentulosono-ɣ-lactone-2,3-enedianisoate) and its metal complexes of biological significance. All synthesized compounds were characterized by Thin layer chromatography (TLC) and FTIR spectra and aldehyde was also characterized by (U.V-Vis), ^{1}HNMR, ^{13}CNMR and mass spectra.
The synthesized Schiff base & its metal complexes were screened for theirinvitro antimicrobial activity against five pathogenic bacteria (*Escherichia coli, Shigella dysentery,Klebsiellapneumonae,Staphylococcusaureus, Staphylococcus Albus*) and two fungal (*Aspergillus Niger,Yeast*).The biological activity ofall complexes is higher than free Schiff base ligand andfollows the order: polymer < pol-Mn< pol-Ni< pol- Co < pol-Cu < pol-Ag < pol-Hg.This means that metal chelation significantly affects the antimicrobial behavior of the organic ligand.
Keywords: Schiff base, polymer metal complexes, antibacterial, antifungal, activity.

Introduction
The Schiff bases and their metal complexes have moreimportance recentlybecause of their application as biological (Lallan&Ragini2000), (Krishnankutty&Basheer 2006), (Saritha, Reddy,Satyanarayan&Jayatyagaraju 2006),biochemical, analytical, antimicrobial, anticancer, antibacterial,and antifungal and anti tumor activity. They have been studied as aclass of ligandsand are known to coordinate with metal ionsthrough the azomethine nitrogen atom. The synthesis oftransition metal complexes with Schiff base ligands are studieddue to sensitivity, selectivity and synthetic flexibility towardsmetal atoms. They used as catalyst, in medicine like antibioticsand anti-inflammatory agents and in the industry asanticorrosion (Spinu&Kriza 2000), (Boghaei&Mohebi 2002), (Liu & Zhang 2006), (Britovsek et al. 2001), (Budakoti, Abid&Azam 2006).
Schiff base and its metal complexes have a variety of applications in biological, clinical, analytical and pharmacological areas. Studies of a new kind of chemotherapeutic Schiff bases are now attracting the attention of biochemists. Earlier work reported that some drugs showed increased activity, when administered as metal complexes rather than as organic compounds (Suresh&Prakash 2010).
L-ascorbic acid (1) is one of the natural antioxidant present in biological system because of its activity to attack the free radicals and other reactive oxygen species, as the literatures points to the great role which ascorbic acid plays to prevent a number of diseases and it importance in food industry (Beifuss, Kunz&Aguado 1999), (Beifuss, Kunz&Voss 2000).In the current study, (Ag, Cu, Ni, Co,Mn and Hg) were employed as complexing metal and the synthesized complexes were evaluated for antibacterial andantifungal activities.

Experimental
Materials and Methods
Preparation of Poly Schiff base
Melting points were determined by electrothermal Stuart melting point apparatus and are uncorrected.IR spectra (in KBr) were recorded on 8400s Shimadzu FT infrared spectrophotometer. ^{1}HNMR spectrum was recorded on Ultra Shield (300 MHz) spectrometer with tetramethylsilane as internal standard.^{13}CNMR spectrum was recorded on a Varian Mercury plus 100 MHz spectrometer. Electronic spectrum was obtained using a (U.V-Vis) spectrophotometer type CECl 7200 England. Mass spectrum was recorded on IEOLJMS-7high resolution instrument. Thin layer chromatography (TLC) was performed on aluminum plates coated with layer of silica gel, supplied by Merck. The spots were detected by iodine vapor. All chemicals were obtained from Fluka or BDH.
Synthesis of 5,6-*O*-isopropylidene-L-ascorbic acid (2)
Dry hydrogen chloride was rapidly bubbled with stirring for 20 minutes into a (250ml) flask containing (10g, 57mmol) of powdered L-ascorbic acid (1) and (100ml) of dry acetone. After addition of (80ml) n-hexane, stirring and cooling in an ice-water, the supernatant was decanted. The precipitate was washed four times with

(154ml) of acetone-hexane mixture (4:7) (v/v), cooling in an ice-water and removal of supernatant after each addition. The last precipitate was dried under reduced pressure to give (2) (95.35%) as a white crystalline residue (Salomon 1963), m.p (206-208˚C). R_f (0.68) (benzene: methanol, 5:5) (v/v). FTIR (KBr, cm^{-1}): 3240 (O-H), 2993 (C-$H_{ali.}$), 2908 (C-$H_{ace.}$), 1751 (C=$O_{lac.}$), 1662 (C=C), 1431 (-CH-$_{asym}$), 1388 (-CH-$_{sym}$), 1141-900 (C-O), 767 δ(O-H) (O.O.P.) (Dudley&Fleming 1995).

Synthesis of 2,3-*O*-dianisoyl-5,6-*O*-isopropylidene-L-ascorbic acid (3)

To a cold solution of (2) (10g , 46mmol) in pyridine (50ml), anisoyl chloride was added as dropwise (17.5ml , 129mmol) with stirring .The resulting mixture was stirred for 2 hours , then kept in dark place at room temperature for 22 hours.

The mixture was poured into ice-water and stirred for 20 minutes, the supernatant was decanted. The oil layer was extracted with chloroform (150 ml), washed with water, dilute hydrochloric acid (5%) (2 × 100ml), saturated aqueous sodium hydrogen carbonate (100ml) and water. Dried over anhydrous magnesium sulfate, Chloroform was evaporated to produce brown syrup and purified from chloroform: petroleum ether (60-80˚C) (1:5) (v/v) to give (3) (76.5%) as a pale yellow solid (Mukhlis et al. 2012), m.p (102-104˚C). R_f(0.80) (benzene: methanol, 5:5) (v/v). FTIR (KBr, cm^{-1}): 3028 (C-$H_{ar.}$), 2983 (C-$H_{ali.}$), 2939 (C-$H_{ace.}$), 2843 (OC-$H_{ali.}$), 1749 (C=$O_{lac.}$), 1683 (C=$O_{est.}$), 1647 (C=$C_{ali.}$), 1604 (C=$C_{ar.}$), 1300-1107 (C-$O_{est.}$), 900-600 δ(C-H) (O.O.P.).

Synthesis of 2,3-*O*-dianisoyl-L-ascorbic acid (4)

Compound (3) (10g , 23.6mmol) was dissolved in a mixture of (65%) acetic acid (30ml) and absolute methanol (10ml) and stirred for 48 hours at room temperature. The TLC showed that the reaction was complete (benzene: methanol, 6:4).

To the resulting solution benzene (40ml) was added and evaporated (repeat this process four times) (Mukhlis et al. 2012).The residue recrystallized from chloroform and then diethyl ether to yield (4) (77.7%) as a white crystals, m.p (130-132˚C), R_f(0.42). FTIR (KBr, cm^{-1}): 3444 (O-H), 3008 (C-$H_{ar.}$), 2972 (C-$H_{ali.}$), 2843 (OC-$H_{ali.}$), 1741 (C=$O_{lac.}$), 1681 (C=$O_{est.}$), 1647 (C=$C_{ali.}$), 1606 (C=$C_{ar.}$), 1319-1112 (C-$O_{est.}$), 900-600 δ(C-$H_{ar.}$) (O.O.P.)(Mukhlis et al. 2012).

Synthesis of pentulosono-γ-lactone-2,3-enedianisoate (5)

To the stirred solution of sodium periodate (5.6g, 26mmol) in distilled water (60ml) at (0˚C), a solution of (4) (10g, 26mmol) in absolute ethanol (60ml) was added dropwise. After stirring for 15 minutes, ethylene glycol (0.5ml) was added as dropwise, stirring was continued at room temperature for 1 hour (Mukhlis et al. 2012).

The mixture was filtered and to the filtrate water (40ml) was added then the product was extracted with ethyl acetate (3×50ml), the extracts dried by anhydrous magnesium sulfate, then filtered and the solvent was evaporated and the residue recrystallized from benzene to yield the pure product of compound (5) (45%) as a white crystals, m.p (156-158˚C). R_f (0.70) (benzene: methanol, 6:4) (v/v). FTIR (KBr, cm^{-1}): 3040 (C-$H_{ar.}$), 2983 (C-$H_{ali.}$), 2843 (OC-$H_{ali.}$), (2671, 2559) (C-$H_{ald.}$), 1782 (C=$O_{lac.}$), 1749 (C=$O_{ald.}$), 1685 (C=$O_{est.}$), 1604 (C=$C_{ar.}$), 1300-1107 (C-$O_{est.}$), 900-600 δ(C-$H_{ar.}$) (O.O.P.).^{1}HNMR (DMSO δ ppm): 12.5 (s, 1H, CHO), 7.00-7.97 (dd, 8H, aromatic), 3.86 (s, 1H, H_4), 3.82 (s, 6H, 2OCH_3) (Dudley&Fleming 1995). ^{13}CNMR (DMSO δ ppm): 167.50 (C=$O_{lac.}$), 163.32 (C=$O_{est.}$), 131.86 (C-4), 131.83 (C-3), 131.81 (C-2), (123.44, 114.31, 114.28, 114.26) ($C_{ar.}$), 55.90 (OCH_3). The signal of aldehydic carbonyl was disappeared due to it showed out of the scale (Carey 2006). MS, (positive ion) m/z (relative intensity): 413 [M+1, (100)], UV (λ_{max}, nm, $CHCl_3$): 300.

Synthesis of poly (vinyl-4-aminobenzoate) (PVAB) (6)

4-Aminobenzoic acid (0.5g, 3mmol) was dissolved in $SOCl_2$ (2ml, 26.9mmol) and refluxed for 5hrs. The excess of $SOCl_2$ was evaporated under vacuum to obtained quantitative yield of 4-aminobenzoyl chloride. The 4-aminobenzoyl chloride was co-evaporated with diethyl ether to remove traces of $SOCl_2$. The resulting 4-aminobenzoyl chloride was dissolved in DMSO (5ml) and to this solution of polyvinyl alcohol(PVA) (0.5g), in DMSO (10ml), KOH (0.5g, 8mmol) was added. The reaction mixture was stirred for 48 hrs at room temperature. After completion of the reaction, the mixture was poured into ice-water and chloroform was added to extract the materials were not reacted. The residuewas evaporated to yield the ester (PVAB) (6)(0.89g), as a pale brown solid.FTIR (KBr, cm^{-1}): 3444 (NH_2), 3000 (C-$H_{ar.}$), 2926 (-CH_2-), 2856 (-CH-), 1688 (C=$O_{est.}$), 1604 (C=$C_{ar.}$), 1419 (-CH-$_{asym.}$), 1315 (-CH-$_{sym.}$), 1261-1111 (C-$O_{est.}$), 900-600 δ(C-$H_{ar.}$) (O.O.P.)(Dudley&Fleming 1995).

Synthesis of poly (vinylbenzoate-imine-pentulose-γ-lactone-2,3-enedianisoate) (7)

A mixture of poly (vinyl-4-aminobenzoate) (6) (0.14g), aldehyde (5) (0.14g), dry benzene (5ml) and 2 drops of glacial acetic acid was refluxed for 24 hrs, then collected the pale brown solid by filtration and washed with dry benzene to give compound (7)(0.3 g). FTIR (KBr, cm^{-1}):3030 (C-$H_{ar.}$), 2983-2879 (C-H_{ali}), 2843 (O-C-H_{ali}), 1770 (C=O_{lac}), 1699-1664 (C=$O_{est.}$), 1612 (C=N), 1577 (C=$C_{ar.}$), 1425 (-CH-$_{asym}$), 1311 (-CH-$_{sym}$), 1271-1107 (C-O_{est}), 927-615 δ(C-$H_{ar.}$) (O.O.P.)(Dudley&Fleming 1995).

Preparation of the poly Schiff base metal complexes

The Silver nitrate ($AgNO_3$) and Mercury chloride ($HgCl_2$) were obtained from Fluka. Nickel chloride ($NiCl_2.6H_2O$), Manganese Sulfate ($MnSO_4.H_2O$), Cobalt chloride ($CoCl_2.H_2O$) and Copper chloride ($CuCl_2.2H_2O$) were obtained from Aldrich.Sabouraud agar, Blood Agar Base,MacConky Agar and Nutrient

Broth were obtained from Oxoid LTD.

General procedure for the preparation of metal complex

The general procedure for preparation of metal complexes by preparing 5% from polymer solution and mixed with equal ratios of metal solution (Cu, Co, Ni, Mn, Ag, Hg) (10mmol),the mixture was stirred for 1 hr.

Evaluation testing of antimicrobial activity:

Antimicrobial susceptibility test measures the ability of an antimicrobial agent to inhibit or kill bacterial growth in vitro. This ability may be estimated by either the dilution method or the diffusion method. In this work we followed the Broth Dilution Method.Certain bacterial and fungi isolates were chosen, *Escherichia-Coli,Shigella dysentery* and *KlebsiellaPeneumoniae* were representing gm-ve isolates, *Staphylococcusaureus* and *Staphylococcus albeus* were representing gm+ve isolates, two fungal (*Aspergillusniger, Yeast*).Those Isolates were taken from about 50 patients at CPHL (Central Public Health Laboratory in Baghdad)

The Broth Dilution Method: Serial twofold dilutions of an antimicrobial agent are incorporated into broth containing tubes that are then inoculated with a standard number of organisms usually (10^5-10^6)colony-forming units (CFU) per milliliter. After the culture has been incubated at $37C^0$ for 18 hr. The lowest concentration that prevents growth after overnight incubation is known as the minimum inhibitory concentration (MIC) of the agent.The MIC is defined as the lowest concentration of antimicrobial agent at which there is no visible growth (Julio 1982), (Collee, Fraser, Marmio& Simmons 1999).

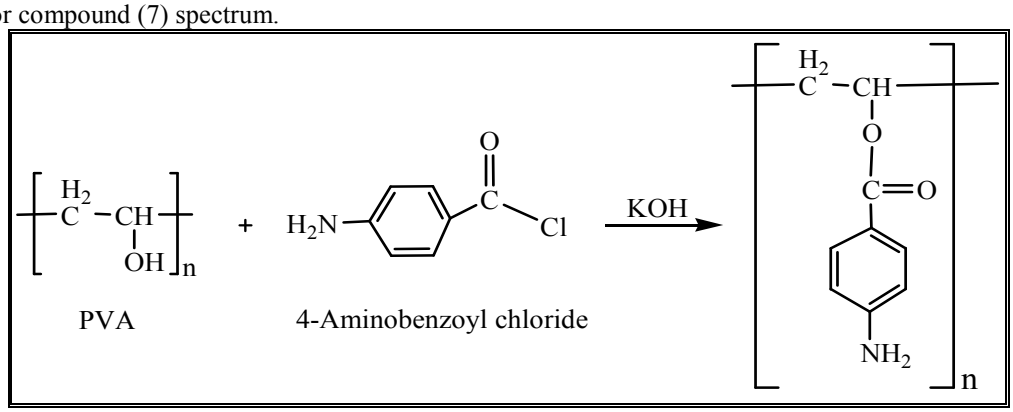
Results & Discussion

In the present work the synthesis of new Schiff bases derivative was achieved from pentulosono-γ-lactone-2,3-enedianisoate (5). The first step employs the protection of the hydroxyl groups at C-5 and C-6 positions in L-ascorbic acid with acetal formation leading to compound (2) using dry acetone in acidic media, following Salomon (Salomon 1963) method. This is followed by esterification of the hydroxyl groups at C-2 and C-3 positions with excess of anisoyl chloride in dry pyridine.

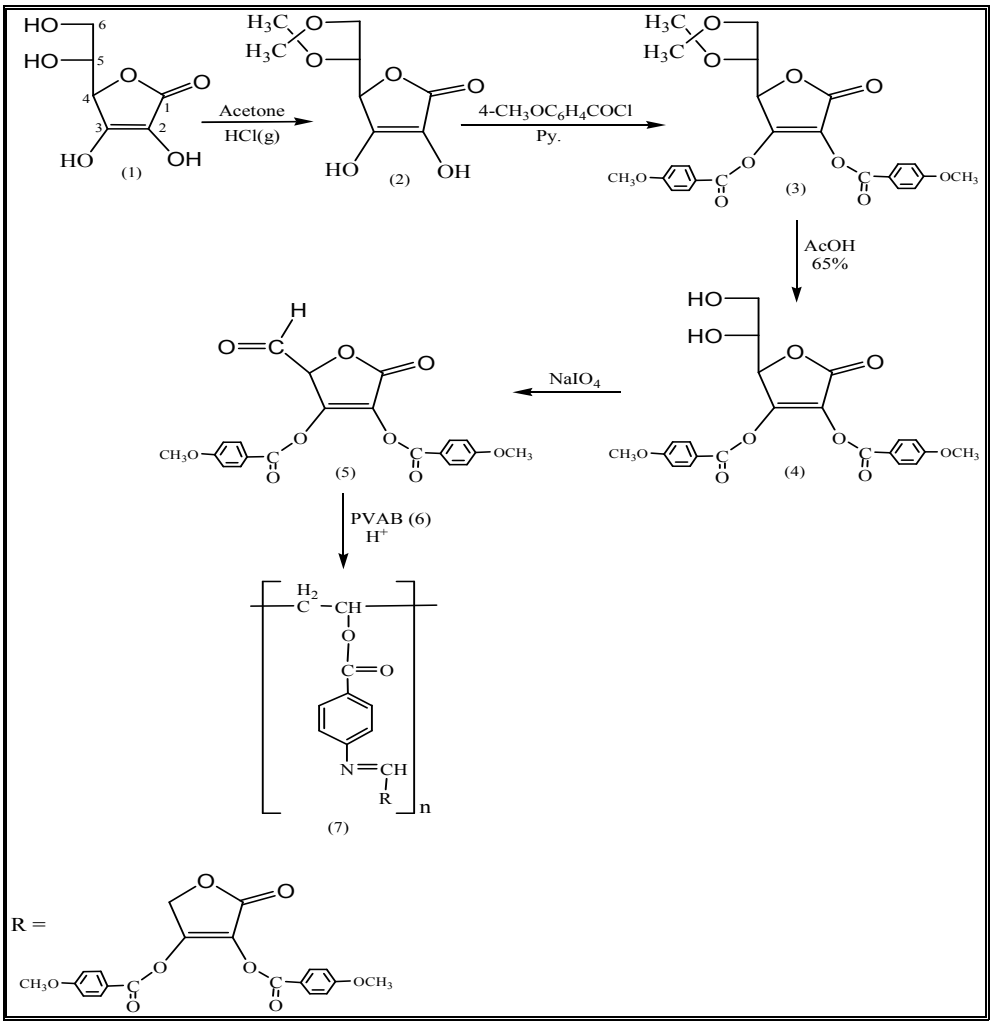
The FTIR spectra for compound (2) and (3) were confirmed the formation of compound (3) by disappearance of the bands for (O-H) of compound (2) and exhibited the band at (1683) cm^{-1} for (C=O) of the ester in compound (3) spectrum.

In order to prepare aldehyde (5), the acetal moiety was cleaved under acidic condition (Gazivoda et al. 2006) (65% acetic acid) for compound (3) to give (4) and oxidation of the product with sodium periodate to result (5), which gave a positive Tolen's test by formation a silver mirror (Vogel 1989). The FTIR spectra for compound (4) and (5) were confirmed the formation of compound (5) by disappearance of the bands for (O-H) of compound (4) and exhibited the band at (1749) cm^{-1} for (C=O) in compound (5) spectrum. The structure of (5) was confirmed by ^{1}HNMR which exhibited a signal at δ (12.5) ppm for (CHO) and was characterized by ^{13}CNMR and (U.V-Vis) spectrum which showed one peak at (300) nm (33333 cm^{-1}) assigned to ($\pi \longrightarrow \pi^*$) and ($n \longrightarrow \pi^*$) transitions. Finally, the mass spectrum showed a highest mass signal at [M+1] =413 with signal intensity 100%.

Compound (6) was prepared from treatment of polyvinyl alcohol with 4-aminobenzoyl chloride in presence of potassium hydroxide and DMSO as solvent with stirring for 48 hours, scheme (1), which was converted to compound (7) by reaction with aldehyde (5) in presence of glacial acetic acid and dry benzene scheme (2). The FTIR spectra for compound (6) and (7) exhibited the band at (3444) cm^{-1}due to (NH_2) for compound (6) spectrum and disappearance this band in compound (7) spectrum and display the band at (1612) cm^{-1} due to (C=N) for compound (7) spectrum.



Scheme (1): The scheme of prepared polyester



Scheme (2): The scheme of prepared polyschiff base

Antimicrobial studies

Antimicrobial activity of the synthesized compound and their corresponding metal complexes was determined against three Gram-negative bacterial strains (*Escherichia coli*,*Shigella dysenter and* Klebsiella *Pneumoniae*), two Gram–positive bacterial strains (*Staphylococcus aureus* and *Staphylococcus Albus*) and two fungal (*Aspergillus niger* and *Yeast*) Tables (1) and (2) respectively.

Table (1): The Antibacterial activity of the poly Schiff base and its metal complexes(minimum inhibitory concentration).

Isolates	Gram Stain	Concentration compounds metal µg/ml						
		PVA Schiff base	PVA Schiff base - Ag	PVA Schiff base - Hg	PVA Schiff base - Cu	PVA Schiff base - Ni	PVA Schiff base - Co	PVA Schiff base - Mn
Escherichia Coli	-ve	1000	150	20	200	800	750	900
Shigella dysentery	-ve	1050	150	30	250	850	750	900
Klebsiella Pneumoniae	-ve	1000	200	20	300	800	900	900
Staphylococcus aureus	+ve	1100	200	30	250	850	850	950
Staphylococcus albus	+ve	1100	200	40	300	850	850	950

Table (2): The Antifungal activity of the poly Schiff base and its metal complexes (minimum inhibitory concentration).

Isolates	Concentration compounds metal µg/ml						
	PVA Schiff base	PVA Schiff base -Ag	PVA Schiff base -Hg	PVA Schiff base -Cu	PVA Schiff base -Ni	PVA Schiff base -Co	PVA Schiff base -Mn
Aspergillus niger	1400	950	850	1000	1150	1150	1300
Yeast	1350	1000	950	1050	1100	1200	1300

The synthesized PVA-Schiff base and all polymer metal complexes exhibited a good degree of inhibitory effects on the growth of different bacterial and fungi isolates. Antimicrobial agents may affect cells in a variety of ways, many of which are poorly understood (Known-Chung& Burnt 1992).
Most of the commonly used antibacterial chemotherapeutic agents act by one of the following basic mechanisms: competitive antagonism of some metabolite, inhibition of bacterial cell wall synthesis, action on cell membranes, inhibition of protein synthesis, or inhibition of nucleic acid synthesis (Andres Goth 1981).
The Compounds (PVA-Schiff base-Hg) and (PVA-Schiff base-Ag) were, however, found to be active against all the Bacteria and Fungi. To the contrary, the compound (PVA-Schiff base),(PVA-Schiff base-Cu),(PVA-Schiff base-Co),(PVA-Schiff base-Ni) and (PVA-Schiff base-Mn)was found to be low active against the all bacteria and fungi.
The Polymer metal complexes showed higher activity than the free metal, these results substantiate our own finding and the findings of some other workers that biologically inactive compounds become active and less biologically active compounds become more active upon coordination (Chohan, Pervez, Rauf, Khan, Maharvi&Supuran 2004, p: 161), (Chohan, Pervez, Rauf, Khan&Supuran 2004,**19,** p: 51), (Chohan, Pervez, Rauf, Khan, Maharvi&Supuran 2004, **19**, p: 85), (Chohan, Pervez, Rauf, Khan&Supuran 2004, **19**, p: 417), (Li-June 2003), (Afanaseva, Ostrakhovitch, Mikhalchik, Ibragimova&Korkina 2001), (Clark&Stubbs 1996) this may be due to, the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials due to which liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of the metal ion is 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. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity in turn enhances the penetration of the complexes into lipid membranes and blocking of metal binding sites on the enzymes of the microorganisms. The metal complex may also be a vehicle for activation of the ligand as the cytotoxic agent (Raman, Muthuraj, Ravhchandran&Kulandaisamy 2003).
In the other side the presence of some compound in the microbial agent which have some groups like (-SH,-NH_2, -COOH,-OH) that attracts the metal elements (Cu, Co, Ni, Mn, Hg, Ag) to form specific chelate complexes and thus it will increase the lipophilicity of the complexes which in turn will facilitate concentration in the bacterial cell, where the eventual action is to impair their ability to synthesis protein on the ribosomes.Irrespective of the fact that Ni and Co were introduced in higher molar amounts and Cu was added in the smallest concentration, according to potency as antimicrobial agents the PVA-Schiff base chelates can be arranged in the following order:
Hgchelate > Ag chelate >Cu chelate > Co chelate > Ni chelate > Mn chelate
Other factors such as solubility,conductivity and dipole moment as influenced by the presence of metal ions may also be amongst the possible reasons causing enhancement of the bactericidal activity of the metal complexes as compared to the uncomplexed Schiff base compounds (Chohan, Zahid, Pervez, Khallid&Supuran, Claudiu 2005), (Chohan, Zahid,ul- Hassan, Mahmood, Khan, Khallid&Supuran, Claudiu 2005).
The fungi were found to be completely resistant to the polymeric preparation in this research irrespective of the fact that it was successful as antibacterial agents. It has been found that prepared metal polymeric complex compounds give better result when used as antifungal drugs, but in undesirable level to be considered as antifungal.

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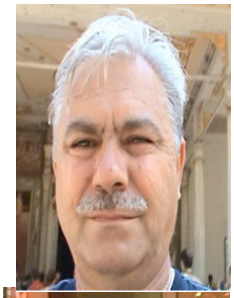

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