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Research Article

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Studies on the interaction and effect of Mn(II), Fe(II), Co(II), Ni(II),Cu(II), Zn(II) and Cd(II) mixed- ligand complexes of cephalexin mono hydrate and furan-2-carboxylic acid to different DNA sources

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ABSTRACT

To evaluate the Interaction of Mn(II), Fe(II), Co(II), Ni(II),Cu(II), Zn(II) And Cd(II) Mixed- Ligand Complexes of cephalexin mono hydrate (antibiotics) And Furan-2-Carboxylic Acid To The Different DNA Sources. All the metal complexes were observed to cleave the DNA. A difference in the bands of complexes .The cleavage efficiency of the complexes compared with that of the control is due to their efficient DNA-binding ability and the other factors like solubility and bond length between the metal and ligand may also increase the DNA-binding ability. The ligands (Cephalexin mono hydrate (antibiotics) and Furan-2-Carboxylic acid and there newly synthesized metal complexes shows good antimicrobial activities and Binding DNA , thus, can be used as a new drug of choice in the field of pharmacy. And for formulating novel medicinal agents.

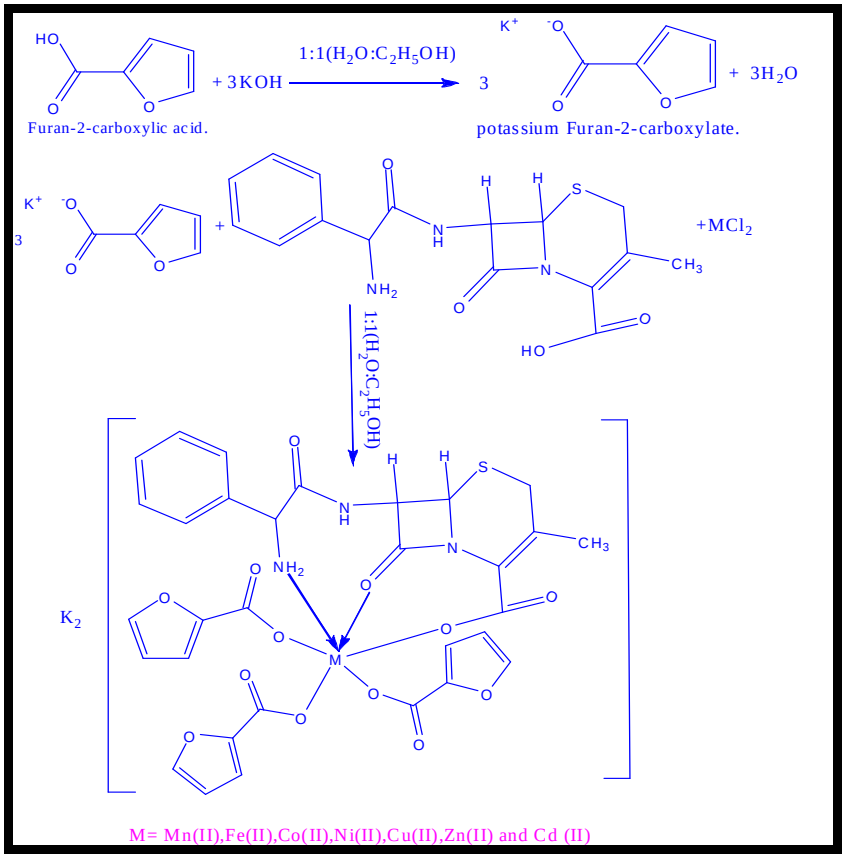
Key words: Binding DNA, (Cephalexin mono hydrate (antibiotics), Furan-2-Carboxylic Acid) complexes.

INTRODUCTION

Transition metal complexes containing heterocyclic compounds have been of considerable interest in terms of structural chemistry, catalysis and biological functions. The field has undergone spectacular growth due to the synthesis of multidentate ligands from heterocyclic compounds and the complexes of such ligands form with metal ions (1-3). The extensive literature on beta-lactam antibiotics compounds revels that there exists a strong connection between wide spectrums of biological activities with (4-7).

Furan-2-carboxylic acid($C_5H_4O_3$) (FCAH) is a heterocyclic aromatic compound with five- membered ring structure consisting of four CH_2 groups, one oxygen atom and a carboxylic group. (8,9).

In continuation of our work on the chemistry of Mn(II),Fe(II),Co(II),Ni(II),Cu(II),Zn(II) and Cd (II), Mixed Ligand Complexes of cephalexin mono hydrate (antibiotics) (CephH) = **(** $C_{16}H_{19}N_3O_5S.H_2O$) and Furan-2-carboxylic acid (FCA H) =($C_5H_4O_3$) . (9) Scheme (1)



Scheme (1): Preparation of $K_2[M(Ceph)(FCA)_3]$ complexes [9]

The resultant complexes are characterized by melting point, conductivity measurement, UV-Vis and Infra-red spectroscopy. Investigation of antimicrobial activities was carried out against the tested organisms. All the complexes are found to be in octahedral geometry. Preliminary results indicate that newly synthesized mixed ligand complexes $Na_2[M(Ceph)(FCA)_3]$ exhibited promising antibacterial activities and they warrant more consideration as prospective antimicrobials. The newly synthesized compounds were screened for their, DNA cleavage.

EXPERIMENTAL SECTION

Chemical and Solvents All the chemicals and reagents were of AR grade and used without further purification. Cephalexin powder DSM (Spain) and Furan-2-carboxylic acid (Merck).

A general method has been used for the newly synthesized
$Na_2[Mn(Ceph)(FCA)_3]$, $Na_2[Fe(Ceph)(FCA)_3]$, $Na_2[Co(Ceph)(FCA)_3]$, $Na_2[NiCeph)(FCA)_3]$, $Na_2[Cu(Ceph)(FCA)_3]$, $Na_2[Zn(Ceph)(FCA)_3]$ and $Na_2[Cd (Ceph)(FCA)_3]$ complexes (9)

Specimens
Plant (Capsicum annuum), Insect (Pierdae), Bacteria (*Escherichia coli*) and human blood.

DNA isolation
Plasmid DNA isolated procedure
E. coli isolates were screened for plasmid content by the alkaline method of (Brinboim and Doly) (10). Separated on a 1% a garose, at 50 ;ol for 1hr. and 1.30 hr. the DNA bands were visualized and photographed under UV light after the gel had been stained with ethidium bromide.

Total DNA for human Blood, Insect, and Bacteria
Promega Genomic DNA Purification Kit (A1120), used for extraction total DNA from human blood, Insect and Bacteria. According to the kit manual.

Plant DNA
Plant DNA extraction according to Ogunkanmi *et al* method (9).

DNA purity

Estimation DNA purity by using nanodrop method (ACT gene, USA). The absorbance at 260 nm (A260) and at 280 nm (A280) for DNA was measured to check its purity. The ratio A260/ A280 was found between 1.65 and 1.84.

RESULTS

DNA cleavage study

Preparation of culture media for the DNA cleavage studies of metal complexes and the isolation of DNA were carried out according to the literature procedure (10).

Circumstances that used in all experiments for gel electrophoresis were 75-100 V, 1-1.5 % Agarose gel for 1-2 h time with incubation of mixture in 37°C for 1-2 h. See Figure (1).

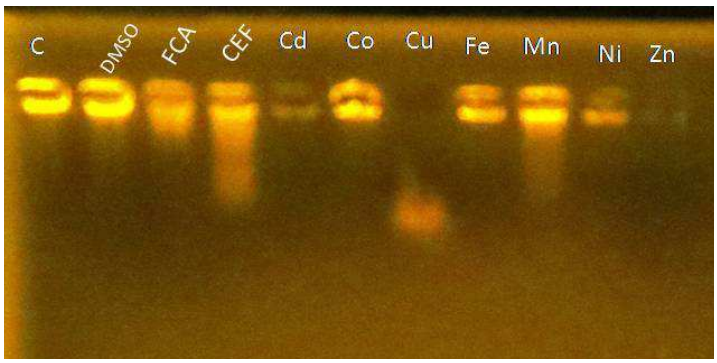


Figure 1: Human DNA-complexes interaction revealed by1% agarose gel electrophoresis 75V for 2h (C. control)

In Human DNA sample, the DMSO seems to be similar as control refers that was no damage, but with FCA, the human DNA shows a little damage as seen in weakness in brightness around the well, CEF shows more DNA damage that can be seen as clear smear far of the well.

Cd sample shows almost complete damage but weak brightness in DNA residues in the well, but it shows no smear that indicates to different molecular weights of small fragments of damaged DNA. In Co a little damage only can be seen, but it can easily compare with control sample but it may belong to the concentration of either the metal or the complex. Cu shows complete damage DNA in the complex with appearing of wide band far in the gel as an indicator for broken DNA that have the same molecular weight of the cuts yielded. A smear of smaller DNA breaks can be seen above in gel as well. Fe shows a little damage compared to control sample, while Mn shows a little damage but there was a smear appears directly after the well as an indicator for DNA damage to small pieces and that might need longer period for incubation before electrophoresis, while Ni breaks DNA a little but the brightness of non moved DNA which still in the well is weak.

Zn damages DNA completely and just a little broken DNA still in the well , the period of incubation might refer to saturation of binding location as in many biological cases as in enzymes.

The repeated results show completely to the division of DNA with Cu which transfers to the smear by the gel. The break is to be less than Zn through moving DNA outside the well but the (Ni, Co, Mn, Fe)is to be similar to control smear according to the gel.

The insects has been shown the little effect in the case of(Zn, Cd)and it has been shown largely the effect DNA in the case of (Co, Ni) with the larger break on (Fe or Mn).The complete break is appeared in (Cu)which is similar in effect in human case. This experiment on insects are repeated for more assurance (Zn,c.1/2DNA,2h,60w,75Vgel)and shows that the (Zn, Ni, Fe, Cd, DMSO) are similar in the movement of DNA breaks and bands in the gel followed up less degree in breaking but Cu, Mn, CEF, DNA breaks are to be complete one according to the arrangement from up to down while FCA, the DNA breaks were different due to the band doesn't more from the well but there is a similar that breaks into very small pieces. See Figure (2).

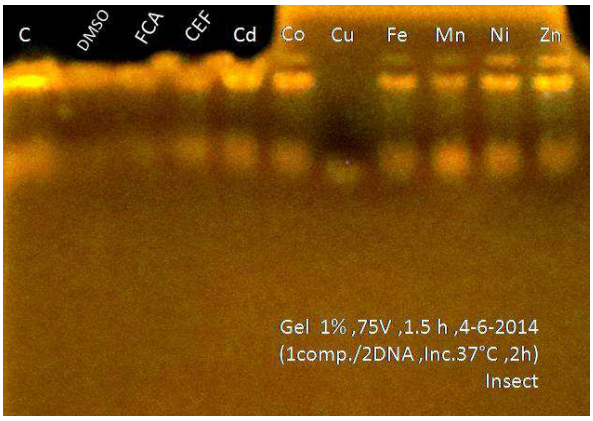


Figure 2: Insect DNA-complex interaction revealed by1% agarose gel electrophoresis 75V for 2h (C. control)

In plant, the experiment shows that the largest degree of break is appeared in Copper in addition to co, Fe but in certain degree. The image showed to not clear band of DNA in gel of (Co, Cd, Zn, Ni) due to it may be DNA mixed with complex through the incubation with 37 which may because pipetting errors. DNA breaks in gel according to the (Cu, Mn, CEF, FCA) with less degree of Cd, DMSO, CO, Fe, Ni, Zn and it has been similar in control. The break appears for (DMSO, CO, Fe, Ni, Zn, FCA, CEf, Cd, Cu, Mn) and the high break is appeared due to the arrangement and the plant material which is used in the experiment. See Figure (3).

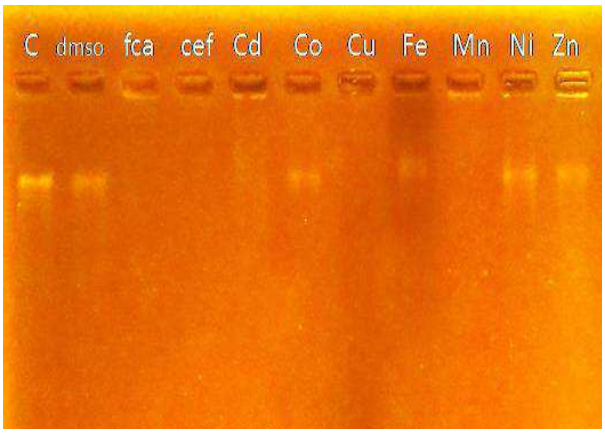


Figure 3: Plant DNA-complex interaction revealed by1% agarose gel electrophoresis 75V for 2h (C. control)

The bacterial (Ni, Cd) is little in effect in DNA, and DMSO is same as the control. The larger break of DNA appears (FCA,CEF ,Mn).The smears were similar in the aspect of effect .It has been shown that the DNA is still in the well and not move in positive pole where the Copper Cu is completely broken in DNA.

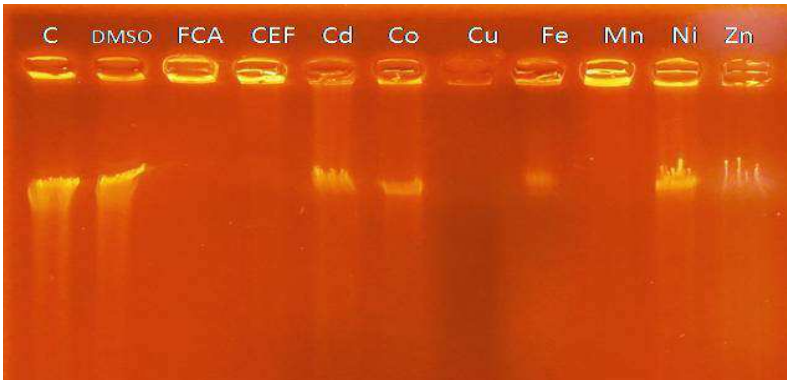


Figure 4: Bacteria DNA-complex interaction revealed by1% agarose gel electrophoresis 75V for 1h (C. control)

The experiment showed to highest break in Fe than Cd while the break is to be similar in co, Mn smears where Ni is more break Zn. The breaking DNA band was farther than the well. Ni compared with Zn which is relatively near to the well. See Figure (4).

The effect of Co is become according to the various smears which included (The plasmid) one gel band, break in DNA with high degree and long scattered smear at the end of gel .The next is Cd which appears two sides of gel that is to be near to the well which mean that the DNA breaks in the well is less than in this case. In Copper, it appears very light band according to the rest complexes bands. The end of smear which contained of DNA is near to the well but with less degree in Cd while in Ni it has been shown the same three bands in the control is still appeared. This case is repeated in Zn which the three bands is also still appeared The break in the end of smear is less high the Ni which refers that the break is happened with less degree of Ni and similar to control in addition to the correspondence of DNA in the well is similar to the control although there is little break refers to the little brightness of the three band in the gel. In CEF ,the bands were very weak while in FCA ,the break is little which refers to the high end break and near to the well compared with CEF in the same time ,the three bands DMSO were appeared but with little brightness. See Figure (5)

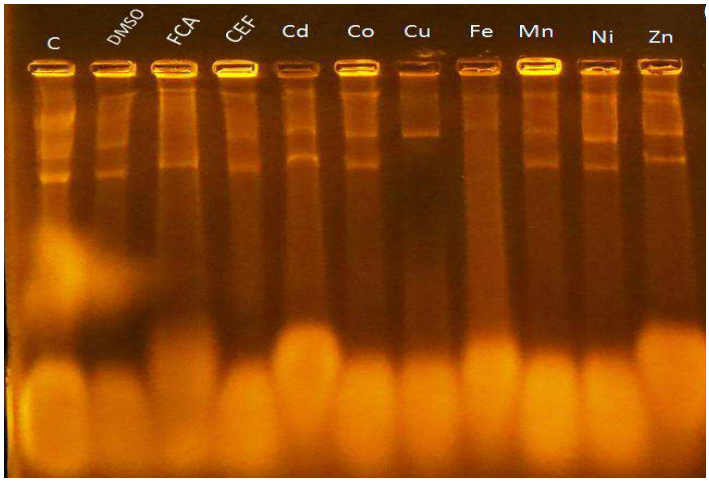


Figure 5: Bacterial plasmid DNA-complex interaction revealed by1% agarose gel electrophoresis 75V for 2h (C. control)

Furan-2-carboxylic acid (FCAH) =($C_5H_4O_3$)

-With FCA, the human DNA shows a little damage as seen in weakness in brightness around the well.
-With FCA, the Insect DNA breaks were different because the band doesn't move from the well but there is a similar that breaks that look like very small pieces.
-Plant DNA with FCA showed complete digestion.
-With bacterial DNA, the larger break of DNA appears FCA The smears were similar in the aspect of effect .It has been shown that the DNA is still in the well and not move in positive pole.
-In plasmid DNA/ FCA complex, the break is little which refers to the high end breaks and near to the well compared with CEF in the same time

Cephalexin mono hydrate (antibiotics) (CephH) /(CEF in picture)

-In Human DNA, CEF shows more DNA damage that can be seen as clear smear far of the well.
-In insect, Cu, Mn, CEF, DNA breaks are to be complete one according to the arrangement from up to down.
-Plant DNA with CEF showed complete digestion.
-With bacterial DNA, the larger break of DNA appears CEF. The smears were similar in the aspect of effect .It has been shown that the DNA is still in the well and not move in positive pole.
-In plasmid DNA/ CEF complex, the bands were very weak.

DISCUSSION

Dimethyl Sulfoxide Solvent (DMSO)

In Human DNA sample, the DMSO seems to be similar as control refers that was no damage , which confirms the effect of dimethysulfoxide (DMSO) against the induction and rejoining of DNA double-strand breaks (DSBs) in mammalian DNA.(11) and accelerate DNA rejoining (2)In insect shows that the DMSO is similar in the movement of DNA bands in the gel with control sample followed up by a less degree of breaking. In plant, no DNA breaks with DMSO, The bacterial DNA/DMSO mixture is no effect on DNA and DMSO is same as the control. (12) In

Plasmid the three bands were appeared with DMSO but with little brightness. All these results confirms that DMSO not only rejoining of DNA double-strand breaks but also enhancing transcription (13) ,even with the presence of Ethidium bromide (that used to make DNA visible under UV light), or with breaking caused by irradiation light because DMSO reducing the indirect action of radiation(14).

M(II) Mixed- Ligand Complexes of Cefalexin And Furan-2-Carboxylic Acid - Different DNA Sources, M= Mn(II), Fe(II),Co(II), Ni(II),Cu(II),Zn(II) and Cd(II)

$Na_2[Cd(Ceph)(FCA)_3]$ / (Cd in picture)

Many reports suggest that DNA can also be taken into account as a potential target of this metal cadmium .(15) because DNA offers many binding sites for cadmium.(16,17,18,19) most studies on cadmium complex are focused on generating new materials up to now and there are few reports about the interaction of cadmium complexes with DNA.(20,21) Cadmium exposure can produce various direct and indirect gene toxic effects, such as DNA strand breaks, DNA-protein cross-linking, oxidative DNA damage, apoptosis, and inhibition of DNA repair.

(22-25) In Human DNA, Cd sample shows almost complete damage but weak brightness in DNA residues in the well, but it shows no smear that indicates to different molecular weights of small fragments of damaged DNA. Cadmium carcinogenesis involves multiple mechanisms, including DNA strand breakage and inhibition of DNA repair.(26,27) and the Experimental evidence shows that cadmium (Cd) could induce oxidative stress and then causes DNA damage in animal cells.(22). Insects DNA it has been shown that there was a little effect in the case of Cd. In plant, Cd showed obvious DNA breaks confirmed that the Oxidative stress induced by Cd accumulation in plants contributed to DNA damages and was likely an important mechanism of Cd-phytotoxicity in Vicia faba plants. (22). the bacterial DNA /Cd mixture is little in effect in DNA. the Plasmid DNA/Cd complex which observed in both sides of the gel that is to be near to the well which mean that the DNA breaks in the well is less in this case even if it has been reported that Cd(II) ion can react with nucleobases, nucleic metallothionein and plasmid DNA causing extensive damage to these targets.(20) , but far from the well the breaks look higher than the other materials supposed that Cd breaks a certain areas from the DNA and/or it may need longer incubation time to do its job .

$Na_2[Co(Ceph)(FCA)_3]$ /(Co in picture)

It was clear that some Cobalt II complexes may cleave DNA (28).In Human DNA, Co a little damage only can be seen, but it can easily compare with control sample, it may belong to the concentration of either the metal or the complex, but In Bacterial DNA, the experiment showed to little breaks with Co compared with the control, that confirms the results the previous researches talked about effect of Cobalt II complex on DNA of Animals and Bacteria(29) .Insects DNA showed largely the effect DNA in the case of Co.In plant, no or very little DNA breaks with Co. in Plasmid it seems that a very little cleaving effect on the DNA as the plasmid DNA bands appeared like that in control. Which confirms the results of using many complexes of Co with different circumstances that this metal bind strongly and cleavage the DNA of different organisms(30,31)

$Na_2[Cu(Ceph)(FCA)_3]$ /(Cu in picture)

Copper (II) complexes with the same ligands normally display analogous Coordination geometry and binding mode toward DNA.(32,and it could cleave DNA via hydrolytic mechanism(33)Copper (II) complexes affected the animal DNA (29, 34) which been clear for human DNA. In Human DNA, Cu shows complete damage DNA in the complex with appearing of wide band far in the gel as an indicator for broken DNA that have the same molecular weight of the cuts yielded. A smear of smaller DNA breaks can be seen above in gel as well. The repeated results show completely to the division of DNA with Cu which transformed to a smear in the gel. In bacteria the Copper (Cu) is completely broken in DNA.), and that means that the Copper (II) complexes inhibit the growth of bacteria to a greater extent as the concentration is increased.

(29, 34) .It was clear that the Copper (II) complexes play important roles in DNA cleavage reactions.(35) like The complete break in Insects DNA which appeared in (Cu) which is similar in effect in human case. And In plant, the experiment shows that the largest degree of breaks appeared were in Copper thus we can say that Plant DNA with Cu showed complete digestion. Even with plasmid the Cu is not completely brakes DNA it may need more time in incubation or higher concentration or preparation of the complex in the mean time of the experiment or less DNA or it might due to saturation of active sites in both DNA and Cu complex.

$Na_2[Fe (Ceph)(FCA)_3]$ /(Fe in picture)

DNA cleaved by oxidative water soluble Iron complexes (36) Iron complexes cleaving DNA oxidatively (37) when we measured the relationship between FE complexes and DNA by gel electrophoresis after incubation we observed that In Human DNA, Fe shows a little damage compared to control sample. Insects DNA showed the larger break on Fe. In plant, no or very little DNA breaks with Fe.in bacterial DNA Fe complex, the experiment showed a high

break in Fe. in Plasmid ,Fe damages the DNA and almost there is no or very weak band in the gel compared to all the other complexes. The weakness in DNA damage may due to Fe concentration when incubated with DNA because it was reported that The effect is stronger at increased concentrations of metal ions ,and even in electrophoresis with TBE medium which contain EDTA ,because the iron forms complexes with EDTA and also is bound by other components.(38).

Na_2[Mn (Ceph)$(FCA)_3$] /(Mn in picture)

The strongest magnetic coupling between Mn (II) ions shows the highest DNA cleavage efficiency (39) Mn (II) are commonly used to promote DNA binding and cleavage (40),after all that In Human DNA, Mn shows a little damage but there was a smear appears directly after the well as an indicator for DNA damage to small pieces and that might need longer period for incubation before electrophoresis .Insects DNA showed the larger break on Mn. In plant, no or very little DNA breaks with Mn. With bacterial DNA, the larger break of DNA appears Mn The smears were similar in the aspect of effect .it's obvious that the DNA is still in the well and not move in positive pole. And with Bacterial Plasmid the Mn is poorly damages the DNA, although it has been confirmed by The DNA cleavage studies that indicate that all the synthesized Mn (II) complexes cleaved gram Negative and positive Bacterial DNA effectively.(41) and the poorly efficiency of cleave DNA by Mn (II) complexes may due to cofactor requirements for the support of DNA binding are much more permissive;(40).

Na_2[Ni (Ceph)$(FCA)_3$] /(Ni in picture)

The mechanism of Nickel (II) effect on DNA is that the metal inhibit the incision step of nucleotide excision repair.(42) Nickel (II), Copper (II) and zinc(II) complexes with the same ligands normally display analogous coordination geometry and binding mode toward DNA. The suggestion to sort out the DNA-binding affinity by both the order of magnitude, going from Ni to Cu to Zn,(43) damage to DNA brought about by its covalent binding with the metal complex.(44) . Ni breaks Human DNA a little but the brightness of non moved DNA which still in the well is weak. Insects DNA showed largely the effect DNA in the case of Ni. In plant, no or very little DNA breaks with Ni. The bacterial DNA/ Ni mixture is little in effect in DNA. in plasmid Ni has been shown the same three bands in the control is still appeared although it seems that there is a very little break. The damage existed but unclear and that may due to the fact that the intensity of the bands on the gel changed due to varied concentrations of the complex. (44).

Na_2[Zn (Ceph)$(FCA)_3$] / (Zn in picture)

Considering the fact that zinc (II) ions play essential role in prostate cells, we can assume that possible formation of Zn–DNA may be related closely with development and progression of a prostate cancer. (45) In Human DNA sample , Zn damages DNA completely and just a little broken DNA still in the well , the period of incubation might refer to saturation of binding location as in many biological cases as in enzymes. The repeated results showed that breaks were less than Zn through moving DNA outside the well. It was reported previously that Zn affected on DNA damage (43-45).Thus different organisms DNA or DNA sources has been tested as Insects DNA which has been shown that there was a little effect in the case of Zn, and in plant, no or very little DNA breaks with Zn. Where incase of Bacteria, the experiment showed obvious breaks with Zn compared with the control. In Plasmid, Zn which the three bands in the gel image of the plasmid DNA is still appeared ,the breaks in the end of the smear is lesser in height than the Ni which refers that the breaks were happened with less degree.

CONCLUSION

We studied binding of **Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) An D Cd(II)** ions into DNA by the use of the simple and well available methods (spectrophotometry and gel electrophoresis).From all experiments we use different source of DNA as available in the laboratory and the differences in results may due not only to DNA sample but also to the concentration and the purity of the DNA itself or to the other components of the DNA extraction materials and materials concentrations and with considering that

There are differences between DNA of the organisms especially in bases sequences and composition. Thus from the above, it was clear concluded that as the complexes was observed to cleave the DNA, therefore inhibits the growth of the pathogenic organism by cleaving the genome [46]

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