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Synthesis, Spectral Characterization of Azithromycin with Transition Metals and a Molecular Approach for Azithromycin with Zinc for COVID-19

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ABSTRACT

Introduction: The discovery of azithromycin (Figure 1) as a type of macrolide was very important in the 20th century which was presented as an example of medicinal chemistry and drug design. Recently, azithromycin has a special and interesting profile in this research on pharmacotherapy for COVID-19.

Aim and Objective: Synthesis, spectral characterization and thermal analysis of azithromycin complexes with transition metals (Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) were discussed.

Method: Azithromycin act as a bidentate ligand with the formation of 1:2 (M: L). measurement of magnetism and spectral data shows octahedral structures for all complexes.

Result: All of them have Oh geometry and these results are confirmed by Nujol and ESR spectra. Azithromycin act as a bidentate ligand through N (CH3)2 group of dopamine and a hydroxyl group. Also have different sites available for coordination that carries more electronegative charges and the computational study confirms these results.

Conclusion: Hyper chemistry program confirmed the binding sites of azithromycin. Azithromycin complexes have higher activity than commercial azithromycin for some strains with the remarkable effect of Zn-azithromycin complex. A molecular approach for COVID-19 was studied.

Key Words: Macrolide complexes, Azithromycin Complexes, Biological activity, COVID-19

INTRODUCTION

The discovery of azithromycin **(Figure 1)** as a type of macrolide was very important in the 20th century which was presented as an example of medicinal chemistry and drug design. Recently, azithromycin has a special and interesting profile in this research on pharmacotherapy for COVID-19. That demonstrated a synergistic antiviral effect with hydroxychloroquine against SARS-CoV-2 in vitro[1] and clinical studies.[2] It has been observed that there is an antiviral effect of azithromycin alone on SARS-CoV-2.[3]Azithromycin can reduce virus entry into cells.[4,5,6]Among the COVID-19 treatment protocol and guidelines, azithromycin and Zinc supplement is recommended in the treatment so the idea of ligands as azithromycin which play roles in determining the nature of interactions in target sites, such as DNA, enzymes and protein receptors provide a high diversity for the design of metallodrugs which may prove a therapeutic activity.[7-11] At the present work biding of azithromycin towards transition metals were identified by IR, electronic spectra, ESR and magnetic susceptibility. Antimicrobial activities of Azithromycin metal complexes were discussed. Applying Hyper Chem. Program to measure charge density of azithromycin atoms is calculated and confirm the biding sites and to give molecular approach Azithromycin **(Figure 1)** with zinc for COVID-19 was studied. [4-7]

METHODS

A Solution of azithromycin was added to hot ethanol, an aqueous solution Cr(III) was added with a molar ratio (1:1). The mixture was refluxed for 2 h at pH 8.4. The obtained solution was filtered and reduced to half of its volume by evaporation of the solvent. the solution is left to form a precipitate. Then it was filtered and washed with an amount of

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ethanol and dried. All other complexes were prepared following the same method using the respective metal salts as chloride. Physical measurements, analytical and spectral data of the complexes are given in **Tables 1 and 2**

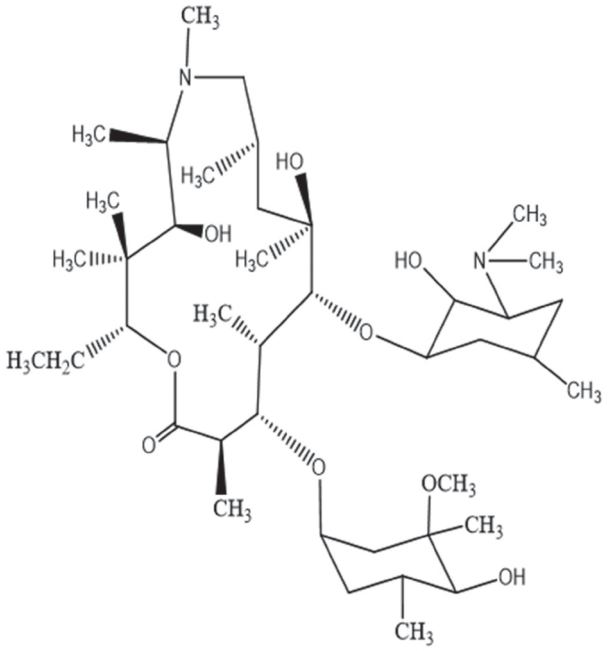

Figure (1): Azithromycin structure.

MEASUREMENTS

Elemental analysis of C, H, S and N for azithromycin and all complexes recorded on CHNS Nr.11042023, at Cairo University. The familiar Volhard method was applied for the determination of the analysis of chloride contents of the [12]The infrared spectra of the azithromycin and their metal complexes were recorded on Perkin Elmer spectrophotometer, Model 1430. The electronic spectra for the solid complexes were measured in Nujol mull spectra.[13] Determination of Molar magnetic susceptibilities, constants were by using Faraday's method at room temperature 25°C. The electron spin resonance spectra were recorded on a spectrometer operating at (9.1–9.8) GHZ in a cylindrical resonance cavity with 100 kHz modulation. The g values were determined by comparison with the DPPH signal. The biological screening of azithromycin and their metal complexes were examined against seven microorganisms representing different microbial categories, three of them are Gram-positive (Staphylococcus Aureas, Micrococcus luteus and Bacillus subtilis), three Gram-negative (Escherichia coli strain, Proteus mirabilis and Pseudomonas aeruginosa) and Candida Albicans as a fungus. Hypercom computer program using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) is applied for ligand.

Table 1: Elemental analysis, m.p. and colour of azithromycin complexes

Calculated/(Found)%					Colour	Complexes
Cl	M	N	H	C		
2.23 (2.33)	3.27 (3.31)	3.52 (2.98)	9.89 (9.99)	61.96 (62.64)	Violet	[Cr(azithromycin)$_2$ (Cl)(H$_2$O)]
0 (0)	3.49 (3.61)	3.56 (3.51)	10.11 (10.82)	62.53 (63.56)	Yellow	[Mn (Athiromycin)$_2$ (H$_2$O)$_2$]
2.22 (2.12)	3.50 (3.46)	3.52 (3.01)	9.87 (9.42)	61.81 (61.67)	Black	[Fe(Azithromycin)$_2$ (H$_2$O)Cl]
0 (0)	3.55 (4.13)	3.55 (3.66)	10.09 (9.92)	62.37 (62.71)	Orange	[Co(Athiromycin)$_2$ (H$_2$O)$_2$]
0 (0)	3.55 (3.60)	3.55 (3.56)	10.09 (10.01)	62.38 (62.82)	Green	[Ni(Athiromycin)$_2$ (H$_2$O)$_2$]
0 (0)	4.01 (4.19)	3.54 (3.77)	10.06 (10.11)	62.19 (62.66)	Brown	[Cu(Athiromycin)$_2$ (H$_2$O)$_2$]
0 (0)	4.12 (4.23)	3.53 (3.34)	10.04 (10.08)	62.12 (62.62)	Yellow	[Zn(Athiromycin)$_2$ (H$_2$O)$_2$]
0 (0)	6.89 (6.91)	3.43 (3.82)	9.76 (9.62)	60.33 (60.40)	Yellow	[Cd (Athiromycin)$_2$ (H$_2$O)$_2$]
0 (0)	11.66 (11.82)	3.26 (3.33)	9.26 (9.23)	57.24 (57.51)	Yellow	[Hg(Athiromycin)$_2$ (H$_2$O)$_2$]

All the complexes have m.p > 300º C

RESULTS AND DISCUSSION

Azithromycin possesses several lone pair rich sites, and amine substituted lactone rings, to form complexes.[12,13,14] The complexation is confirmed through IR bands of free ligand azithromycin and the metal complexes where the spectra of azithromycin there have two very strong absorption peaks at 1751 cm^{-1} of lactone and 1653 cm^{-1} due to ketonic carbonyl groups. The absorption peaks of 1000 cm^{-1} are due to the ethers while the peak of 1251 cm^{-1} is due to amine functions. The CH_2 bending is evident by peaks between 1340 and 1460 cm^{-1} and alkane stretching peaks appeared among 2800-2880 cm^{-1}. Coordinated water appeared as bands between 3353 and 3652 cm^{-1} with peak maxima at 3652 cm^{-1}. In metal complexes of azithromycin, some very prominent peak shifting has been observed along with the change in intensities of several important peaks indicating azithromycin has undergone complexation reaction with metals as shown in **Table (2).** In [Cr(azithromycin)$_2$(Cl)(H$_2$O)] complex as an example, the aliphatic amine of azithromycin with the peak of 1251 cm^{-1} was shifted to 1163 cm^{-1}The same results were observed in azithromycin with all prepared metal complexes. In the light of these observations, it can be fairly concluded that the N (CH3)$_2$ group of dopamine and a hydroxyl group, have been utilized in the complex formation. In the far IR spectra, the bonding of oxygen is provided by the presence of bands at 437.5 cm^{-1} (M-O).[14,15]

Table 2: Fundamental infrared bands (cm^{-1}) of azithromycin and its metal complexes

Compound	N_{OH} of H_2O	ν(lactone)	ν(C=O)	ν (amine)	ν (CH_2)	ν_{M-N}	ν_{M-O}
azithromycin	-	1751	1653	1251	1340	-	-
[Cr(azithromycin)$_2$(Cl)(H_2O)]	3652	1752	1652	1163	1460	436	402
[Mn (Athiromycin)$_2$(H_2O)$_2$]	3498	1752	1654	1172	1460	494	405
[Fe(Azithromycin)$_2$(H_2O)Cl]	3495	1753	1653	1180	1460	475	404
[Co(Athiromycin)$_2$(H_2O)$_2$]	3592	1752	1652	1164	1460	488	404
[Ni(Athiromycin)$_2$(H_2O)$_2$]	3593	1753	1651	1163	1460	479	405
[Cu(Athiromycin)$_2$(H_2O)$_2$]	3428	1752	1653	1163	1460	471	404
[Zn(Athiromycin)$_2$(H_2O)$_2$]	3496	1751	1652	1165	1460	463	408
[Cd (Athiromycin)$_2$(H_2O)$_2$]	3597	1752	1653	1160	1460	471	421
[Hg(Athiromycin)$_2$(H_2O)$_2$]	3353	1770	1654	1150	1459	472	420

Electronic spectral and magnetic studies

The electronic absorption spectra for the violet [Cr(azithromycin)$_2$(Cl)(H_2O)] showed three bands at 288, 410, 540 nm due to $^4A_{2g} \rightarrow {}^4T_{2g}$ (F), $^4A_{2g} \rightarrow {}^4T_{1g}$(F) and $^4A_{2g} \rightarrow {}^4T_{1g}$(p) transitions suggested an octahedral structural with μ_{eff} values which equal 4.90. while the Yellow electronic absorption spectrum of [Mn (Athiromycin)$_2$] gave two bands at 272.8, 446.8 which assigned to $^6A_{1g} \rightarrow {}^4A_{1g}$, while the second is due to $^6A_{1g} \rightarrow {}^4T_{2g}$ transition with μ_{eff} value of 5.7 at room temperature suggest the existence of O_h configuration**,** while The brown electronic absorption spectra of [Fe(Azithromycin)$_2$(H_2O)Cl] These bands are due to CT ($t_{2g} \rightarrow \pi^*$) and CT ($\pi \rightarrow e_g$). The electronic absorption spectra of [Co(Azithromycin)] and complex, gave bands at 288, 480, 536, nm bands are assigned to $^4T_{1g}$(F) $\rightarrow$ $^4T_{2g}$(P) transition with magnetic moment value equal to 5.85 typified the existence of the complex in O_h geometry**.** The green electronic absorption spectra for [Ni(Azithromycin)$_2$] showed three bands at 248, 330, 550 nm due to $^3A_{2g} \rightarrow {}^3T_{1g}$(p), $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) transitions with octahedral geometries, further deduced from the μ_{eff} values which equal (2.9) B.M **(Figure 2 and 3).** The copper complex,[Cu(Azithromycin)], exhibited bands at 290, 425 nm with μeff=1.8 B.M. The latter broadband is assigned to the $^2E_g \rightarrow {}^2T_{2g}$ (D) transition assignable to the octahedral environment. [16,17] Zn, Hg and Cd complexes exhibited only a high-intensity band at 373-426 nm, which are assigned to ligand →metal charge transfer. Owing to the d10- configuration of Zn(II), Cd(II) and Hg(II), no d-d transition could be observed and therefore the stereochemistry around these metals in their complexes can be hardly determined **(Table 3 and figure 4)**.

Table 3: Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff}, 298°K) and geometries of azithromycin metal complexes.

Complex	λ_{max} (nm)	μ_{eff}	Geometry
[Cr(azithromycin)$_2$ (Cl)(H_2O)]	288, 410, 540	4.90	O_h
[Mn (Athiromycin)$_2$ (H_2O)$_2$]	272.8, 446.8	5.7	O_h
[Fe(Azithromycin)$_2$ (H_2O)Cl]	359, 423, 519	5.8	O_h
[Co(Athiromycin)$_2$ (H_2O)$_2$]	288, 480, 516	5.85	O_h
[Ni(Athiromycin)$_2$ (H_2O)$_2$]	248, 330, 550	2.9	O_h
[Cu(Athiromycin)$_2$ (H_2O)$_2$]	290, 425	1.8	O_h
[Zn(Athiromycin)$_2$ (H_2O)$_2$]	426	Diamagnetic	O_h
[Cd (Athiromycin)$_2$ (H_2O)$_2$]	337	Diamagnetic	O_h
[Hg(Athiromycin)$_2$ (H_2O)$_2$]	343	Diamagnetic	O_h

By applying hyper chem. program and measure charge density of azithromycin atoms is calculated, figure (3) confirmed azithromycin coordination through the

–N(CH_3)$_2$ and hydroxyl group of desosamine sugar moiety which has highest charge.

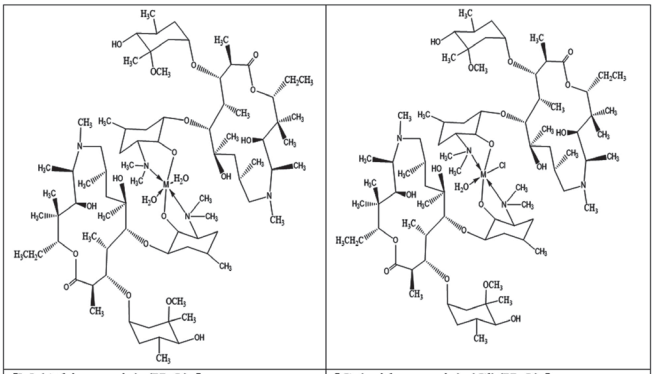

Figure 2: Proposed structures of Azithromycin complexes.

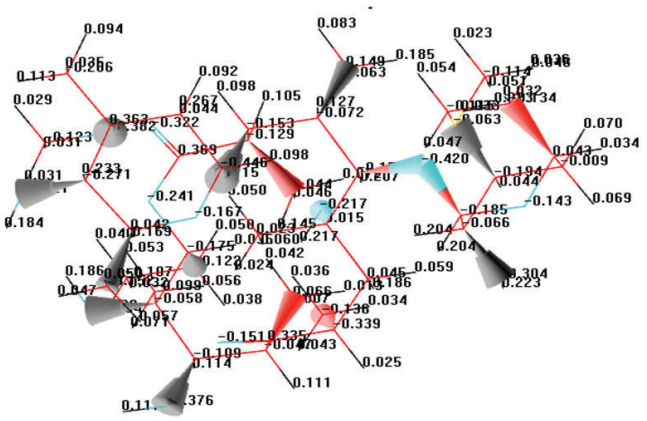

Figure 3: Charge density of azithromycin atoms.

Electron spin resonance of [Cu(Athiromycin)$_2$(H$_2$O)$_2$]

At The room temperature anisotropic nature of [Cu(Athiromycin)$_2$(H$_2$O)$_2$] complex polycrystalline X-band ESR spectral pattern, with g_s= 1.98 and value of A= 169 figure(4)

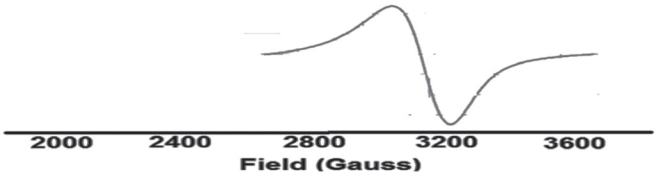

Figure 4: ESR of [Cu(Athiromycin)$_2$(H$_2$O)$_2$].

Biological activity

Table (4) shows that some of the investigated compounds have higher antimicrobial activity and antifungal activity than azithromycin as a free ligand. It's observed for *Escherichia coli* that all complexes show higher activity than azithromycin except for [Co(Athiromycin)$_2$(H$_2$O)$_2$] and [Mn (Athiromycin)$_2$(H$_2$O)$_2$] have lower activity. In *Pseudomonas aeruginosa* all investigated compounds show higher activity than azithromycin while in *Micrococcus luteus* compounds shows lower activity than azithromycin except for [Zn(Athiromycin)$_2$(H$_2$O)$_2$] has a remarkable activity. [14,15,16] In *Bacillus subtilis* all investigated compounds show higher activity than azithromycin except for [Mn (Athiromycin)$_2$(H$_2$O)$_2$] and [Cu(Athiromycin)$_2$(H$_2$O)$_2$] while for *Proteus mirabilis* compounds show lower activity than azithromycin except for [Zn(Athiromycin)$_2$(H$_2$O)$_2$] has an observable activity. In *MRSA* it showed activity in the same range of azithromycin except for [Zn(Athiromycin)$_2$(H$_2$O)$_2$] show higher activity than all compounds. Azithromycin not only shows antimicrobial activity also shows antifungal activity (**Table 4).** [Zn(Athiromycin)$_2$(H$_2$O)$_2$] in all strains shows the highest activity than all compounds, hence the idea of study [Zn(Athiromycin)$_2$(H$_2$O)$_2$] it is very important COVID-19. Metal complexes show higher activity than free ligands which refer to increased activity of the metal chelates which may be explained by bases of overtone's concept and chelation theory.[17, 18]

Table 4: Antimicrobial activity of Azithromycin metal complexes (20 µg/8 mm disc), as compared to azithromycin

Compounds	CA	EC	PA	ML	BS	PM	MRSA
Azithromycin	20	23	21	34	-	30	29
[Cr(Azithromycin)$_2$ (Cl)(H$_2$O)]	20	25	25	23	30	20	25
[Mn (Athiromycin)$_2$ (H$_2$O)$_2$]	20	-	-	-	-	21	28
[Fe(Azithromycin)$_2$ (H$_2$O)Cl]	25	25	-	30	25	30	22
[Co(Athiromycin)$_2$ (H$_2$O)$_2$]	21	20	25	22	20	32	20
[Ni(Athiromycin)$_2$ (H$_2$O)$_2$]	25	25	22	24	21	25	24
[Cu(Athiromycin)$_2$ (H$_2$O)$_2$]	24	24	25	25	-	22	25
[Zn(Athiromycin)$_2$ (H$_2$O)$_2$]	28	30	28	37	30	38	30

*(CA: Candida albicans, EC:Escherichia coli, CT: Citrobacterium , PA: Pseudomonas aeruginosa, ML: Micrococcus luteus, BS: Bacillus subtilis, PM: Proteus mirabilis and MRSA: Methicillin-ResistantStaphylococcus aureus.)

Effect of [Zn(Athiromycin)$_2$ on the Replication of SARS-CoV-2 and on the Assembly of Viral Particles

It is reasonable to consider that, in a host cell infected with the SARS-CoV-2 virus. [19] the main target for the therapeutically beneficial drugs is the human ribosome, followed by individual proteins and enzymes of the virus,[20] which is also synthesized by the ribosome itself. In fact, except for the RNA genome that encodes all viral proteins, the SARS-CoV-2 virus

contains neither major molecular material nor any protein synthesis machinery to produce the viral proteins and enzymes necessary for their replication and/or to the synthesis of viral particles. Among the viral individual proteins and enzymes targeted by antiviral drugs is the SARS-CoV-2 RNA is common to all RNA viruses containing any DNA phase.[20] It is an RNA-dependent RNA polymerase (RdRp), which catalyzes the formation of an RNA strand complementing the viral RNA genome as a template.[20] Thus, RdRp is the primary enzyme for the viral RNA synthesis machine responsible for the reproductive cycle of SARS-CoV-2, and as such, it is a prime target for antiviral drug development.[20] According to this observation, Zn^{2+} has previously been shown to inhibit coronavirus RdRp in vitro, while zinc ions inhibit virus replication in cell culture.[21]Thus, on the one hand, it is tempting to suggest that $Zn(Athiromycin)_2$ complex would represent the Zn^{2+} provider of infected human host cells to inhibit viral RdRp and prevent SARS-CoV-2 replication. Instead of targeting RdRp with antiviral drugs, it is not preferable to use small-molecule inhibitors of human ribosomes to inhibit universal protein synthesis of all viral proteins and enzymes. Interestingly, antibiotics are the most common small-molecule inhibitors of the ribosome, and among them, azithromycin is particularly suitable for the following reason: antibiotics of the macrolides class (including azithromycin) is located at the upper part of the ribosomal protein exit tunnel that is a universal feature of the ribosomes in all kingdoms of life.[22]Therefore, this class of antibiotics would be expected to be associated with all types of ribosomes, the 70S as well as type 80S, with similar affinity. **Figures 5 and 6** show the protein exit tunnelling in the crystal structure of the 50S ribosomal subunit of Haloarcula marismortui,[23] in the absence or presence of macrolides (i.e., carbomycin).

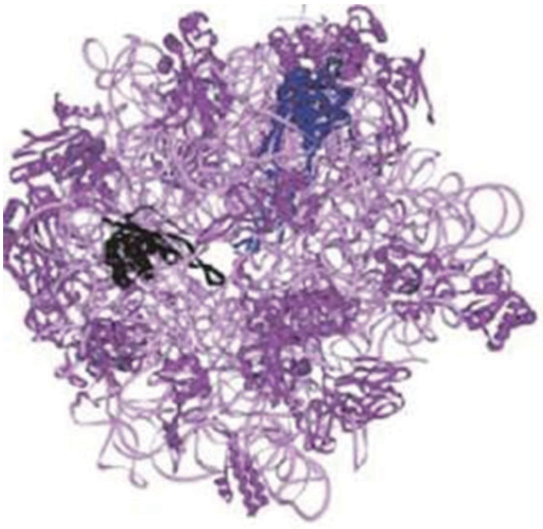

Figure 5: Protein exit tunnel of the ribosomal 50S subunit of the archaeon *Haloarcula marismortui* in the absence of the macrolide carbomycin.

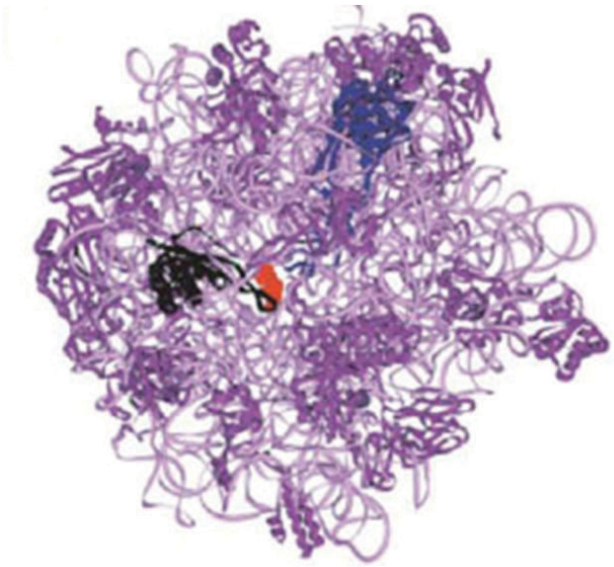

Figure 6: Protein exit tunnel of the ribosomal 50S subunit of the archaeon *Haloarcula marismortui* in the presence of the macrolide carbomycin.

Whether or not azithromycin binds alone as a $Zn(Athiromycin)_2$ complex the azithromycin complex should be elucidated by the protein exit tunnelling of the ribosome. Additionally, the schematic diagram of the azithromycin binding site on human 80S ribosomes is shown in Figure 4. Azithromycin and macrolide are observed to inhibit protein synthesis by interfering with the progression of the peptide originating in the protein exit tunnel (**Figures 7 and 8).** [20]

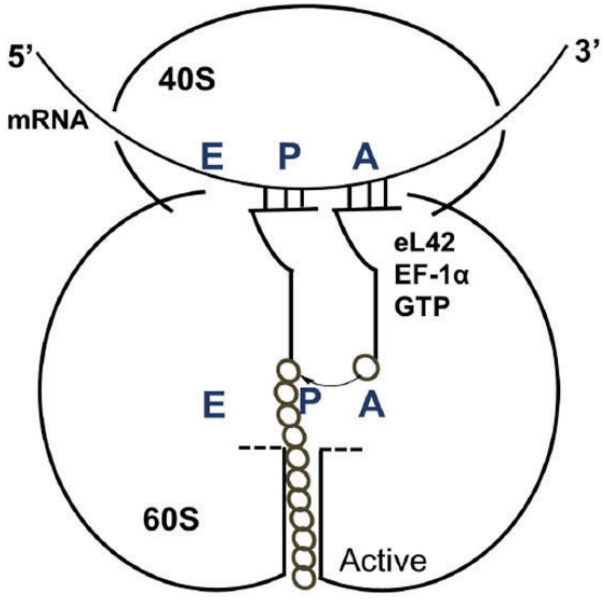

Figure 7: Schematic of the binding site of azithromycin on the human 80S ribosomes. In the absence of azithromycin.

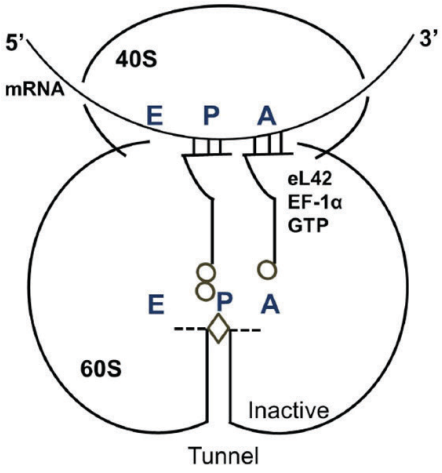

Figure 8: Schematic of the binding site of azithromycin on the human 80S ribosomes. in the presence of azithromycin.

In this respect, it is well documented that azithromycin has multiple anti-infection properties, including antiviral properties. For example, azithromycin is known as the gold standard in treating papillomavirus in dogs. [21] It is interesting to note that Zn^{2+} has previously been shown to inhibit translation initiation.[26] This observation indicates that the zinc ion is not only an effective inhibitor of RdRp but is also capable of preventing the entire ribosome from synthesizing the RNA synthesis mechanism responsible for the SARS-CoV-2 repeat cycle. Other roles of zinc include impeding the reproduction of RNA viruses, by interfering with the correct analytical processing of viral proteins, and improving antiviral immunity through higher regulation of alpha-interferon production and thus increasing antiviral activity, anti-inflammatory activity, etc. [22] Altogether, these observations indicate that Zn^{2+} can be considered a powerful antiviral agent in the treatment of COVID-19. Another potential effect of azithromycin (or erythromycin) on the ribosomes of human host cells infected with SARS-CoV-2 is that this antibiotic, as discussed above, can form a complex with a zinc atom attached to the N terminal region of the large ribosomal protein of the eL42 subunit (Fig.9). Formerly L42A or L42AB in yeast, L36a or L36a in humans, or L44e in archaea. [21,22] This newly discovered ribosomal protein was shown to actively and directly contribute to the catalytic activity of the ribosome, in the elongation step of translation, through interactions with the afferent A-site bound to aminoacyl-tRNA.It is widely accepted that the domains of zinc fingers are essential for DNA: protein interactions and/or for the maintenance of the three-dimensional structure of zinc-containing proteins, it is conceivable that azithromycin (or erythromycin) captures zinc from the catalyst. Ribosome protein eL42, which leads to the activation of 80S ribosomes in SARS-CoV-2-infected human host cells upon treatment with this antibiotic.[23] Altogether, these results indicate that $Zn(Athiromycin)_2$ complex can be considered a multi-action compound against COVID-19.

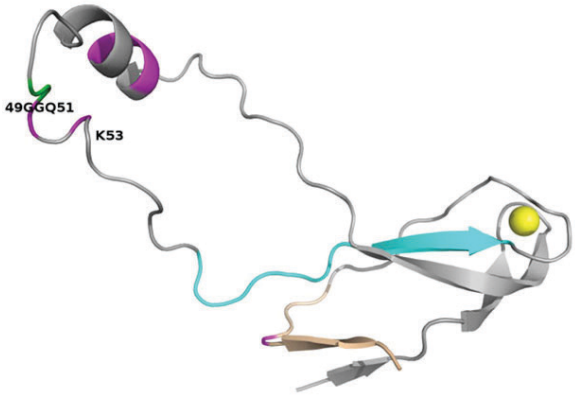

Figure 9: Model of the human eL42 protein. Ribbon representation of the 3-D structure of human rp eL42.

CONCLUSION

Azithromycin metal complexes are synthesized and characterized by different spectroscopic methods. All of them have Oh geometry and these results are confirmed by Nujol and ESR spectra. Azithromycin act as a bidentate ligand through $N(CH3)_2$ group of dopamine and a hydroxyl group. Also have different sites available for coordination that carries more electronegative charges and the computational study confirms these results. Azithromycin complexes show higher activity than commercial Azithromycin for some strains. Evidence-based on quantum mechanics molecular simulations for the molecular events surrounding the interaction of Zinc- Azithromycin complex, a key ingredient in the therapy proposed.

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Authors' Contribution:

Dr. Sherif A. Kolkaila: procedure, preparation and discussion

Prof. Dr. Alaa E Ali : Idea and discussion

Dr. Gehan S. Elasala: Manuscript editing and discussion

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