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Amyloid β (1-16) Peptide and Copper-Induces Toxic Effects on Conformational Changes in DNA Sequence: Relevance to Alzheimer's Disease

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Abstract

Copper is an essential metal for life that plays a key role in CNS development and acts as a cofactor for numerous enzymes. Low concentrations of copper cause an incomplete development, whereas an excess, is injurious. Redox reactions are the basis of copper toxicity. Copper directly binds to DNA and proteins alter the structures and stability of proteins and DNA. Interactions between Aβ peptides and copper ions may play a role in the promotion of toxic aggregation and produce ROS that may link to Alzheimer's disease. DNA conformation and stability are important in the life cycle of an organism. Any change in the conformation and stability alters the gene expression and is one of the risk factors for neuronal death in neurodegenerative disorders. In the present study, we have attempted to study the binding of copper and Aβ1-16 with the DNA sequence through the Circular dichroism and these results were further supported by the UV-VIS absorbance, fluorescence studies, and in-silico Molecular docking studies.

Keywords: ***Alzheimer's disease (AD); Circular dichroism, Docking studies; DNA sequence; Amyloid β (1-16)***

1. Introduction

Some Copper (Cu) is an essential trace metal that plays an important role in human health and as a cofactor for many enzymes that plays an important role in CNS development, cell nuclear chromatin, and DNA synthesis. Copper is essential for the human body with only 50-120 milligrams, whereas excess may be toxic and injurious which plays a key factor in the development of Alzheimer's disease (AD) [1]. Copper levels in a normal aging brain's hippocampus and frontal cortex are 0.1 micromol/g but in an Alzheimer patient's brain Cu levels are inconsistent (in moderate AD it is lower by 0.02 micromol/g, in severe it is lower by 0.08 micromol/g and in the control group it is lower by 0.1 micromol/g [2]. Copper is one of the metals involved in DNA

synthesis. It has a strong affinity with the bases of the DNA and perturbs the hydrogen bonding between the base pairs and causes DNA damage and conformational change [3].

DNA is a genetic material of life that carries hereditary information that facilitates the biological synthesis of proteins and enzymes through replication and transcription. DNA is the major intracellular target for a wide range of drugs, metals, and radiation [4]. This study analyzes the effects of Cu and Aβ1-16 peptides on DNA conformation. DNA carries the genetic code that gives us our unique characteristics. Furthermore, the conformations of DNA are affected by sequence length, nature, and the concentration of metal ions and proteins. Major conformations of DNA are- A, B, and Z, these have different properties and exhibit different properties [5]. A synthetic form of the DNA sequence that reflects the human genome was used in this study to analyze the overall interactions with metals and peptides. Circular dichroism was used to study the conformational changes, and the specific interactions were studied using an ultraviolet (UV) spectrophotometer, and a fluorescent spectrophotometer. These results were further supported by Molecular docking that deduces the binding mode and minimum energy complex formed between the DNA sequence and copper.

2. Materials and Method

2.1 DNA repeat sequence

GCA ATC TAA TCC CTA sequence was purchased from MWG Biotech GmbH and dissolved in MilliQ water. 5 mM of Tris-HCl (pH of 7.4) buffer was used for further dilutions and to provide a stable pH for the circular dichroism (CD), fluorescence, and UV studies.

2.2 Aβ 1-16 peptide

The 16 amino acid residues of Aβ with sequence DAEFRHDSGYEVHHQK with 1956 Da as molecular weight was procured from M/s USV Peptides.

2.3 Copper chloride ($CuCl_2$ $2H_2O$)

High-quality copper chloride was purchased from Merck Schuchard and used in this experiment. A Stock solution (1 mM) of this was prepared with MilliQ water and was diluted further for various studies.

2.4 UV/VIS absorption studies

The UV-VIS absorption studies of DNA sequence and its binding ability to copper chloride, and Aβ1-16 peptide with various concentrations were investigated using a Jasco V-530 Spectrophotometer equipped with a Peltier temperature controller. Absorbance spectrum measured at a wavelength between 220 nm and 320 nm with a matched set of 1-cm pathlength quartz cuvettes. Buffer background was subtracted using the built-in feature of Jasco software and the resultant spectrum was recorded. The objective of the study is to measure the absorption of UV light by DNA as the copper concentration is increased.

2.5 Circular dichroism studies

CD spectra of DNA sequence were titrated against different concentrations of copper chloride (50 µM 100 µM, 250 µM, 500 µM), Aβ1-16 peptide (10-50 µM), using a Jasco-J-715 Spectropolarimeter at 25°C, using a path length of 1 mm quartz cuvette

at 1 nm intervals in the wavelength between 200 and 320 nm. Spectra were recorded as an average of four repetitive scans using a scan speed of 20 nm /min. Buffer background was subtracted from the spectra of DNA and DNA-Cu, DNA-Aβ1-16 complex using the built-in feature of Jasco software, and the resultant spectrum was recorded.

2.6 Fluorescence studies

Fluorescence spectroscopy is an important technique for probing the structure and dynamics of nucleic acids. The utility of fluorescence techniques stems from the ability of fluorophores to reflect changes in their molecular environment through measurable alterations in emission properties. Fluorescence emission studies were carried out using equimolar concentrations of DNA sequence and EB (1:1) with different concentrations of $CuCl_2$ (25 µM to 500 µM). DNA/EB solutions were excited at 530 nm and emission spectra were recorded from 550 nm to 650 nm using a Jasco J-600 spectrofluorimeter. In this study, DNA will be exposed to fluorescent light and the emission spectra were measured with the increase in copper concentration.

2.7 *In silico* molecular docking studies

Molecular docking was carried out to understand the nucleotide interactions between Aβ-(1-16), Copper, and DNA. The selected target DNA sequence B chain (TTCCTATTGCGCAATCCAGTT) and D chain (AAACTGGATTGCGCAATAGG) were retrieved from the protein data bank [6] with PDB ID: (1NWQ) and having consensus DNA site (ATTGCGC). Further, the Aβ-(1-16) fragment was used for docking analysis with DNA. The copper metal ion ligand [Cu (II) PubChem CID: 27099) was retrieved from the PubChem database [7]. The ligands and target DNA were minimized by using CHARMm force filled with potential energy (kcal/mol) of -4147.69.

Docking was carried out using CDOCKER protocol in Discovery Studio 3.5 [8] CDOCKER, A CHARMm-based molecular dynamics (MD) simulated-annealing-based algorithm, a conventional molecular mechanics force field was used for docking analysis [9]. CHARMm-based molecular dynamics (MD) scheme to dock ligands into a receptor binding site. Random ligand conformations were generated using high-temperature MD. The conformations were then translated into the binding site. Candidate poses were then created using random rigid-body rotations followed by simulated annealing. A final minimization was then used to refine the ligand poses. While DNA is kept rigid, the ligands, Aβ-(1-16) and copper are treated as fully flexible, and a final minimization step is used to refine the docked poses. Thus, the optimized structure of the Aβ-(1-16), metal was docked DNA structure.

3. Results

3.1 UV-VIS absorption studies

The UV-vis absorption measurement is an effective technique to study the interaction of small molecules with DNA. The absorption spectra of DNA sequence in the absence and presence of copper were recorded and are shown in FIG. 1A. The absorption maximum of the DNA sequence was found at 260 nm, and the absorbance of DNA was gradually increased in the presence of various concentrations of $CuCl_2$ with a small blue shift to 259.5nm. Hyperchromicity is due to the binding of copper to the DNA through hydrogen bonding, it opens up the double-stranded DNA, and the DNA fragment starts to denature and the bases start to stack up which increases the absorption of UV light compared to the normal double-stranded DNA without any interactions with Cu. This wavelength region of the absorption spectra is sensitive to π–π^* transitions that increased positive

base pair tilting due to the binding of copper to bases and cause distortion in DNA structure [10]. This structural change confirms the interaction between copper and DNA sequence.

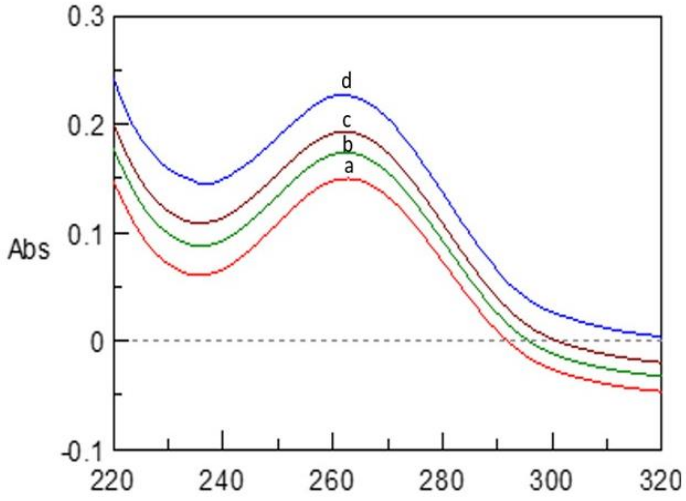

FIG. 1A. **Effect of $CuCl_2$ on the UV spectra of DNA sequence with Tris-Hcl Buffer (pH 7.4) a. DNA sequence. b. DNA+100 µM $CuCl_2$. c. DNA+250 µM $Cucl_2$, d. DNA+500 µM $CuCl_2$.**

The interaction between the Aβ1-16 peptide and DNA sequence was studied and the UV spectral changes are shown in FIG. 1B. The absorption peak of the DNA sequence is at 259 nm and 202 nm. The peak at 259 nm is the DNA sequence and the absorbance steadily increased without a peak shift at 259 nm and an increase in the absorbance with a peak shift from 202 nm to 204 nm (redshift) in the presence of Aβ1-16 peptide. The increase in the absorbance with the redshift is due to the binding of the Aβ1-16 peptide with the DNA that weakens the hydrogen bonds between the bases of DNA and forms the complex of DNA-Aβ peptide. The interaction of copper with Aβ peptide was analyzed and is shown in FIG. 1C. The peak maximum of Aβ peptide was exhibited at 275 nm and 205 nm. Upon the addition of copper gradually increase the absorbance in both bands indicating the interaction of copper with Aβ peptide.

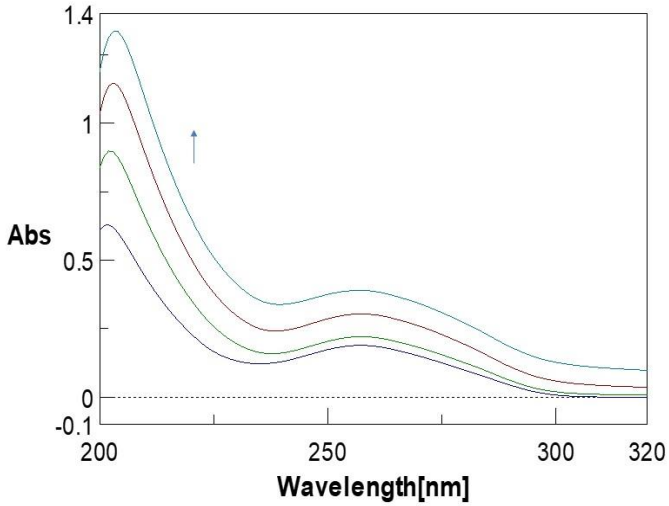

FIG. 1B. **Effect of 1-16 on the UV spectra of DNA sequence with Tris-Hcl Buffer (pH 7.4) a. DNA sequence. b. DNA+Aβ1-16 50 mµM, b. DNA+75 µM Aβ1-16, d. DNA+Aβ1-16, 100µM.**

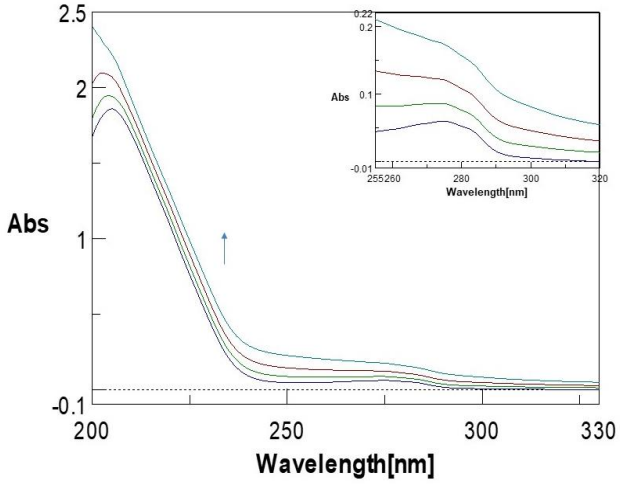

FIG. 1C. **Effect of copper on the UV spectra of Aβ1-16 with Tris-Hcl Buffer (pH 7.4) a. Aβ1-16, b, Aβ1-16+ 50 µM copper, c., c, Aβ1-16 +100 µM copper, d, Aβ1-16,+ 250 µM copper.**

3.2 Fluorescence studies

Fluorescence emission studies are the most widely used technique to study interactions of small molecules with DNA. We monitored the equimolar concentrations of DNA: EtBr with and without copper ions to verify the local structural information due to the interaction of copper with DNA sequence. The fluorescence spectra of the DNA-EB complex were excited at 530 nm and emission spectra were recorded from 550 nm to 650 nm as shown in FIG. 2A. Upon addition of copper chloride to the DNA-EB complex, the fluorescence intensity decreased with increasing concentration of copper. The decrease of fluorescence intensity with the addition of copper indicates that binding of Cu^{2+}ions with the N7 position of guanine of DNA forms a new non-fluorescent complex of Cu-DNA–EB, which shows that Cu^{2+} ions efficiently quench the fluorescence of the intercalation complex of ethidium bromide with DNA sequence [11]. This data shows that Cu^{2+} ions displace EtBr to bind the DNA at Micromolar concentrations causing DNA damage. Aβ1-16 will not show any changes and not compete with EtBr (results not shown).

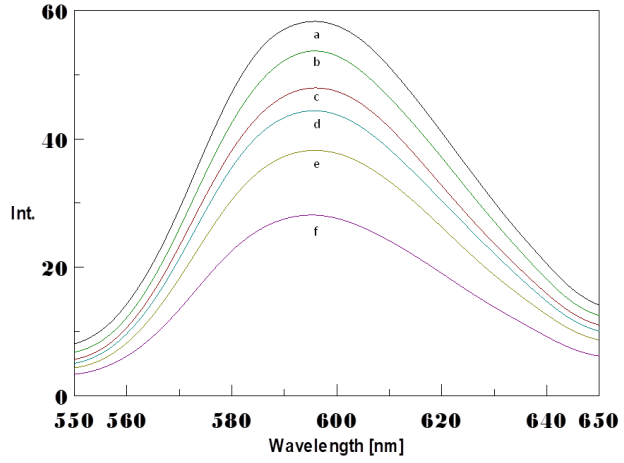

FIG. 2A. **Effect of copper on the fluorescence spectra DNA sequence with Tris-Hcl Buffer (pH 7.4) a. GCA alone, b. GCA+25 µM Cu, c. GCA+25 µM Cu, d. GCA+50 µM Cu, e GCA+100 µM Cu,f GCA+25o µM Cu, f. GCA+500 µM Cu.**

Fluorescence spectra of Aβ1-16 peptide were exited at 280 nm and emission spectra were recorded from 290 nm to 460 nm. FIG. 2B shows a peak maximum at 338 nm and 419 nm, upon subsequent addition of DNA sequence there is a gradual decrease in the peak at 338 nm with an evidence redshift to 343 nm due to binding of imidazole group of histidine to the bases of DNA sequence and not much changes at the peak at 419 nm is direct evidence of the interaction between Aβ1-16 peptide and DNA.

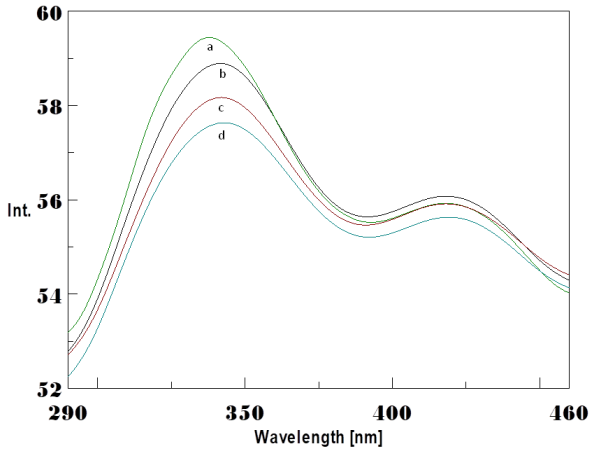

FIG. 2B. **Effect of DNA sequence on the fluorescence spectra Aβ1-16 with Tris-Hcl Buffer (pH 7.4) a. Aβ1-16 alone, b. Aβ1-16+5 µM GCA sequence, c. Aβ1-16 +10 µM GCA sequence, d. Aβ1-16 +15 µM GCA sequence.**

3.3 CD studies

Circular dichroism is a sensitive technique to study the conformational changes in DNA sequence binding with small molecules. Structural transitions of DNA sequence are shown in FIG. 3A, the CD spectrum of DNA sequence displays B-DNA conformation with two conservative bands in the UV region. a characteristic positive peak at 269.6 nm due to base stacking and a negative peak at 246.6 nm due to the right-handed helicity of classical B-DNA form which is sensitive to the interaction of small molecules [12]. In the presence of lower concentrations of copper, it noticed negligible changes, and on subsequent addition of 100 µM to 500 µM $CuCl_2$ show a decrease in the magnitude of the positive band with a red shift to 273 nm (2.5nm) and a decrease in the negative band with a band shift from 246.6 nm to 248.8 nm (2.2 nm) intersection points at 258 nm. It also shows a positive band at 218 nm and has shifted to 219.8 nm. The data reveal that at lower concentrations, copper ions interact electrostatically with the anionic phosphate ions of the DNA backbone, and at higher concentrations, copper binds to the bases of DNA and competes with hydrogen bonds that disrupt interactions between DNA bases. The decrease in the positive bond shows the perturbation on the base stacking and a decrease in the negative band due to the perturbations of the helicity due to the unwinding of the DNA helix [13]. It is also noticed that copper ions disrupt interactions between DNA bases and weaken base stacking, causing a decrease in the intensities of the CD bands due to the unwinding of the double helix. Conformational change of DNA sequence in the presence of Aβ 1-16 peptide is shown in FIG. 3B, in the presence of Aβ 1-16 peptide to DNA, it was noticed a decrease in the intensity of both bands and a small shift from 269.6 nm to 268.8 nm (Blueshift). With the addition of 100 µM and 250 µM copper, the positive band shows more changes with the band shift to 275 nm and negligible changes at 246.4 nm peak, the decrease in the intensity of both bands with the band shift is due to the binding of copper and amyloid peptide. In the presence of Aβ peptide copper induces more DNA damage to the DNA sequence. Aβ1-16 peptide interaction with DNA sequence is also analyzed and is shown in FIG. 3C. Upon addition of the Aβ1-16 peptide observed a negligible change at the positive and negative bands and showed an increase in the intensity with the red shift from 205 nm to

208 nm. This band is due to the binding of the Aβ1-16 peptide to the DNA sequence and the differences in the shapes of the spectral changes are due to perturbations in the secondary structure of the DNA sequence and the Double-stranded DNA winds up making more space for Aβ1-16 peptide causing more absorption of light and thus increasing intensity at 205 nm.

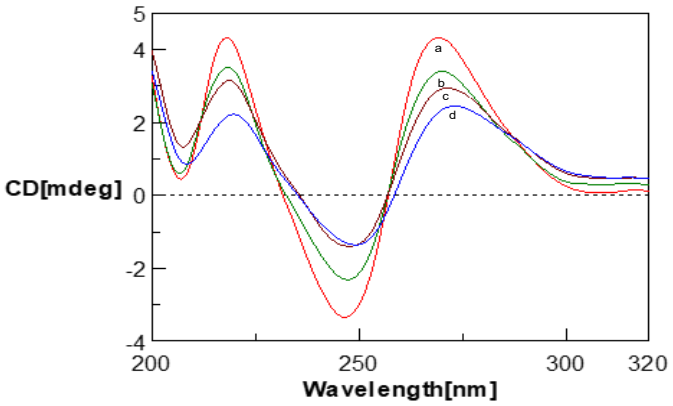

FIG. 3A. **Effect of $CuCl_2$ on the CD spectra of DNA sequence in 5 mM Tris-Hcl Buffer (pH 7.4). A. DNA sequence. b. DNA+100 µM $Cucl_2$, c. DNA+250 µM $Cucl_2$, d. DNA+ 500 µM $CuCl_2$.**

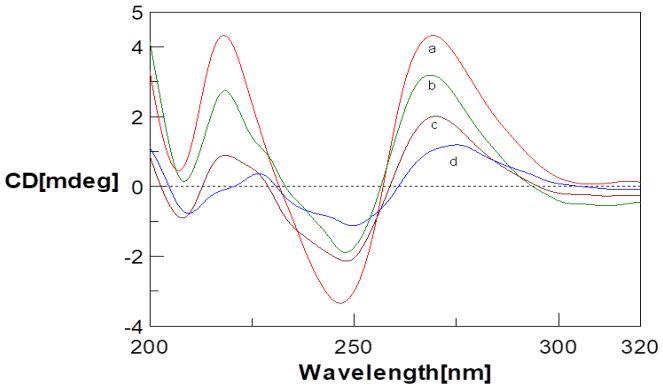

FIG. 3B. **Effect of $CuCl_2$ on the CD spectra of DNA sequence-Aβ complex with Tris-Hcl Buffer (pH 7.4) a. DNA sequence. b. DNA+100 µM Aβ1-16, c. DNA-Aβ complex +100 µM $Cucl_2$, d. DNA-Aβcomplex+ 250 µM $CuCl_2$.**

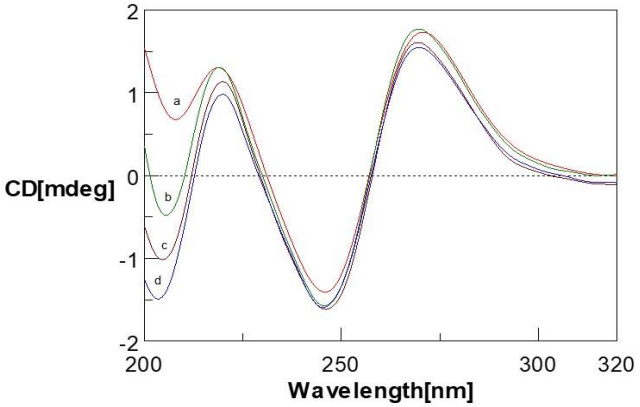

FIG. 3C. **Effect of Aβ1-16 on the CD spectra of DNA sequence withTris-Hcl Buffer (pH 7.4) a. DNA sequence. b. DNA+50 µM Aβ1-16, c. DNA+100 µM Aβ1-16, d. DNA+ 150 µM Aβ1-16.**

The results of CD support the binding of copper and Aβ1-16 peptide to DNA sequence that affects the changes in the secondary structure of DNA due to DNA damage leading to altered B-DNA, these results are supported by the UV absorption and fluorescence studies. The conformational changes will change the ability of the DNA in the normal process of DNA replication and transcription, which may be implicated in many neurological disorders.

3.4 Docking Studies

The result of molecular docking analysis of DNA with Aβ-(1-16) fragment and copper were evaluated and presented in (FIG. 4A-E) tabulated in (TABLE 1). As evident from the results (FIG. 4A-E & TABLE 1), the amino acid residues of Aβ-(1-16) namely, HIS6, ASP7, HIS13, LYS16 interact with D chain CYT, GUA, and THY of DNA D chain and form 6 hydrogen bonds across the major and minor groove. Most of the docked poses shown in the figure **(**FIG. 4B) indicate that the major and minor groove interactions are the relevant binding modes for the Aβ-(1-16) fragment across the (ATTGCGC) rich regions. Hence the formation of hydrophobic and hydrogen bonds recommends interaction between Aβ and DNA. Conclusively Aβ-(1-16) interacts in the major groove of the DNA with a CDOCKER score of docking score of −65.4785 kcal/mol. Interestingly; our results reveal the interaction of Aβ-(1-16) at different binding sites on the DNA molecule, indicating a higher binding probability/affinity to DNA.

Similarly, copper is also seen to interact with nucleotides B chain. Cytosine Guanine and Adenine form strong covalent metal-adenine–Cytosine complexes. These docking results confirm the strong binding of these ligands to Aβ-(1-16) leading to probable changes in the DNA conformation and breakage. Thus, in the current study, the *in silico* docking studies show interactions of Aβ-(1-16) and copper in the major groove of DNA via the formation of hydrogen bond and hydrophobic bond with a docking score of −65.4785 kcal/mol.

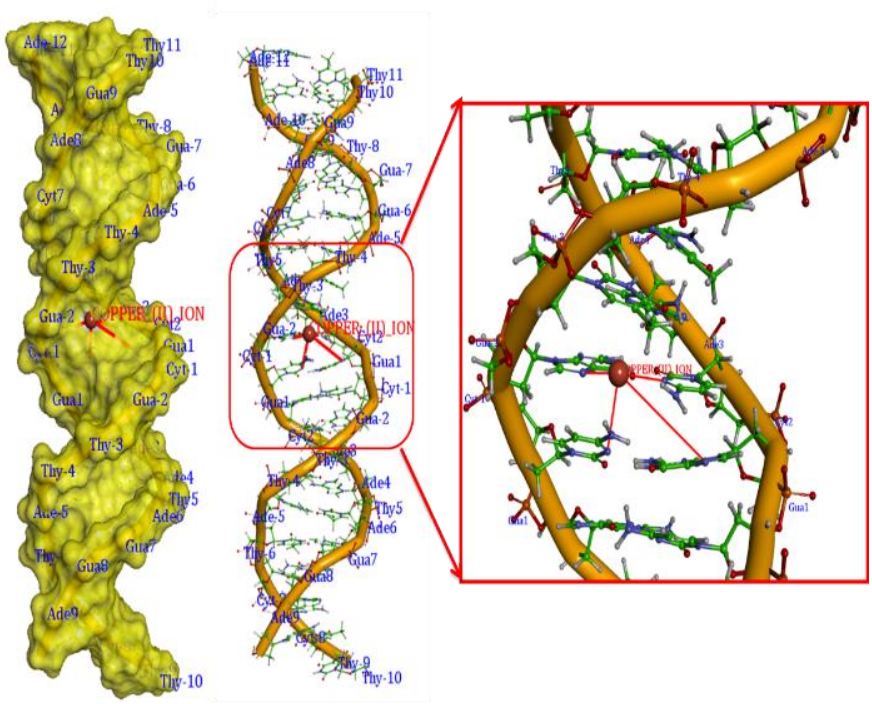

FIG. 4A. **DNA Interactions with Copper.**

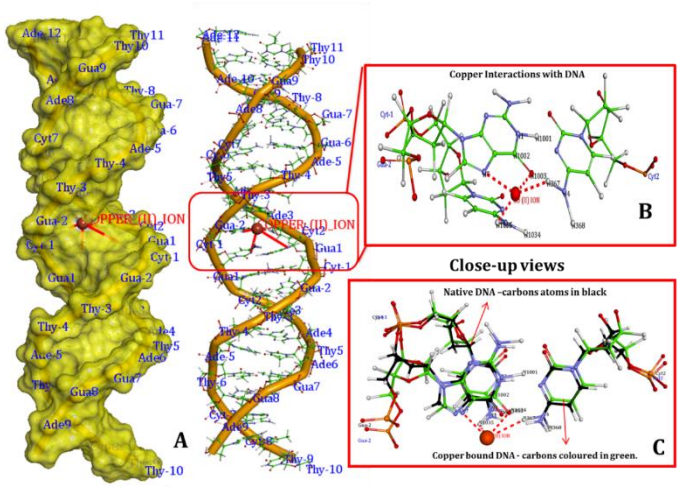

FIG. 4B. **DNA interactions with copper B. Zoomed /close-up views of DNA and copper C. Native DNA bound to copper.**

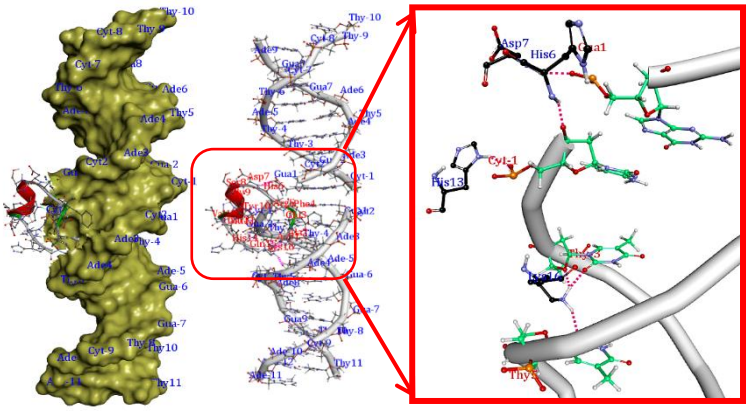

FIG. 4C. **a) Aβ-(1-16) with DNA. b) Aβ-(1-16) reisdues HIS6, ASP7,HIS13 and LYS16. interaction with DNA nucleotides.**

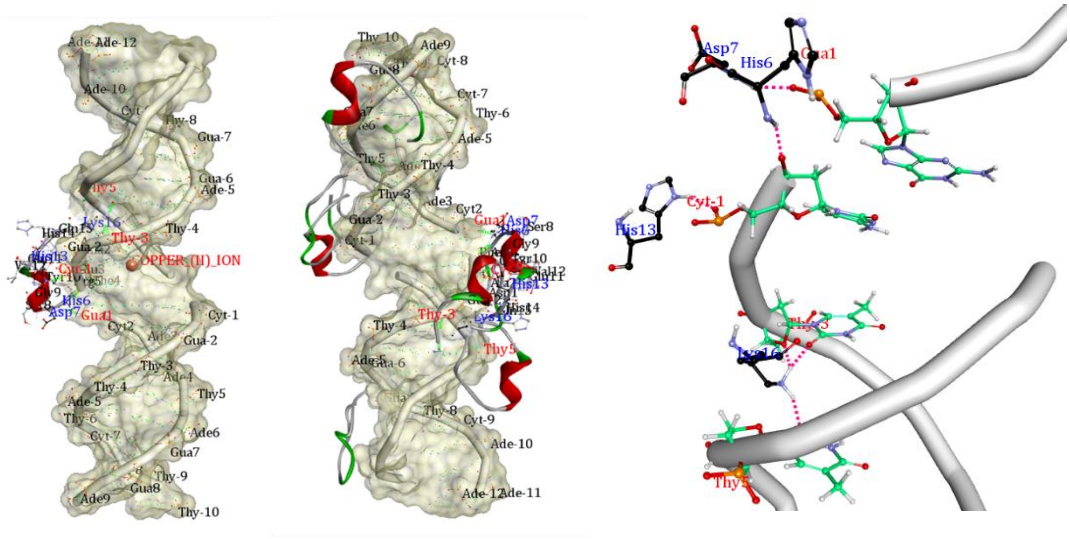

FIG. 4D. **A) Aβ-(1-16), and copper with DNA. B) Multiple interactive sites of Aβ-(1-16) residues with DNA.**

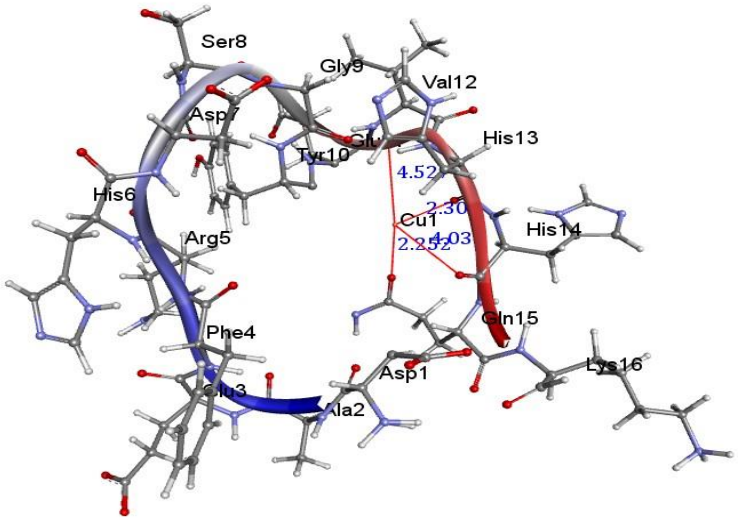

FIG. 4E. **A) Aβ-(1-16), Multiple interactive sites of Aβ-(1-16) reisdues with copper.**

TABLE 1. **Interaction of copper and Aβ 1-16 with DNA sequence.**

S. NO.	Aβ-(1-16) Amino acid residues interacting	Nucleotide Chain and Nucleotide residues interacting	Aβ-(1-16) and Nucleotide interacting atoms	Hydrogen Bond distances in Aº
1.	HIS6	D - CYT-1	A:HIS6:H - D:DC-1:O3	3.204
2.	ASP7	D - GUA-1	A:ASP7:H - D:DG1:OP1	2.937
3.	HIS13	D - CYT-1	A:HIS13:HD1 - D:DC-1:OP2	2.846
4.	LYS16	D- THY-3	A:LYS16:HZ1 - D:DT-3:O4'	2.706
		D-THY-3	A:LYS16:HZ1 - D:DT-3:O2	3.175
		D-THY-5	A:LYS16:HZ3 - B:DT5:O2	2.906

4. Discussion

DNA stability and conformation are important in the life cycle of an organism and DNA instability and changes in conformation can affect various reactions including replication, transcription, epigenetic modifications, recombination, and repair. This is postulated to be one of the risk factors for neuronal death in neurodegenerative diseases [14-16]. Copper is a physiologically important metal and micronutrient required for several biological functions and plays a role in the central nervous system development. Copper is toxic at higher concentrations and acts as a mediator in the formation of ROS and oxidative stress, copper Directly binding with proteins and nucleic acids induces conformational changes that have been linked to Alzheimer's disease [17] B-DNA is the normal and most common conformation of DNA in cells that carry out all biological functions. Any change in DNA conformation and stability leads to diseases [18]. Interactions of copper and iron to DNA cause DNA damage

that is responsible for genomic instability in aging brains and is one of the risk factors for Alzheimer's disease. AD is a progressive neurodegenerative disorder in which the brain is affected leading to memory and behavior problems [19]. Results of the circular dichroism show the changes in the DNA structures with the band shift due to the binding of copper and Aβ1-16 peptide. Copper binding with Aβ peptide may play a role in the promotion of toxic Aβ aggregation and the production of ROS that cause DNA damage, accumulated DNA damage and conformational changes in DNA may be ineffective during transcription and gene expression [20]. Through this study, it has been demonstrated with evidence that copper and Aβ1-16 peptide binding with DNA fragments causes DNA damage which is evidence for a change in conformation and stability that may have significance to neurodegeneration.

Copper and Aβ peptides are the suspected etiological factors in the pathology of AD. Copper binds to DNA that has a very high affinity towards nitrogenous bases. It binds to the guanine and cytosine bases through the hydrogen bonds. Copper preferentially binds to the N-7 position of guanine and is also capable of forming chelation complexes with the O-6 in the same guanine and with other nearby bases [21-22] and induce oxidative DNA damage that may lead to DNA damage by breaking the hydrogen bonds. N-7 position of guanine in DNA is a highly reactive site and more susceptible to oxidation in the major groove [23-24]. May be either more accessible due to supercoiling-dependent changes in the DNA or a more attractive binding site for copper due to changes in the electronic distribution within the DNA bases. Copper binds to N-7 in guanine and N-3 in cytosine [25-26] driving the base pairs towards the center of the helix to maximize the distance between the N and O sites on the bases and the phosphate backbone, the rearrangements in the coordination geometry may cause the conformational change in the DNA strand from B-DNA to an altered B-DNA conformation are understood to cause neurodegenerative diseases such as Alzheimer's [27].

Molecular docking studies evidenced more DNA damage upon binding with copper in the presence of the Aβ1-16 peptide due to copper binding to imidazole rings of histidine and initiating the aggregation and misfolding of the proteins in the brain which may result in neurotoxic and DNA damage. Repeated redox reactions of DNA-bound copper led to repeated formation of 'OH' radicals at the specific binding site of the DNA resulting in the formation of strand breaks accumulated in the brains. Copper–mediated toxicity and aggregations of the amyloid beta peptide could severely affect genomic integrity and accumulation of oxidative DNA damage and altered conformations may diminish the capacity for DNA repair which may contribute to the earlier stage of neurodegenerative conditions of AD.

In conclusion, the interaction of copper and Aβ1-16 peptide with DNA sequence investigated by CD studies show the DNA damage and changes in the conformation from B-DNA to altered B-DNA. The changes in conformation and stability may cause genomic instability that may contribute to the early progression of AD.

5. Acknowledgement

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6. Conflict of Interest

The authors report no conflict of interest.

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