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Original Article

Interactions of dopamine and copper with supercoiled DNA: Spectroscopic and molecular docking study

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ABSTRACT

Copper is an essential trace metal that plays a vital role in the biochemistry of the human nervous system and is important for the function of several enzymes and proteins and for DNA synthesis. Perturbations in copper metabolism are associated with some neurological disorders. It is also reported that dopamine may play a role in cell death. Copper in the presence of dopamine generates reactive oxygen species (ROS) and hampers the DNA repair mechanism. There is now increasing evidence that altered metal homeostasis provides a link between oxidative damage and neuronal cell loss in the brain and plays a role in neurodegenerative disorders. In the present study, we have attempted to understand the binding of copper and dopamine with DNA that alters the DNA conformation. This will provide clues as to how neurodegeneration may progress in the presence of both dopamine and copper. DNA damage and conformational changes induced by copper were studied by circular dichroism (CD). These observations were further supported by *in silico* molecular docking.

KEYWORDS: Alzheimer's disease (AD), circular dichroism, dopamine, copper, supercoiled DNA, docking studies.

INTRODUCTION

DNA is an important genetic material that plays an important role in life processes; it bears genetic information and enables the biological synthesis of proteins and enzymes through replication and transcription [1]. However, DNA molecules are prone to be damaged under various conditions such as the interaction of some metals and drugs that can influence numerous biological processes in which DNA participates. The role of small molecules with DNA has been of interest to many research groups over the years. Metal binding to DNA distorts its backbone causing conformational changes [2]. Researchers have also looked into the stability of DNA and the conformational changes which may have led to neurological symptoms [3], but a detailed understanding of the physiological consequences of these conformations is still elusive.

Copper is an essential trace metal that plays an important role in human health. It is comprised of many enzymes and is an important component of cell nuclear chromatin. Copper has a strong affinity to the base pairs of DNA and perturbs the hydrogen bonding between the base pairs causing damage and destabilization of DNA [4]. This study has been of particular interest because of the involvement of copper ions in oxidative DNA damage and because of its involvement in conformational changes in DNA, providing clues that Cu(II) might be one of the suspected etiological factors causing neuronal cell death in brain disorders [5, 6]. Copper ions participate in the redox reactions that generate the highly reactive hydroxyl radical's oxygen species *via* the Fenton reaction, which causes catastrophic damage to DNA and other macromolecules [7]. An increase in

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oxidative DNA damage may be accompanied by a decrease in the DNA repair capacity in many neurodegenerative disorders [8]. It has also been found that the neurotransmitter dopamine, an endogenous catechol derivative, is a factor that induces DNA damage in the presence of copper ions in the pathology of Parkinson's disease [9]. The present study evidenced the structural transitions of supercoiled DNA concerning stability, conformational changes, and damage because of binding with copper and dopamine. In this study, the effect of copper and dopamine on DNA was studied using circular dichroism, fluorescence spectroscopy, UV-visible spectrophotometry, gel electrophoresis, CD melting studies, and molecular modeling studies. These studies provide the basis to understand the factors that dictate the stability and structural conformation of supercoiled DNA in the presence of copper. The role of copper and copper with dopamine in DNA damage and pathogenesis concerning neurodegenerative disease, more importantly, Alzheimer's disease is discussed.

MATERIALS AND METHODS

Materials

pUC19 supercoiled DNA (cesium chloride purified) was purchased from Bangalore Genei, India. A stock solution of 1 mg/ml was prepared using Milli Q water and was diluted for further use.

Copper chloride ($CuCl_2.2H_2O$) was procured from Merck Schuchard. 50 mM stock solution was prepared by dissolving 9.5 mg of $CuCl_2.2H_2O$ in 1.1 ml of Milli-Q water. Further dilutions were used as and when required for experimentation. Similarly, dopamine was procured from Sigma Aldrich. Dilutions of dopamine were prepared using Milli Q water.

UV/VIS absorption studies

The electronic absorption studies of scDNA and its binding ability to copper chloride and dopamine at varying concentrations were studied using a Jasco V-530 Spectrophotometer equipped with a Peltier temperature controller. scDNA samples were prepared in Tris-HCl buffer (5 mM, pH 7.4) in the absence and presence of $CuCl_2$ (50 μM,100 μM, 250 μM,500μM) and various concentrations of Cu (25 μM, 50 μM, 75 μM 100 μM,250 μM,500 μM) were titrated with dopamine at a wavelength range between 230 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.

Circular dichroism studies

The scDNA was titrated against different concentrations of copper chloride (250 μM, 500 μM,) and dopamine (10, 50 μM) using a Jasco-J-715 Spectropolarimeter maintained at 25 °C, with a 1 mm path length quartz cuvette at 1 nm intervals at a wavelength between 200 and 320 nm. Spectra were recorded as an average of four repetitive scans using a scan speed of 20 nm/min. (scDNA sample prepared in Tris–HCl buffer (5 mM, pH 7.4) and the total sample is 300 μl). Buffer background was subtracted from the spectra of DNA, DNA-Cu, and DNA-dopamine complex using the built-in feature of Jasco software, and the resultant spectrum was recorded.

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 detect changes in their molecular environment through measurable alterations in emission properties. Fluorescence emission studies were carried out using equimolar concentrations of scDNA and EB (1:1) with different concentrations of $CuCl_2$ (10 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.

Gel electrophoresis

DNA samples [scDNA, scDNA +10 μM Cu, 100 μM, 250 μM, 500 μM, and 1 mM] were loaded on 1% agarose gel in TAE buffer and electrophoresed at 50 volts at room temperature for 2 hours. DNA concentration loaded in all the lines was 1μg. The gels were stained with ethidium bromide (0.1 μg/ml) and photographed under UV light.

In silico molecular docking studies

In silico molecular docking studies were carried out to understand the interactions between dopamine, copper, and DNA. The selected target DNA sequence (CGCGAATTCGCG) was retrieved from the

protein data bank [10] with PDB ID: 1BNA. The structure of B-DNA Dodecamer was used for docking analysis with the dopamine having Pubchem CID: 681, molecular formula of C8H11NO2, and a molecular weight 153.18 g/mol. Similarly, the metal ion ligand (Cu (II) with PubChem CID: 27099) was taken from the PubChem database [11]. The ligands and target DNA were minimized by using a CHARMM force field with potential energy -978.23719 kcal/mol. Docking was carried out using the CDOCKER protocol in Discovery Studio 3.5 (http://www.accelrys.com/) [12], which is a CHARMM-based molecular dynamics (MD)-simulated annealing algorithm [13]. While DNA was kept rigid, the ligands, dopamine, and copper were allowed for flexible ligand docking and the docked poses were refined *via* the minimization step. Thus, the optimized structure of the DNA-Cu complex was docked with dopamine to investigate the conformational perturbations.

RESULTS

UV absorption studies

The UV-vis absorption measurement is an effective and simplest technique to study the interaction of small molecules with DNA. The absorption spectra of scDNA in the absence and presence of copper were studied and are shown in Fig. 1A. The absorption maximum of scDNA was found at 257 nm, and the absorbance of DNA gradually increased in the presence of various concentrations of $CuCl_2$ with a blue shift to 245 nm (12 nm). Hyperchromicity is mainly the result of increased base stacking and the interaction of copper and base pairs of DNA. 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. This structural change confirms the interaction between copper and scDNA.

The interaction between scDNA and dopamine was monitored based on the UV spectral changes shown in Fig. 1B. The absorption peak of scDNA at 258 nm gradually increased with a red shift to 280 nm indicating that dopamine gives rise to noticeable changes in the UV spectrum of DNA. Dopamine exists as a cation that could interact with DNA, and this implies that there are intensive binding interactions between dopamine and DNA, and a new Dopamine-DNA complex is formed. The reaction between copper and dopamine was also investigated and the UV spectra are shown in Fig. 1C. The absorption peak maximum of dopamine was detected at 278 nm. In the presence of copper, the peak was shifted to 295 nm with a gradual

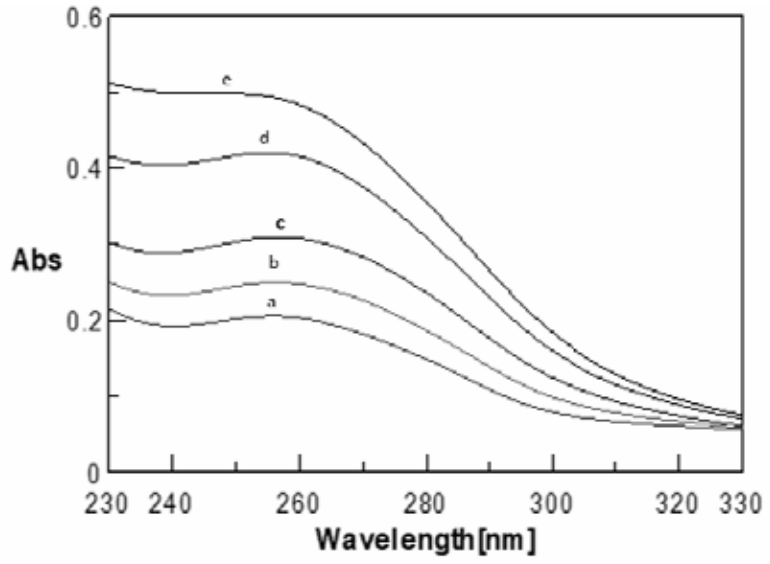

Fig. 1A. Effect of Cu on the absorption spectra of scDNA in 5mM Tris-Hcl buffer (pH 7.4). The concentrations were **a**. scDNA, **b**. 50 µM Cu, **c.**100 µM Cu, **d**. 250 µM Cu, **e**. 500 µM Cu. (Peak shift 256 nm-227 nm).

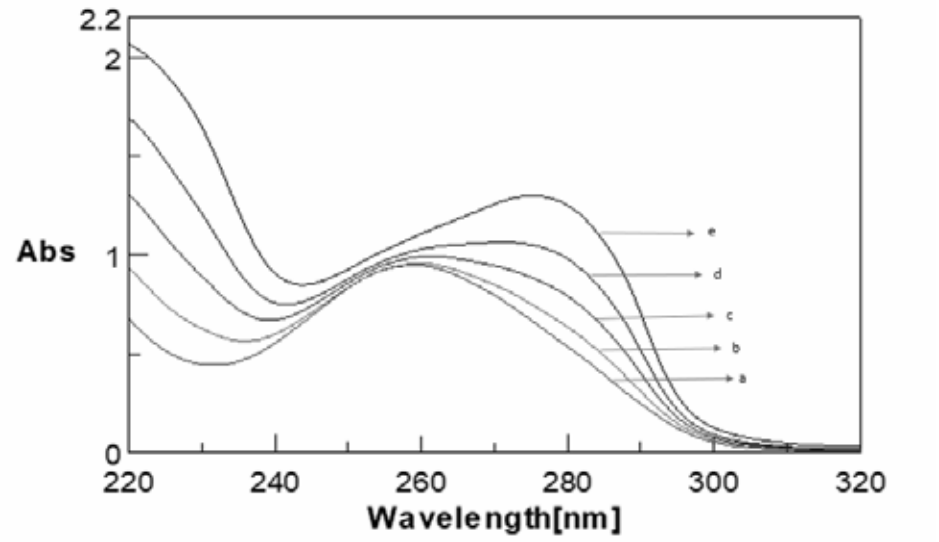

Fig. 1B. Effect of dopamine on the absorption spectra of scDNA. **a**. scDNA, **b**. scDNA+25µM dopamine, **c.** scDNA + 50 µM dopamine, **d**. scDNA + 75 µM dopamine, **e**. scDNA+ 100 µM dopamine.

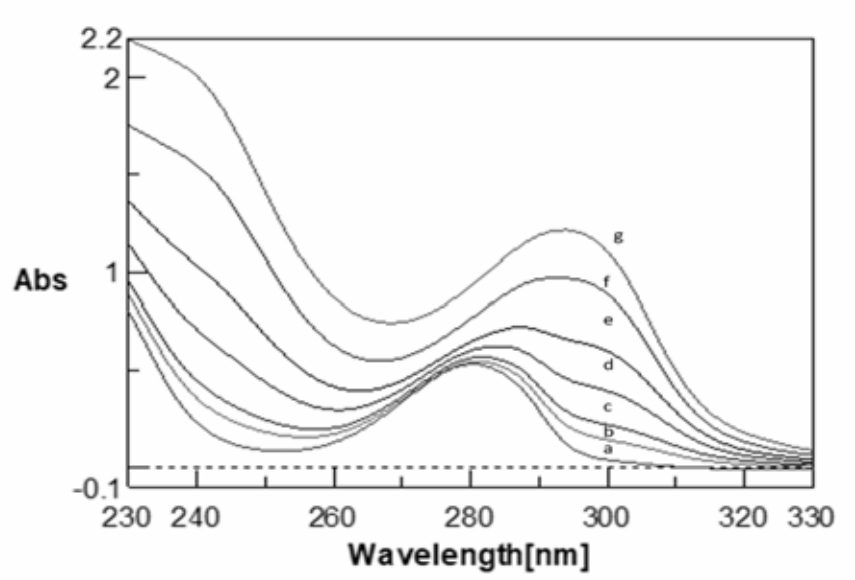

Fig. 1C. Effect of $CuCl_2$ on the absorption spectra of dopamine The concentrations were **a**. dopamine, **b**. 25 µM $CuCl_2$, **c.** 50 µM $CuCl_2$, **d**. 75 µM $CuCl_2$, **e**. 100 µM $CuCl_2$, **f**. 250µM $CuCl_2$, **g.** 500 µM $CuCl_2$.

increase in absorbance. This indicates the formation of a certain product from dopamine through the interaction with copper.

The situation became different when copper was added to the dopamine-DNA complex. Fig. 1D shows the UV spectra of scDNA influenced by the addition of dopamine and copper. The absorption peak of scDNA shows a peak maximum at 256 nm and in the presence of 100 µM copper it only increased the absorption of the peak of DNA as shown in Fig. 1D. Upon addition of dopamine to scDNA, it displays the redshift with a peak maximum of 280 nm, and in the presence of 100 µM copper, it further shifted to 290 nm with an increase in absorbance. The increase in the absorbance of scDNA in the presence of copper is attributed to the interaction between scDNA and copper forming a DNA-Cu complex. The presence of

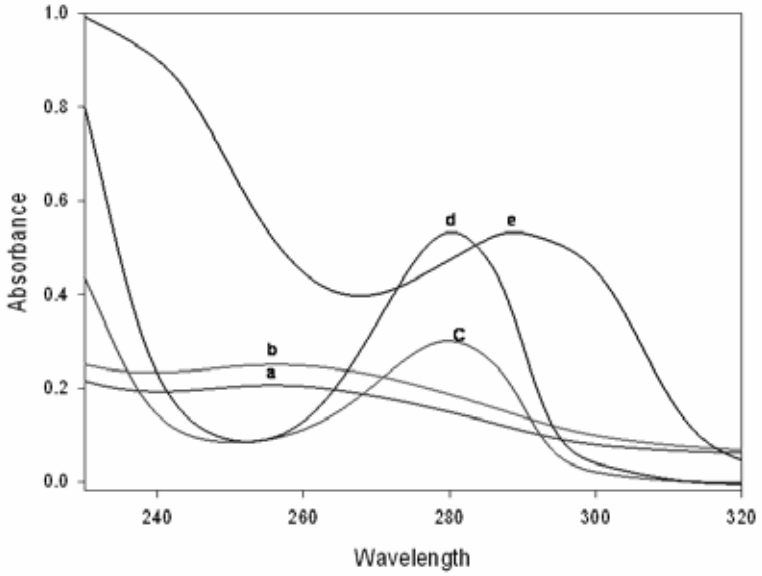

Fig. 1D. Effect of $CuCl_2$ and dopamine on the absorption spectra of scDNA. **a**. scDNA, **b**. scDNA+100 µM $CuCl_2$, **c.** scDNA + dopamine, **d**. scDNA+ $CuCl_2$+ dopamine, **e**. dopamine.

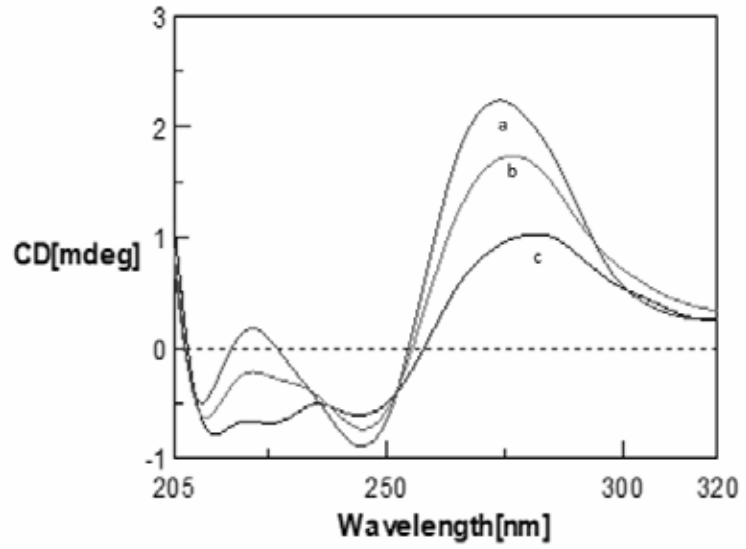

Fig. 2A. Effect of $CuCl_2$ on the CD spectra of scDNA in 5mM Tris-Hcl Buffer (pH 7.4). **a**. sc DNA alone, **b**. scDNA+250 µM $Cucl_2$, **c**. scDNA+500 µM $Cucl_2$.

copper is believed to cause more damage to the DNA-Dopamine complex [11]. Because dopamine is a reductive compound and copper may act as an oxidation species, according to their electrode potentials dopamine can be easily oxidized by the Cu–DNA complex [12]. The absorbance of the DA-DNA-Cu complex was found to increase with time. The results confirmed that supercoiled DNA destabilizes interaction with copper and dopamine.

CD Studies

Circular dichroism is a useful and sensitive technique to study the conformational changes in supercoiled DNA binding with small molecules. Structural transitions of scDNA in the absence

and presence of copper were investigated by circular dichroism. As shown in Fig. 2A, the CD spectrum of scDNA displays B-DNA conformation with a characteristic positive peak at 275 nm due to base stacking and a negative peak at 245 nm due to the right-handed helicity of classical B-DNA conformation. Lower concentrations of copper did not show visible changes to the DNA conformation, but on the addition of 250 μM and 500 μM $CuCl_2$ a decrease in the magnitude of the positive band with a red shift to 281.5 nm (6.5 nm) and narrow changes at the negative band with intersection points at 255 nm and 235 nm were observed. The data revealed that at lower concentrations of copper, the ions interact electrostatically with the anionic phosphate ions of the DNA backbone, and with higher concentrations, copper binds to bases of DNA. This in turn weakens base stacking, causing a decrease in the intensities of the CD bands due to the unwinding of the double helix. As the winding angle increases, the magnitude of the band decreases causing the conformational change. This is in line with our earlier results [13, 14].

The conformational change of scDNA in the presence of dopamine is shown in Fig. 2B. In the presence of dopamine, it caused the perturbation of the supercoiled DNA at the positive band and a negligible change at the negative band. This characteristic decrease in the positive band at 275 nm, without change in the negative band at 244 nm is characteristic of C DNA conformation [15]. This evidence provides information that dopamine also exists as a cation that will interact with DNA mainly by a static electronic force and did little damage to the DNA structure [16, 15] but dopamine in the presence of copper showed more DNA damage and the spectral change is shown in Fig. 2C. The situation became quite different and the damage to the DNA is more progressive with time after incubation of the complex for two hours as shown in Fig. 2D. An inverted CD spectrum was observed with the new positive band at 307.5 nm and the negative band at 270 nm (positive band of 275 nm has been inverted to the negative at 270 nm) and a positive band at 233 nm resembling the Ψ-DNA [17]. These results suggest that copper binds to scDNA and plays a crucial role in DNA damage leading to altered B-DNA forms. Similarly, copper and dopamine together cause more DNA damage that exhibits conformational change from B-DNA to C- DNA and after incubation for 2 hrs from C-DNA to Ψ-DNA, and these results are supported by the UV absorption studies. These conformational changes will change the ability of the DNA in the normal process of DNA replication and transcription, which is implicated in many neurological disorders.

Thermal melting studies

The effects of temperature on the CD spectrum of scDNA are shown in Fig. 3, which provides information on conformational changes. CD spectrum of scDNA with a varying temperature range from

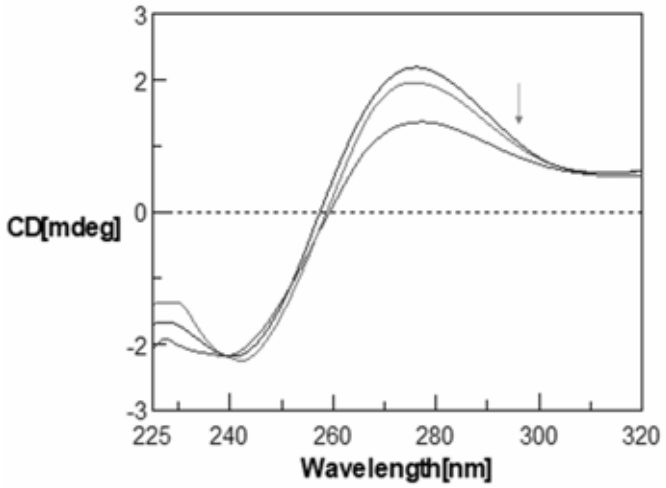

Fig. 2B. Effect of dopamine on the CD spectra of scDNA in 5mM Tris-Hcl Buffer (pH 7.4).

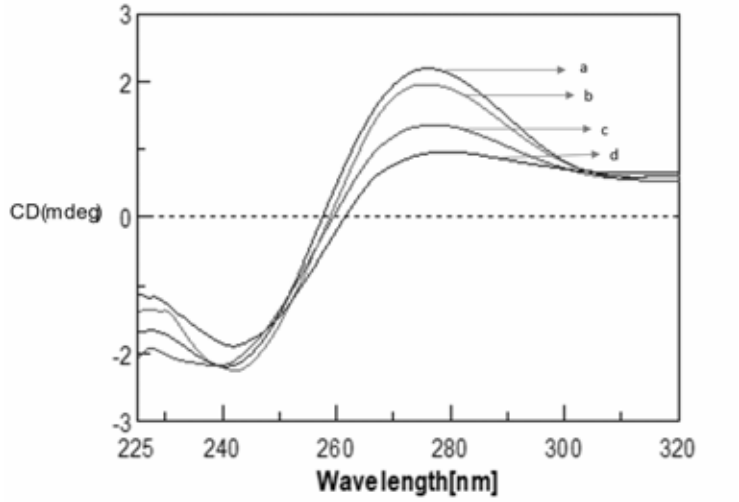

Fig. 2C. Effect of $CuCl_2$ and dopamine on the CD spectra of scDNA in 5mM Tris-Hcl Buffer (pH 7.4). **a**. scDNA alone, **b**. scDNA+Dopamine, **c**. scDNA-dopamine+100 µM $Cucl_2$. **d**. scDNA-dopamine+ 250 µM $Cucl_2$.

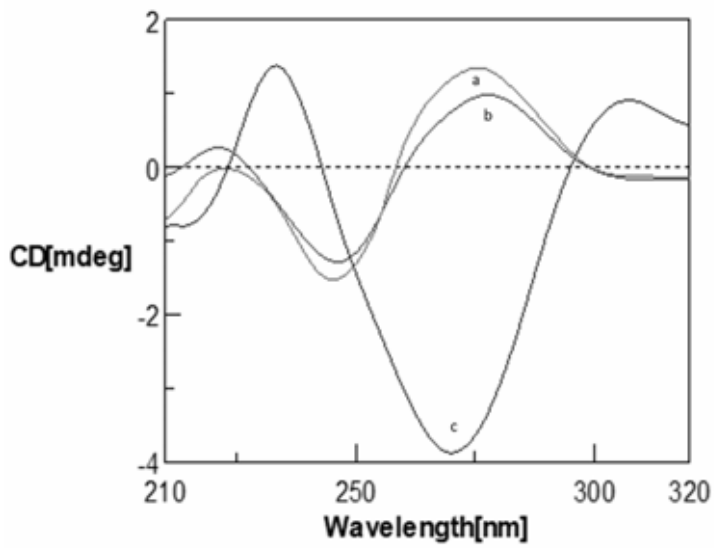

Fig. 2D. Effect of $CuCl_2$ and dopamine on the CD spectra of scDNA in 5mM Tris-Hcl Buffer (pH 7.4) with varying time. **a**. scDNA alone, **b**. scDNA+dopamine, **c**. scDNA-dopamine+250 µM $Cucl_2$.

20 °C to 110 °C with a variation of 10 degrees shows that it is highly stable up to 60 ºC and from 70 ºC to100 ºC minor changes in the positive peak of 275 nm and major changes in the negative band at 245 nm were observed. The major effect to note is the complete loss of both positive and negative bands at 110 ºC, indicating loss of B- conformation which may be due to base stacking and perturbations. This, in turn, leads to destabilization and change in the conformation of scDNA [17]. Our previous studies show a decrease in melting temperature in the presence of copper; hence copper plays an important role in the destabilization of DNA strands.

Fluorescence studies

Fluorescence emission spectra were monitored for equimolar concentrations of scDNA:EtBr with and without copper ions to understand conformational

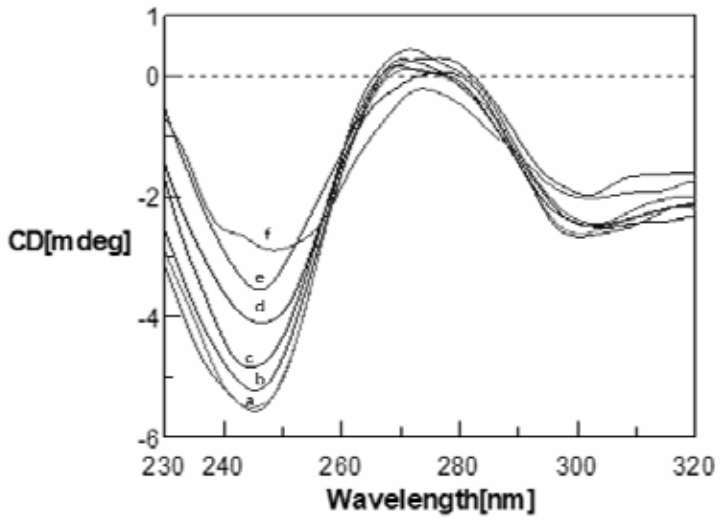

Fig. 3. Effect of temperature on the CD spectra of scDNA in 5mM Tris-Hcl buffer (pH 7.4) **a**. scDNA-25 °C, **b**. 70 °C, **c.** 80 °C, **d**. 90 °C, **e**. 100°C, **f**. 110 °C.

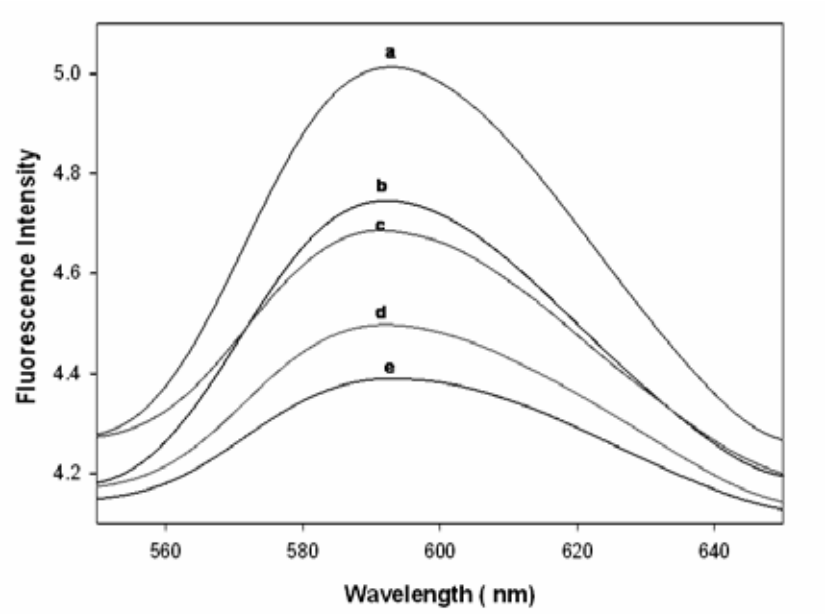

Fig. 4. Effect of $CuCl_2$ on the emission spectra of scDNA . **a**. scDNA, **b**. scDNA+10 μM $CuCl_2$, **c.** 100 μM $CuCl_2$, **d**. 250 μM $CuCl_2$,**e**. 500 μM $CuCl_2$.

changes upon the addition of copper with scDNA. The fluorescence spectra of scDNA-EB complex were excited at 530 nm and emission spectra were recorded from 550 to 650 nm (Fig. 4). Upon addition of different concentrations of copper chloride to scDNA:EB complex, the fluorescence intensity decreased with increasing concentration of copper. The decrease of fluorescence emission with the addition of copper indicates that binding of Cu^{2+} ions with the N7 position of guanine of scDNA:EB complex forms a new non-fluorescent complex of Cu-scDNA–EB, which shows that Cu^{2+} ions efficiently quench the fluorescence of the intercalation complex of ethidium bromide with scDNA [18]. This data shows that Cu^{2+} ions displace EtBr and bind to scDNA at micromolar

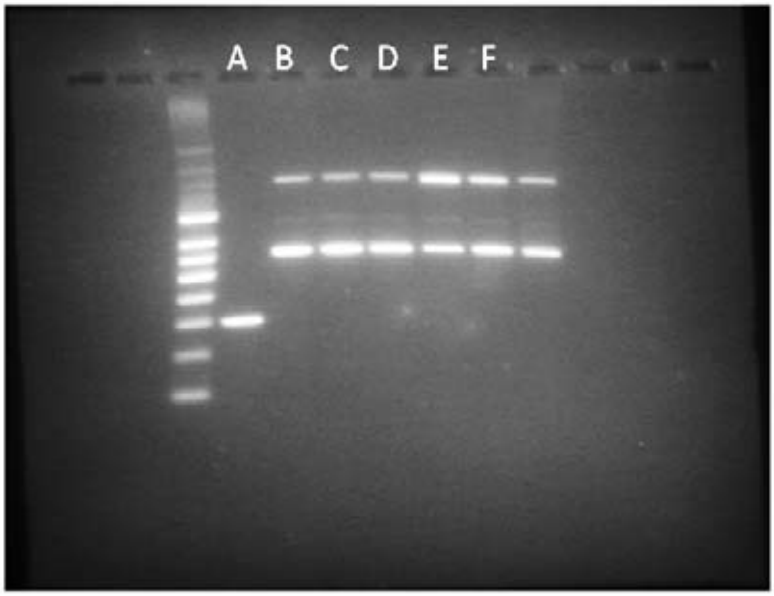

Fig. 5. Effect of $CuCl_2$ binding on scDNA mobility in 1% agarose. scDNA was incubated in the absence and presence of copper chloride for 2 hours at 37 ºC and then separated by 1% agarose gel electrophoresis. Lane A: scDNA alone (cesium chloride purified) Lane B: scDNA with 10μM Cu^{2+}, Lane C: scDNA with 100μM Cu^{2+}, Lane D: scDNA with 250 μM Cu^{2+}, Lane E: scDNA with 500μM Cu^{2+}, Lane F: scDNA with 1mM Cu^{2+}.

concentrations, which will address the destabilization of scDNA.

Gel electrophoresis

The cleavage reaction on scDNA by Cu (II) was monitored by agarose gel electrophoresis. Samples (scDNA, scDNA + 10 μM Cu, 100 μM, 250 μM, 500 μM, and 1mM) were loaded on 1% agarose gel in TAE buffer and electrophoresed at 50 volts at room temperature for 2 hours. DNA concentration loaded in all the lines was 1 μg. The gels were stained with ethidium bromide (0.1 μg/ml) and photographed under UV light. The agarose gel electrophoresis patterns for the cleavage of scDNA by Cu(II) are shown in Fig. 5 .The experimental results for scDNA show fast migration; in the presence of copper the DNA strands get damaged which leads to a linear form of the plasmid that slows down the migration. The cleavage efficiency was found to increase with an increase in the concentration of copper.

Docking studies

To get a more comprehensive understanding of the interaction of dopamine, and copper with DNA, *in silico* docking studies were carried out considering the different types of hydrogen bonding between dopamine, copper, and DNA bases in its grooves and phosphate backbone region. Our docking results indicate that hydrogen bonds are formed between dopamine complexes with different bases of DNA, mainly with thymine (T) Adenine (A) and Cytosine (C).

As evident from the docking studies (Fig. 6, 7 and 8 & Table 1), the nucleotide residues of DNA, namely ADE17 of B chain, THY8 of A Chain, and CYT9 of A chain interact with dopamine and nitrogenous bases of B-DNA and form 4 hydrogen bonds across the minor groove. The benzene ring of dopamine and DNA bases thymine and cytosine, face each other during hydrogen bonding which suggests the possibility of π–π interaction along with the hydrogen bonding. Further, the NH3 group of dopamine is hydrogen-bonded with the Adenine base and Pentose Sugar. It is apparent that the hydrogen bonding of the bases in the minor groove region of DNA with dopamine plays a significant role. Docking studies depict that dopamine interferes with the groove region of DNA with a CDOCKER energy of 26.0276 and

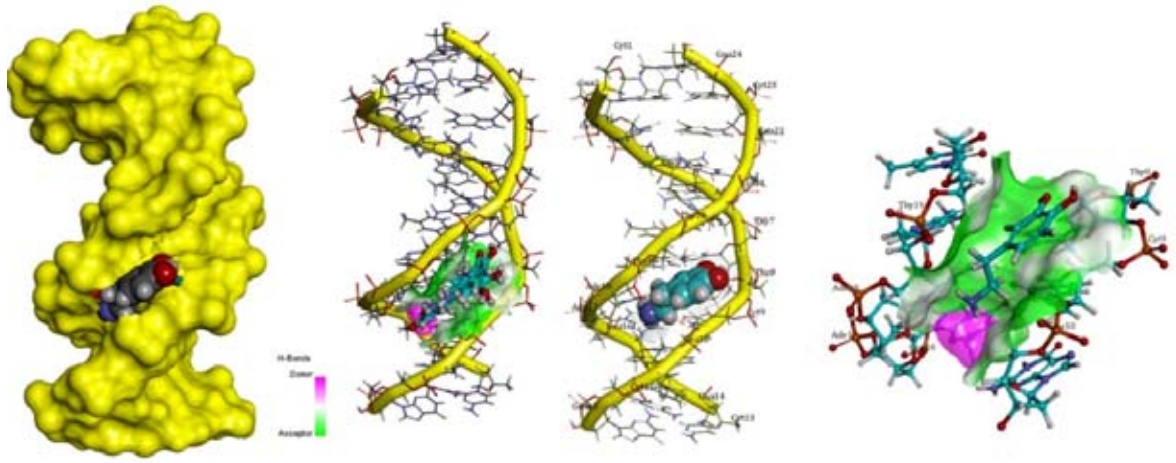

Fig. 6. Docking interactions of dopamine with the phosphate backbone of DNA. Dopamine molecules are represented in CPK space-filling models that incorporate both the covalent and van der Waals radii of atoms into their design.

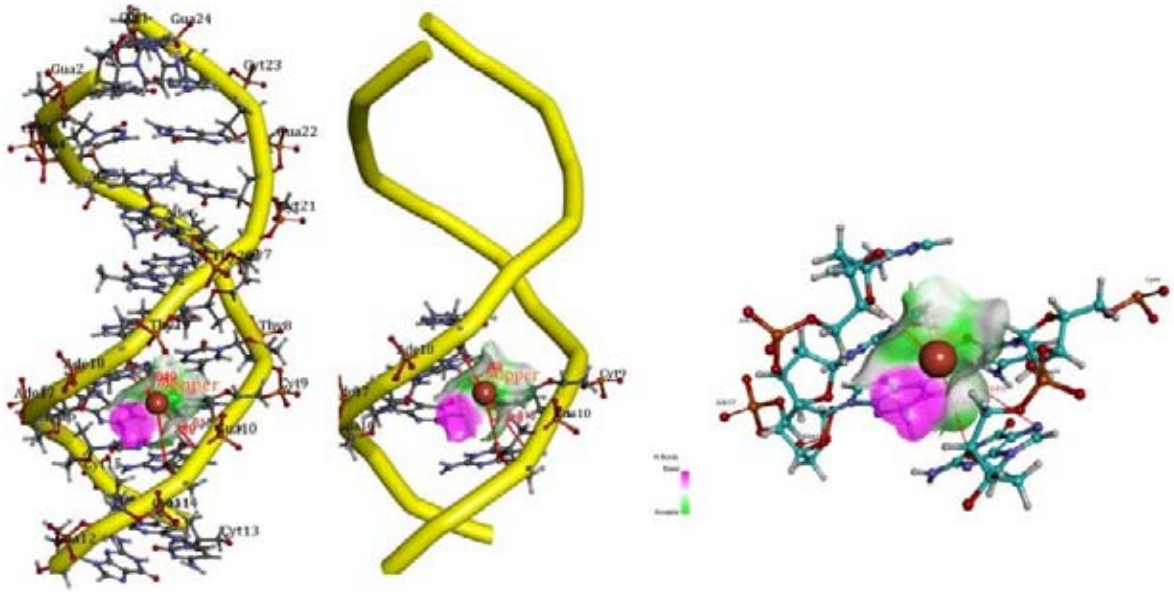

Fig. 7. Docking interaction of copper with DNA.

CDOCKER interaction energy of 25.184. The hydroxyl and amine groups of dopamine form a hydrogen bond with thymine whereas the amine group mainly interacts with the adenine bases of DNA. The interaction of dopamine with the bases in the minor groove region enhances the hydrogen bonding between the Watson−Crick base pairs.

Similarly copper also interacts with nucleotides CYT9 and GUA10 of the A chain and ADE 17 and ADE18 of the B chain. Cytosine, guanine, and adenine form strong covalent metal complexes with a binding CDOCKER energy of 32.2179 and CDOCKER interaction energy 32.1162. Thus, the molecular docking results shown in the figures indicate that the minor groove interactions are the relevant binding modes for dopamine and copper at different binding sites on the DNA molecule, indicating a higher binding probability/affinity to DNA.

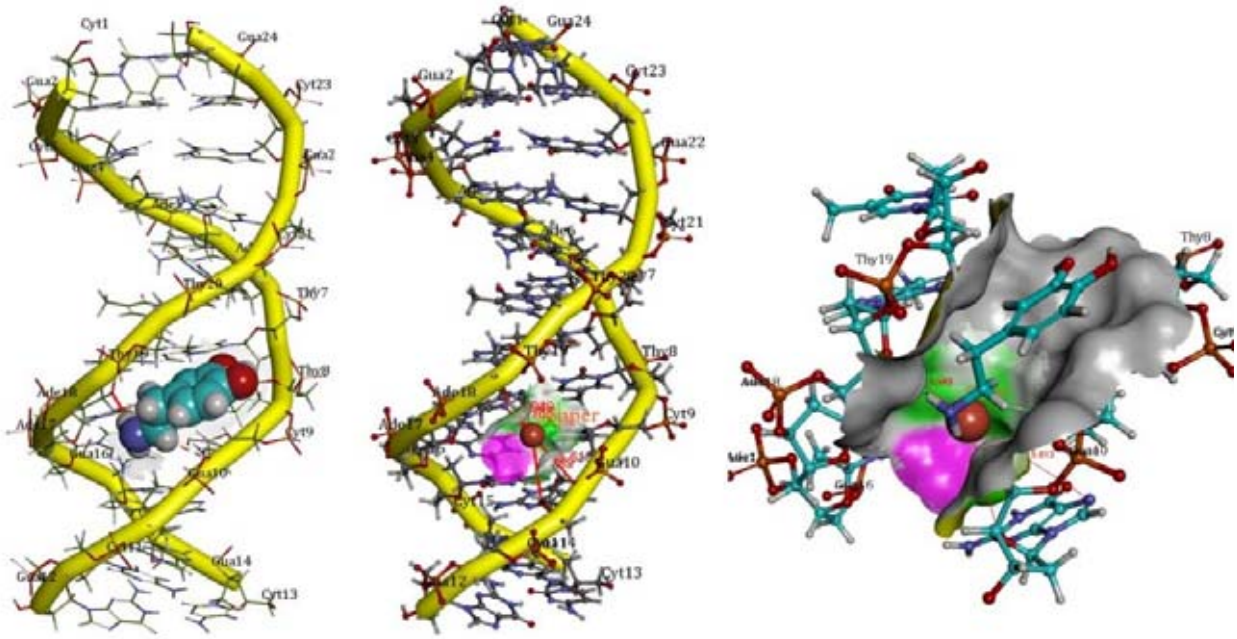

Fig. 8. Docking interaction of dopamine and copper with DNA.

Table 1. Interaction of dopamine and copper with DNA and hydrogen bond distances.

Sl. No	Molecule	Ligand	Residues Interacting	Hydrogen Bond and Distance in A°	Highest - CDOCKER energy (kcal·mol−1)	Highest -- CDOCKER interaction energy (kcal·mol−1)
1	DNA	COPPER (2+)	CYT9 GUA10 ADE 17 ADE 18	3.282 4.006 2.362 2.312	32.2179	32.1162
		DOPAMINE	ADE17 THY8 CYT9 CYT9	3.189 2.776 3.475 3.471	26.0276	25.184

DISCUSSION

Copper is a physiologically important metal and micronutrient required for several biological functions and plays a role in the central nervous system development; it is toxic and injurious to health when it is in excess. Studies from the past few years have shown that copper is implicated in the pathogenesis of Alzheimer's disease, and Parkinson's disease [19] and may bind to proteins like prion protein and the Amyloid precursor protein in the brains of Alzheimer's patients, implicating its role as a mediator of oxidative stress in neurodegenerative diseases [20]. Our previous studies [21] and the present study evidenced that copper binds to DNA and proteins to induce conformational changes and DNA damage at micromolar concentration leading to cell death.

UV results show that the binding of copper to scDNA caused an increase in absorbance due to the binding of the copper ion with the bases of the DNA. 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 [22, 23]. It also confirmed the binding of dopamine with DNA. However, the addition of copper to the DNA-Dopamine solution gave rise to significant changes in its UV spectrum and induces DNA damage due to the formation of 'OH' radicals in the presence of copper. Dopamine is a reductive compound and copper may act as an oxidation species. Hence, dopamine may be easily oxidized by copper ions and is prone to react with oxygen, yielding H_2O_2 and free radicals that will damage the DNA structure.

Results of CD studies show that at low concentrations of copper (500 nm to 100 μM) the positive and negative bands show very small increase in magnitude due to the interaction between Cu^{2+} ions and the phosphate oxygen groups. Higher concentrations of copper (250 μM to 500 μM) results in a decrease in the magnitude of the positive band with an evident band shift to 281 nm and a negligible change in the negative band due to base pair tilting and an increase in the winding angle of DNA [24]. The B to C transition is associated with an increase in winding angle of 2.6° per base pair and a change in the tilt of bases from -2° to -6° [25]. Many reports show that within the DNA molecule copper (II) forms complexes with guanine and cytosine bases and the reduction of copper (II) to copper (I) results in the formation of ROS [26, 27]. Copper (II) binds preferentially 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 [28, 29] and induces oxidative DNA damage by breaking the hydrogen bonds. The N-7 position of guanine in DNA is a highly reactive site and more susceptible to oxidation in the major groove [30, 31]. 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 accumulation of strand breaks in the brains.

Dopamine is a neurotransmitter and has o-diphenol groups in its structure; it may induce DNA damage when it interacts with copper. Upon addition of dopamine and copper to scDNA the positive band is decreased without change in the negative band and with copper, more DNA damage is seen and the conformation is more towards the C form [32]. However on incubation with dopamine and copper, an inverted CD spectrum was observed with the new positive band at 308 nm and the negative band at 270 nm thus resembling the Ψ-DNA. This resembles the Z-DNA which lacks a tertiary structure. The Cu-induced DNA damage in Ψ-DNA was shown to be structurally and immunologically closely related to the Z-DNA family [33].

Results of CD, fluorescence analysis, and other techniques reveal that copper at lower concentrations binds to oxygen present in the phosphate groups of the DNA backbone, thereby tilting the base pairs causing an unwinding of the DNA helix and hence DNA damage. Copper interacts with bases in the presence of dopamine possibly preventing the strands from coming close to each other. In the case of C-DNA the bases tilt in such a way that they move further apart from the helix. Copper binds to N-7 in guanine and N-3 in cytosine [34, 35] 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; thus this kind of rearrangement in the coordination geometry may cause the conformational change in the DNA strand [36].

DNA stability and conformation are important in the life cycle of an organism and changes in the DNA stability is postulated to be one of the risk factors for neuronal death in neurodegenerative diseases [37]. Changes in DNA conformation and instability can potentially affect various reactions including replication, transcription, epigenetic modifications, recombination, and repair [38]. Our results on the interaction of copper and dopamine with DNA are evidenced by the change in conformation from B-DNA to C-DNA and Ψ-DNA [39]. Our studies evidenced copper-induced DNA damage in the presence of dopamine. Copper-mediated toxicity could severely affect genomic integrity and increase in oxidative DNA damage and diminished capacity for DNA repair may contribute to the earlier stage of neurodegenerative conditions.

CONCLUSION

In conclusion, the interaction of copper with DNA that results in DNA damage was investigated by CD studies Copper in the presence of dopamine

induces more damage to the DNA causing conformational changes from B-DNA to altered B-DNA, C-DNA, and Ψ-DNA. The resultant conformational change induces genomic instability and is known to change its integrity thereby affecting the replication and transcription processes. Both copper and dopamine could induce the formation of free radicals that cause damage to the native structures of DNA which results in neurotoxicity that eventually leads to neurological disorders. Hence through this study, we can deduce that the dopamine-copper complex can induce DNA damage and hence the progression of neurodegeneration.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

REFERENCES

1. Ni, Y. N., Wei, M. and Kokot, S. 2011, Int. J. Biol. Macromol., 49, 622-8.
2. Sissoeff, I., Grisvard, J. and Guille, E. 1976, Prog. Biophys. Mol. Biol., 31(2), 165-199.
3. Schneider, B. and Berman, H. M. 2006, Springer, 1-44.
4. Roychaudhuri, R., Yang, M., Hoshi, M. M. and Teplow, D. B. 2009, J. Biol. Chem., 284, 4749-4753
5. Berhard spingler and Chiara Da Pieve, 2005, Dalton Trans., 5(9), 1637-1643.
6. Noy, A., Perez, A., Lankas, F., Luque, F. J. and Orozco, M. 2004, J. Mol. Biol., 343, 627-638.
7. Martha Patricia Cervantes-Cervantes , J Víctor Calderón-Salinas, Arnulfo Albores and José Luis Muñoz-Sánchez, 2005, Biol. Trace Elem Res., 103(3), 229-48.
8. Scott Maynard, Evandro Fei Fang, Morten Scheibye-Knudsen, Deborah L. Croteau and Vilhelm A. Bohr 2015, Cold spring harbor perspective in madicines, 5(10), a025130.
9. Spencer, J. P. E., Andrew Jenner, Okezie, I. Aruoma, Patricia J. Evans, Harparkash Kaur, David T. Dexter, Peter Jenner, Andrew J. Lees, David C. Marsden and Barry Halliwell, 1994, FEBS Letters, 353(3) 246-250.
10. Jun Liu, Qingwen Li, Yadong Yu and Xiang Fang, 2003, Analytical Sciences, 19, 1099-1102.
11. Nida Rehmani, Atif Zafar, Hussain Arif, Sheikh Mumtaz Hadi and Altaf A. Wani, 2017, Toxicology, 40, 336-346.
12. Jun Liu, Qingwen Li, Yadong Yu and Xiangfang 2003, Analytical Sciences, 19, 1099-1102.
13. Dugoid, J., Bloomfield, V. A., Benevides, J. and Thomas, G. J. Jr. 1993, Biophys. J., 65, 1916-1928.
14. Sagripanti, J. L. and Kraemer, K. H. 1989, J. Biol. Chem., 264, 1729-1734.
15. Eichhorn, G. L. and Shin, Y. A. 1968, J. Am Chem Soc., 90, 7323-7328.
16. Yang Pin, Ren Rui and Yang Bin-sheng, 1993, J. Mol. Science, 9, 2103-109.
17. Altan-Bonnet G., Libchaber A. and Krichevsky, O. 2003, Phys. Rev. Lett., 90, 138101-04.
18. Jean–Jacques Lawrence, Daniel, C. F. Chan, and Lawrence H. Plette, 1976, Nucleic Acid Res., 3(11), 2879-2893.
19. Lovell, M. A., Robertson, J. D., Teesdale, W. J., Campbell, J. L. and Markesbery, W. R. 1998, J. Neurol. Sci., 158(1), 47-52.
20. Sayre, L. M., Perry, G. and Smith, M. A. 1999, Curr. Opin. Chem. Biol., 3, 220-225.
21. Govindaraja, M., Shekar, H S., Sateesha, S. B., Vasudevaraju, P., Sambashivarao, K. R. S. and Rao, K S J. 2013, Journal of Pharmaceutical Analysis, 3, 354-359.
22. Tracey D. McGregor, Wendi Bousfield, Yun Qu and Nicholas Farrell, 2002, Journal of Inorganic Biochemistry, 91, 212-219.
23. Yang Pin, Ren Rui and Yang Bin-sheng 1993, J Mol. Science (China), 9(2), 103-109.
24. Christoph Zimmer and Gerhard Luck, 1973, BBA-Nucleic acids and protein synthesis, 312, 215-227.
25. Arnott, S. 1970, Progr. Biophys. Mol. Biol., 21, 265-319.
26. Halliwell, B. and Gutteridge, J. M. C. 1989, Clarendon Press Oxford, 30-74.

27. Aruoma, O. I., Halliwell, B., Gajewski, E. and Dizdaroglu, M. 1991, Journal of Biochemistry, 273, 601-604.
28. Sagripanti, J. L. and Kraemer, K.H. 1989, J. Biol. Chem., 264, 1729-1734.
29. Hutchinson, H. 1985, Prog. in Nucleic acids Res. and Mol Biology, 32, 115-155.
30. Frelon, S., Douki, T., Favier, A. and Cadet, J. 2003, Chem. Res. Toxicol., 16, 191-197.
31. Ivanov, V. I., Minchenkova, L. E., Schyolkina, A. K. and Poletayev, A. I. 1973, Biopolymers, 12, 89-110.
32. Eichhorn, G. L. and Shin, Y. A. 1968, J. Am. Chem. Soc., 90, 7323-7328.
33. Guliang Wang and Karen M. Vasquez 2006, Mutation Res., 598, 103-119.
34. Bryan, S. E., Vizard Douglas, L., Beary David, A., LaBiche Ronald, A. and Hardy Kenneth, J. 1981, Nucleic Acids Res., 9(21), 5811-23.
35. Howlett, N. G. and Avery, S. V. 1999, FEMS Microbiol. Lett., 176, 379–386.
36. Hegde, M. L., Pavana, M. Hegde, Luis, M. F. Holthauzen, Tapas K. Hazre, Rao, K. S. J. 2010, The J. Biol. Chemistry, 285(37), 28812-28825.
37. Hegde, M. L., Anitha, S., Latha, K. S., Mustak, M. S., Reuven Stein, Rivka Ravid, Rao, K. S. J., 2004, J. Mol. Neurosci., 22, 19-31.
38. Crapper, D. R., Quittkat, S. and de Boni, U. 1979, Brain, 102, 483-495.
39. Anitha, S., Rao, K. S. J., Latha, K. S. and Viswamitra, M. A. 2002, J. Neuromol. Med., 2, 287-295.