

# A Brief Review on Applications of Gold and Silver Nanoparticles in Drug Delivery and DNA Interaction

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## Abstract

Nanoparticles (NPs) are among the several NMs that can function as nano carriers because of their improved solubility, prolonged release, targeting potential, and aid in medication dosage reduction. Recent developments are discussed in this overview. To distribute medications, these small materials can locate the precise location in the body. In addition, they can lessen the negative effects of medications and assist patients in taking fewer pills while still achieving the same or better benefits. The development of nanoparticle medication delivery systems has been one of the most important research fields. This brief overview will concentrate on the traits that make for effective drug delivery systems based on nanoparticles as well as the numerous disease conditions where these nanoparticle systems have shown promise.

**Keywords:** Gold Nanoparticles, Silver Nanoparticles, DNA interaction, Drug delivery.

## Graphical Abstract

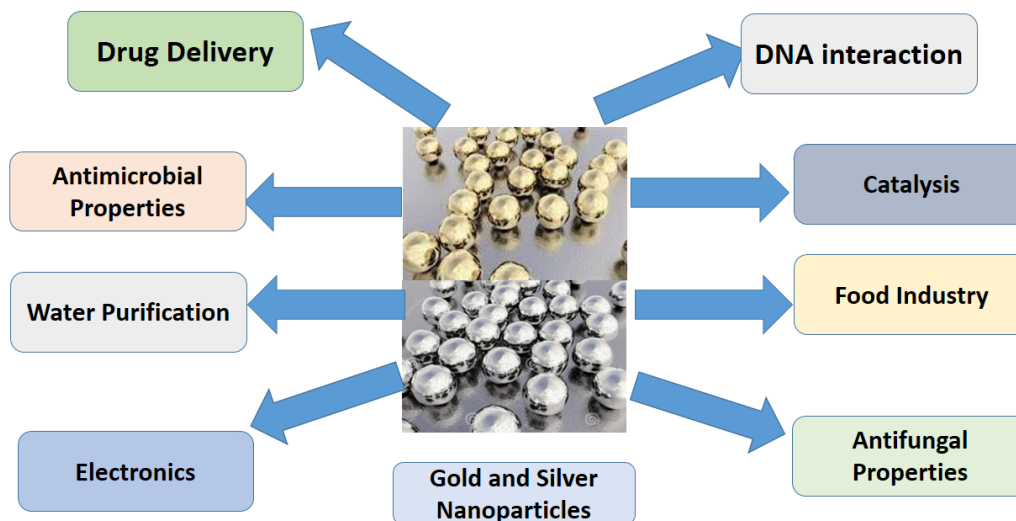


Figure 1: Different applications of Gold and Silver Nanoparticles

## 1. INTRODUCTION

The simplest type of structures with dimensions in the nanometer (nm) range are called nanoparticles. In general any group of bounded atoms having a structural radius of less than 100 nm can be categorized as nanoparticle [1]. They consist of a variety of biodegradable substances, such as metals, lipids, or polymers, whether they are manmade or natural. Although larger micro molecules can be used as effective delivery and transport systems since they are less effectively absorbed by cells than nanoparticles [2]. For medicinal purposes, drugs can either be attached to the particle surface or integrated within the particle matrix [3]. A drug targeting system should have control over a medication's course after it reaches the biological environment. Numerous investigations have been done on nano systems with different biological properties and compositions for use in gene delivery and medicine [4]. Targeting and controlling the medication release are essential components of a perfect drug delivery system. The therapy will be more effective and have fewer adverse effects if it is targeted, particularly when dealing with medications that are supplied to healthy cells but have the potential to kill cancer cells as well. Through regulated release, adverse effects can also be minimized or avoided. For a variety of reasons, including the increased ratio between the number of atoms or molecules on the surface and the total number of atoms or molecules, the development of nano sized systems for the administration of pharmaceuticals is particularly appealing to scientists [5]. The special physical, chemical, and large surface area characteristics of noble metals enhance the performance of biosensors for sensitive and precise biomolecular detection [6, 7]. Many nanoparticles, including gold, platinum, titanium, zirconium, and magnetic nanoparticles, are now being employed in a variety of sensors to enhance the methods for detecting biomolecules [8]. Among them, gold nanoparticles stand out for their appealing properties

and are used to immobilise probes and detect targets on sensing surfaces with higher detection limits [9]. Silver (Ag) nanoparticles are attractive in biotechnology domains such as antimicrobial, diagnostic, and therapeutic, similar to the gold nanoparticle [10]. Additionally, it has been utilised in electrical components, conductive materials, cosmetic items, and sensor materials. Because to Ag nanoparticles' strong thermal, chemical durability, electrical conductivity, and catalytic activity, the limit of detection of the target has increased [11]. According to past investigations and evidenced by their stability analysis, Ag nanoparticles are generally stable [12]. Electrostatic attraction is a method that can be used to adhere Ag nanoparticles to sensor surfaces. To generate a strong bond, it is often advised to do the surface chemical modification affixing to the surface. Depending on the intended molecular attachment, several surface chemical alterations of the Ag nanoparticle are suitable. One of the appropriate chemical functionalizations for Ag nanoparticles via the silane reaction is (3-aminopropyl) triethoxysilane. This occurs because the Ag nanoparticle, which was exposed to ambient moisture, has oxide groups on it. [13] Due to their distinct optical, electrical, photothermal and bioactive characteristics, gold and silver nanoparticles (AuNPs and AgNPs) have received the most attention of all known nanoparticles [14].

## **2. APPLICATION OF AuNPs IN DRUG DELIVERY**

Recently, nanoparticles of gold were recently used as a great candidate for delivering a variety of medications to their target areas [14, 15]. Small medication molecules to larger macromolecules including proteins, RNA, and DNA make up these payloads. Effective release of these payloads must be taken into account in order to provide effective treatment. Utilizing both internal stimuli, including glutathione, pH, and more, as well as stimuli from the outside, such as light [16]. The release of a therapeutic chemical from gold nanoparticles can be induced. Drug targeting may be divided into either active or passive treatment categories. A drug or nanoparticle is accumulated at the intended spot via "passive targeting" which makes use of its physiochemical properties, such as size, weight, extravasations, and pharmacological characteristics [17]. To target specific cells, the drug component or nanoparticles are transformed at the "active target" stage by being joined to a specific active molecule.

## **3. DIRECT CONJUGATION OF AuNPs WITH DRUG**

### **3.1 Anti- Cancer Drug**

With the aid of physical digestion, covalent, as well as ionic bonding, AuNPs are capable of being directly conjugated with medication or antibiotic components. One of them is methotrexate (MTX), an oral folic acid analogue that was combined with gold nanoparticles with a 13 nm dispersion in order to prevent cancer cells from metabolizing folate. It is primarily employed in the form of cytotoxic anti-cancer medicine.

### **3.2 Anti-tumor Cells**

The capacity of the carboxylic groups within the methotrexate molecule to bond with outermost layer of gold nanoparticles was demonstrated following incubation period of overnight, as well as stated, the amount of AuNP coupled methotrexate in the tumour cells was greater than the quantity of pure methotrexate. Additionally, in animal models of Lewis lung carcinoma, the conjugated form of methotrexate was seven times more cytotoxic than free methotrexate [18].

## **4. ALTERATIONS IN AuNPs' SURFACE FOR DRUG CONJUGATION**

The surface chemistry within a nanomaterial is crucial for the interaction of nanoparticles to biomolecules. Four primary factors that determine why modifying surface of AuNP may be worthwhile for the mechanism of drug delivery.

- The major reason is to reduce or stop the conjugate's clearance through reticulo-endothelial network (RES),
- The secondary reason is to allow for the right adherence of drugs with desired targeting.
- Modifying the surface may tackle the issue of cytotoxicity into gold nanoparticles caused by native capping ligands.
- Reducing the formation of aggregates of nanoparticles as well as improving their ability to remain stable. [19]

## **5. LIMITATIONS OF AuNPs IN DRUG DELIVERY**

Although gold nanoparticles have a promising future in the area of drug delivery, it is crucial to take into account their potential negative effects.

- The non-specific targeting of nanoparticles made of gold in medication administration is one of their main drawbacks.
- The capacity to activate the immune system of the host.

Gold nano conjugates are also modified utilizing targeted ligands to get over these in vivo challenges. However, this extensive surface modification might result in harmful hazardous consequences [20].

## **6. GOLD-BASED NANOPARTICLES DNA INTERACTION**

Gene therapy is the best method for treating diseases that are genetically transmitted [21]. In addition to serving as a vehicle for extremely effective gene therapy, viruses can also cause random

cytotoxicity and immunological responses, which raises safety issues. On the other hand, non-viral gene delivery techniques have been shown to be less effective at the moment [22]. An efficient delivery method should allow for quick entrance into the cell, nucleic acid protection from nuclease breakdown, enabling release from the nucleic acid within its functional form into the nucleus [23]. Nanoparticles are highly effective in drug delivery system for all oligonucleotides, including single stranded DNA (ssDNA), double-stranded DNA (dsDNA) and viruses including single-stranded RNA (ssRNA). Nucleic acids are shielded by gold nanoparticles like nanorods and nanospheres, which stop nuclease from destroying them. For the delivery of genetic material & gene therapy procedures, oligonucleotide & siRNA-modified AuNPs, which conjugates are employed for intra-cellular gene regulation agents that can trigger genes associated with the immune system [24].

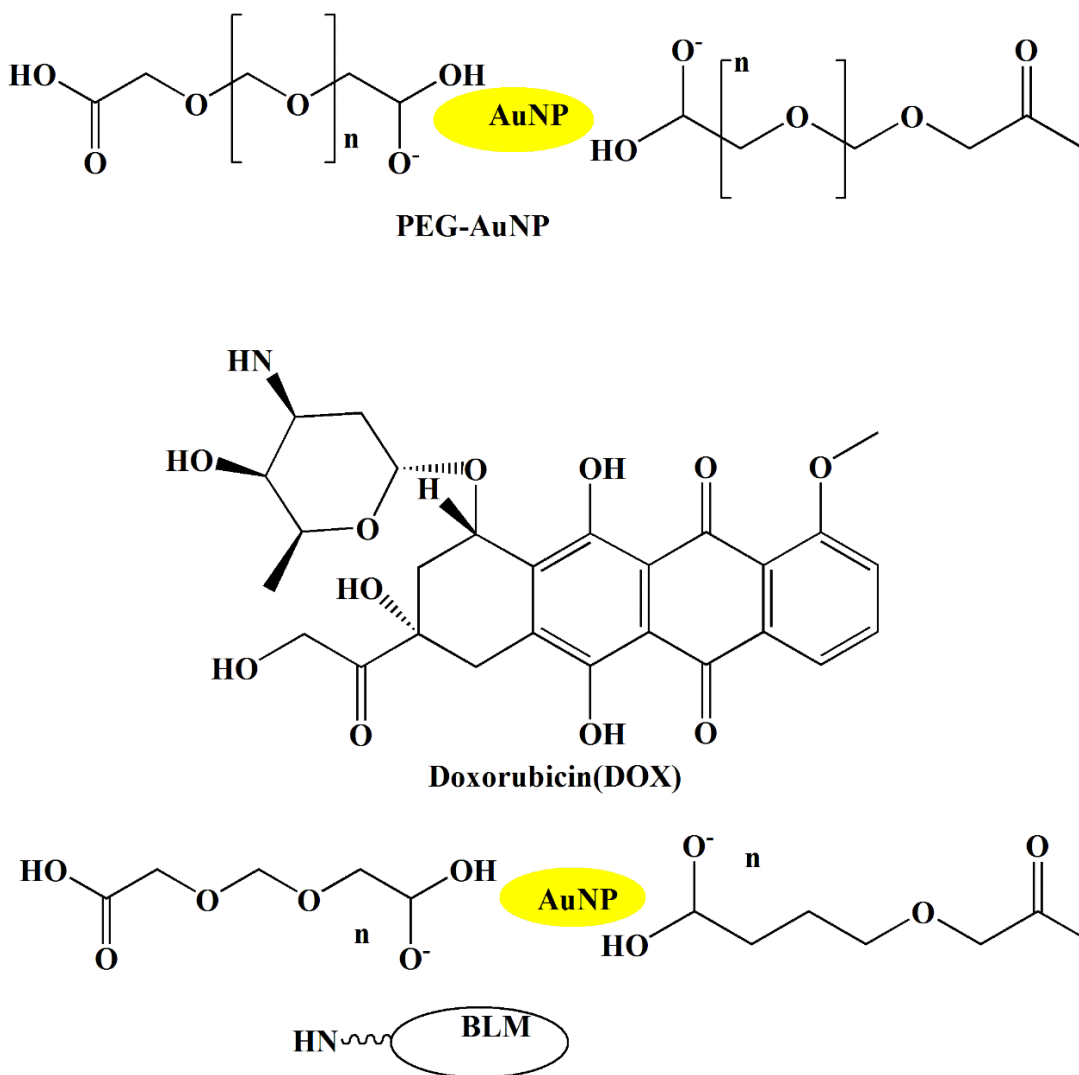


Figure 2: Interaction of Gold nanoparticles with drugs.

### **6.1 AuNPs Conjugated With Oligonucleotides.**

Various covalent & non-covalent connections can be used to couple AuNPs onto oligonucleotides. Thiols (-SH) can be used to modify DNA strands so they can be covalently grafted onto nanoparticles. In one work, cyclical disulphides (DTPA) attaching groups & alkyl-thiol mooring groups were used to integrate citrate-capped AuNPs with complementary oligonucleotides to create tetrathionate nanoparticles as mono-thiolated objects. The particle complexes demonstrated 99% greater cellular internalisation without cytotoxicity and were shown to have an exceptionally high affinity factor for the corresponding nucleotide sequence. Antisense oligonucleotide duplexes that were coupled to AuNPs with DNase decomposed considerably more slowly than unbound analogue oligonucleotide duplexes [25]. A group has reported the Thiol-modified nucleic acids and AuNPs interact covalently to form polyvalent nucleic acid and AuNPs conjugates. The resulting conjugate demonstrated significant cellular internalization and was unaffected by any enzyme-mediated breakdown [26].

### **6.2 Nucleic Acids Conjugated With AuNPs**

Non-covalent couplings can also be used to bind nucleic acids to AuNPs. Through electrostatic interactions, cationic AuNPs may communicate with substantially anionic nucleic acids. The capacity of gold clusters shielded by blended monolayer enriched with quaternary ammonium ions to transmit plasmid DNA was examined. The findings indicated that a number of variables, including hydrophobicity and DNA: AuNPs, contribute to the effective transfection assemblies [27]. In order to stimulate the development of human mesenchymal stem cells (MSCs), Zhao et al. [28] created gold nanoparticles tiny-carriers using poly-allylamine hydrochloride (PAH) as well as poly-sodium 4-styrenesulfonate (PSS). Nanoparticles have the ability to transport a small interfering RNA (siRNA) targeting the LSD1 gene. By administering siRNA, the findings of this study may help with tissue regeneration treatment. By adding amino acids to AuNPs, a powerful scaffold for attaching gold colloids to DNA may be created. According to studies, AuNPs modified by lysine dendron are 28 times more effective at expressing genes than polylysine [29].

### **6.3 Silver Nanoparticles as Drug Delivery Vehicles.**

The utilization of silver is currently restricted due to its difficulty in synthesis; when modified using the conventional salt ageing method, it showed a reduction to durability, and there were concerns regarding silver toxicity in the past. Gold and other molecules have historically been employed in nanoparticles- predicted drug delivery systems. The clinical use of silver nanoparticles as effective antibacterial therapies for wound care, together with recent in vivo studies demonstrating the safety of systemic exposition to silver nanoparticles have rekindled interest in silver nanoparticles-based biomedical research.

It was discovered in a 2008 rat research because there was a greater majority of dosages over 300 mg/kg/day across 28 days and only a minimal induction of secondary signs of liver damage, despite the identification of severe orally AgNPs at dosages more than that at that time. Increased predominant trust regarding the appropriateness of AgNPs over in vivo investigations that seek to lower the minimum amount for successful AgNPs daily doses through the incorporation of their drug

Table 1: Anticancer Medicines coated with gold nanoparticles in drug delivery system.

Drugs loaded	Surface coatings/ Ligands	Treatments	Key findings	Reference
5-FU	Thiols thioglycolic acid (TGA) and glutathione (GSH)	Colon cancer tissue samples were obtained from patients and incubated with TGA/GSH AuNPs-5FU or 5-FU alone	TGA/GSH–AuNPs–5-FU exhibited 2-fold Higher anticancer effect compared with free 5-FU	[30]
Doxorubicin (DOX)	PEG	Carcinoma cells were intraperitoneally injected into female Balb/c mice and treated with DOX	PEG coatings showed high drug accumulation compared to passive targeting without PEG	[31]
TGF- $\beta$ 1 antibody and Methotrexate	Folic acid	MDA-MB-231 breast cancer cell line	Folate conjugation enhanced the cellular uptake and TGF- $\beta$ 1 antibody on the AuNPs reduced extracellular TGF- $\beta$ 1 of cancer cells by 30%	[32]
Mitoxantrone (MTX)	Methoxypolyethylene-glycol (mPEG)	Combination of photodynamic therapy (PDT) and chemotherapy on human melanoma (DFW) and breast cancer (MCF7) cell lines	MTX–mPEG–AuNP complex improved the efficacy of PDT with a light emitting diode	[33]
Doxorubicin (DOX)	Oligonucleotides (ONT)	DOX–ONT–AuNP complex treated SW480 CRC cell line and xenogra mice which were subcutaneously inoculated by the transfected SW480 cells	DOX–ONT–AuNP complex reduced cell viability and inhibited tumor growth in CRC xenogra mice	[34]

load prospective as well as electromagnetic field-studies amplifying properties may result from observations regarding security and the lack of adverse effects related to silver nanoparticles managed at "moderate" doses. AgNPs are now more suitable for applications involving drug delivery due to improved optical properties and improved biocompatibility brought on by surface modification.

The use of silver nanoparticles as sensors that are biological labels, along with substrates over surface enhanced being absorbed, fluorescence, and photochemistry has attracted interest due to their unique field properties, which include possessing a light scattering the cross-section that is almost ten times bigger than that of a gold nanoparticles of comparable size. In comparison to other metallic nonmaterial's, AgNPs also have higher extinction the coefficients and shifted blue Plasmon resonant peaks, which makes them a superior option for photo controlled drug delivery applications along with potential surface-enhanced the photochemistry of confined substances, including nitro benzyl derivatives and other uses. AgNPs have well-described optical characteristics and are bio-compatible. They show discrete blood plasma comparative absorption maxima at around 420 nm. It is challenging to distinguish the function of the plasmon from the nitrophenylethyl (NPE) that may be absorbed by micro RNA (miRNA) complexes, in this difference. The nonthermal phase is most likely caused by strong electrical fields that surround ions and mote in the oscillatory open Plasmon zone, which lowers the reaction's energizing energy. Silver nanostructures have been used to describe metal enhanced fluorescence. A photoactive molecules and a metallic nonmaterial share the linked photon's resonance state, which results in a more effective photon conversion.

#### **6.4 AgNPs as Delivery Systems in Cancer Therapy.**

With an anticipated 9.6 million deaths from cancer in 2018, it is the second biggest cause of death worldwide. Lung cancer is the leading cause of cancer-related fatalities, next to colorectal, abdomen, liver, and cancers of the breast, according the findings of the World Health Organization. The utilization of alternative therapies, such as metallic nanoparticles as delivery agents, to replace traditional cancer therapies like radiation or chemotherapy presents a difficulty. The adverse effects of traditional methods, which may harm both healthy and tumor cells, are the primary cause of this requirement for replacement. Currently, chemotherapy treatment does not distinguish between cancer cells and healthy cells; instead, it tries to destroy rapidly dividing cells. Chemotherapy causes the destruction of rapidly proliferating cells (such as intestinal epithelium and hair follicles) in the body. Additionally, the present cancer treatments (which include the infection-causing agent daunorubicin, bleomycin & cisplatin) are thought to be only partially successful, which is followed by additional drawbacks such lack of selectivity, expensive prices, high toxicity, & susceptibility to resistance [35].

With the aim of reducing the rate of release and amount of necessary therapeutic dosage, a wide range of shapes and sizes of nanoparticles have been produced for use in cancer therapy. At this time, researchers are interested with polymeric, material made of ceramics as well as metallic nanoparticles in addition to nanometric materials including dendrimers, micelles, and liposomes. Different kinds of nanoparticle structures are now being researched, with a focus on metallic nanoparticles. This is mainly because metallic nanoparticles have tremendous medicinal promise because they can be coupled with medicines, ligands, and antibodies. Some of the materials that have been studied the most for usage in nanometric particles in many fields of medicine are gold, silver, and platinum.

A variety of different cell types have been shown to be susceptible to cytotoxicity caused by silver nanoparticles via apoptosis and necrosis. Additionally, they show results against side effects of existing treatments such DNA damage, the production of reactive oxygen compounds (ROS), an increase in lactate dehydrogenase (LDH) leakage, and stem cell differentiation inhibition [36].



Table 2: Use of Silver Nanoparticles in Cancer treatment.

Synthesis method of Nanoparticles	Type of nanoparticles	Type of Cancer cells	Therapeutic agent	Therapy	Ref.
Green Synthesis using bacteria <i>Bacillus clausii</i>	Spherical shape 8–20 nm	Human <i>ovarian</i> cancer A2780 cells	AgNPs + Salinomycin	AgNPs + Salinomycin Higher level of ROS DNA fragmentation Enhanced LDH release Alteration of cell morphology Mitochondrial dysfunction	[39]
Green Synthesis using leaf extract of <i>Vitex negundo L. induce</i>	Spherical shape 5–47 nm	Human <i>colon</i> cancer HCT15 cell line	AgNPs	AgNPs DNA fragmentation Inhibited proliferation of human colon cancer cell line HCT15 Increased apoptosis	[40]
Green synthesis using molecule <i>resveratrol</i>	Spherical shape 3–20 nm	Human <i>ovarian</i> cancer A2780 cells	AgNPs + Gemcitabine	ROS production DNA breakage Increased LDH leakage Loss of cellular viability Cell proliferation	[39]
Green Synthesis using leaf extract of <i>Sesbania grandiflora</i>	Spherical shape 22 nm	Human <i>breast</i> cancer MCF-7 cells	AgNPs	AgNPs Generation of ROS Loss of cell membrane integrity Promote apoptosis of cancer MCF-7 cells	[41]
Green synthesis using <i>Sinigrin</i>	Spherical shape 20–40 nm	Human <i>cervical</i> cancer HeLa cells	AgNPs + Camptothecin	Increased ROS level Decreased Cell viability HeLa cell proliferation Altered mitochondrial membrane permeability	[42]

## 6.5 Structure of C-Ag<sup>+</sup>-C DNA Interaction

Studies on the composition of C-Ag<sup>+</sup>-C by using Fluorescence Resonance Transfer of Energy, Ono [37] established the C-Ag<sup>+</sup> interaction's existence in 2008 and postulated that a C-C mismatch on DNA double strand may attract silver ions, forming a C-Ag<sup>+</sup>-C structure. DNA double strands' conformation is often unaffected by structure, however the reliability of the pair of strands may be improved. Utilizing the thermally induced transition patterns of mismatched C-C double stranded DNA, the authors of the study discovered that the temperature at which they melted T<sub>m</sub> (melting temperature) for DNA double strands in the presence of Ag<sup>+</sup> was 39 °C. In contrast, as can be shown in Fig. 3A, the degree of melting was as low as 31 °C. Results show that Ag<sup>+</sup> has great selectivity and can stabilize DNA double strands efficiently. Additionally, it was discovered using 1D 1H NMR that the addition of Ag<sup>+</sup> caused the generation of a new peak in the imino proton

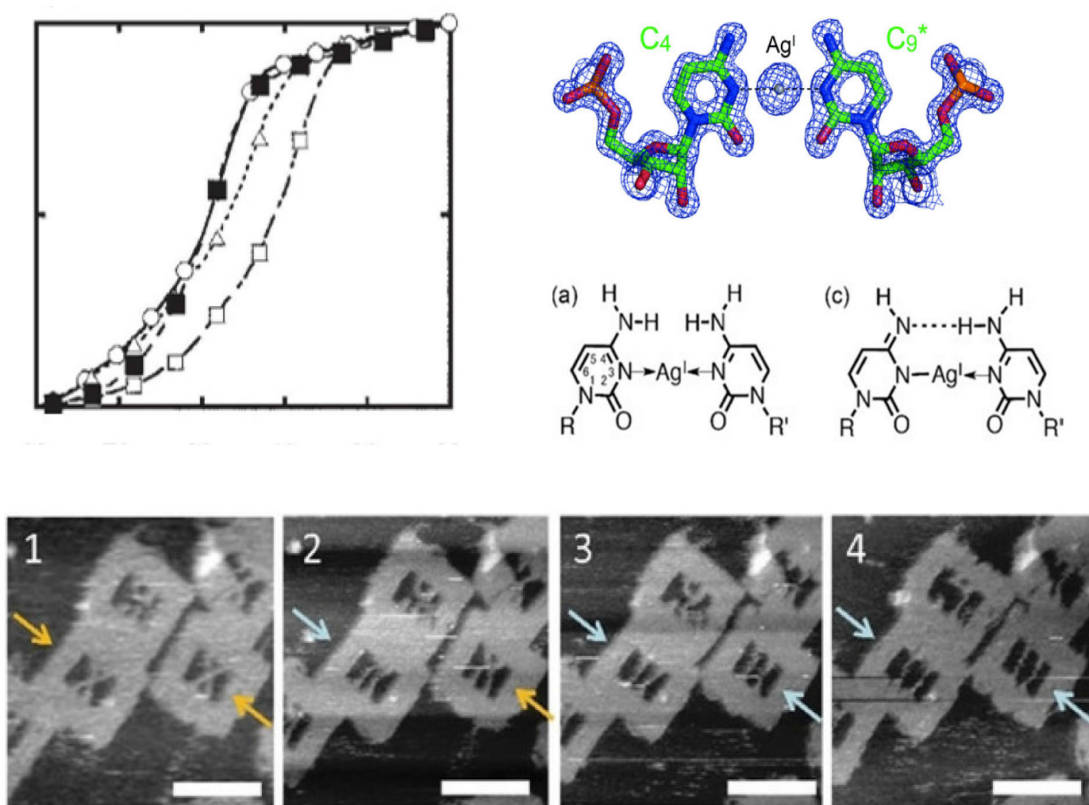


Figure 3: (A) DNA double-strand thermally induced curve with C-C. (B) RNA forms a C-Ag<sup>+</sup>-C local structure when Ag<sup>+</sup> is present. (C) Ag<sup>+</sup>-RNA compound shows N<sub>3</sub>-Ag-N<sub>3</sub> structure (D) Possible isomerizes structure. (E) Double-stranded DNA structural changes on the DNA origami frame in the Ag<sup>+</sup> solution observed via AFM. Connected strands are shown by yellow arrows (forming an X shape), whereas divided shapes are indicated by blue arrows [30].

area, which was then amplified as the silver concentration increased. The mole ratio of Ag<sup>+</sup>/double strand was almost 1:1 at the maximal strength. The binding ratio among Ag<sup>+</sup> and C-C mispairing is explained by these phenomena. C-Ag<sup>+</sup>-C's binding mechanism is yet unknown. As seen in Fig. 2B, Kondo [38] performed an X-ray analysis of the RNA lattice in 2015 and demonstrated that the improper pairing of Ag<sup>+</sup> with C-C combined via linear coordinating of N<sub>3</sub>-Ag<sup>+</sup>-N<sub>3</sub>, which had no impact on the double-strand conformation. Despite the findings, there are still significant issues with X-ray lattice analysis. Examples include (1) isomerizing the molecule in Figure 3C into Figure 3D, where the repulsive glutamate-amino group has been deprotonated via an amino group and subsequently joined by hydrogen bonding. However, due to the inadequate clarity of hydrogen atoms in the RNA duplex crystal structure, it is hard to structurally distinguish among (C) and (D) in Fig. 3. (2) Both DNA and RNA can occasionally not be arranged in helical fashion. Therefore, each duplex's chemical composition of C-Ag<sup>+</sup>-C should be investigated separately. (3) It should be noted that according to the geometry of Fig. 3C, the paired cytosine residues' amino groups may repel one another due to steric/electrostatic repulsion. The method to prevent its amino-amino steric

in addition to electrostatic resistance inside a duplex of DNA should thus be explained if C-Ag<sup>+</sup>-C adheres to the c type structure shown in Fig. 3.

In 2019, Xing [43] created a DNA framework that allows for the single-molecule observation of DNA morphological changes using the DNA origami approach. This technique offers a multipurpose framework to embed the substrate DNA strands, enabling molecular monitoring of the system. A rapid Atomic Force Microscope (AFM) was then used to view the single-molecule structure. In Fig. 2 E, the structural alteration is depicted. The C-Ag<sup>+</sup>-C base pairings in the dsDNA dissolve from an X form to a separated shape, indicating that they were not as stable within the DNA frame. Two topologically limited DNA strands must be wound in order for a helix to form during the development of a dsDNA within the DNA frame. Despite the C-Ag<sup>+</sup>-C pairings in the dsDNA being generated in solution, the dsDNA was mechanically unrevealed by the structural tension associated to the DNA frame.

Despite the impressive advances achieved in recent years, it is still difficult to comprehend the precise structure of C-Ag<sup>+</sup>-C. Understanding the insertion procedure requires a Transmission Liquid Cell Electron Microscope in order to dynamically view the relationship between C and Ag<sup>+</sup> [44].

## 7. CONCLUSION

Nanotechnology, which is essentially an interdisciplinary field of research, has benefited greatly from the formulation of novel therapeutic and diagnostic modalities by physics, chemistry, biology and pharmaceutical science. This investigation has shown that there are new prospects for flexible and secure treatment alternatives due to the use of nanotechnology in drug administration and medicine. In the end, changing molecule size and surface properties enable researchers to give pharmaceuticals over longer period of time with less frequent dosing (sustained release), with more precision, and with penetration in challenging regions.

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