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Synthesis of various DNA hybrid nanocomposites and investigation of peroxidase mimic activity

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Abstract

Purpose: The aim of this study is to synthesize hybrid nanocomposites from various DNA sequences and to investigate their peroxidase mimic activities.
Method: The DNA sequences were used as the organic component and the copper (II) ions were used as the inorganic component for the synthesis. The effect of different synthesis conditions (pH and concentration) on morphology was investigated using a scanning electron microscope. Additionally, the peroxidase mimic activity of nanocomposites was examined.
Findings: DNA sequences coded as C20, C20A and C20AA were used at various concentrations within three synthesis environments with different pH levels. This resulted in the formation of flower-like hybrid nanocomposite structures. These structures also exhibited effective peroxidase mimic activity.
Conclusion: Various DNA hybrid nanocomposites can be synthesised successfully. These nanocomposites could be used in DNA-related drug delivery systems.

Keywords: DNA; nanocomposite; peroxidase mimic activity

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Çeşitli DNA hibrit nanokompozitlerin sentezlenmesi ve peroksidaz benzeri aktivitenin incelenmesi

Özet

Amaç: Bu çalışmanın amacı çeşitli DNA sekanslarından hibrit nanokompozitler sentezlenmesi ve peroksidaz benzeri aktivitelerinin araştırılmasıdır.
Metod: Sentez için organik kısım olarak DNA sekansları, inorganik kısım olarak bakır (II) iyonları kullanılmıştır. Taramalı elektron mikroskobu ile farklı sentez şartlarının (pH, konsantrasyon) morfolojiye olan etkisi incelenmiştir. Ayrıca nanokompozitlerin peroksidaz benzeri aktivitesi araştırılmıştır.
Bulgular: C20, C20A ve C20AA kodlu DNA sekansları farklı konsantrasyonlarda kullanılarak farklı pH değerine sahip üç farklı sentez ortamında istenilen çiçek benzeri hibrit nanokompozit yapılar oluşmuştur. Bu yapılar etkili peroksidaz enzim benzeri aktivite de sergilemişlerdir.
Sonuç: Çeşitli DNA sekanslarından DNA hibrit nanokompozitler başarıyla sentezlenebilmektedir. Bu nanokompozitler DNA ilişkili ilaç taşıyıcı sistemlerde kullanılabilme potansiyeli taşımaktadır.

Anahtar kelimeler: DNA; nanokompozit; peroksidaz benzeri aktivite

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1. Introduction

Nanomaterials have been recognised as one of the most prominent materials in recent years. They are often referred to as the "material of the 21st century" due to their unique design and structural properties compared to traditional materials [1]. Hybrid nanomaterials are formed by two or more components connected at the nanometer scale. They combine the unique properties of their components with additional properties due to synergistic effects between their components [2,3]. Hybrid materials have a wide range of applications in fields such as optics, microelectronics, smart coatings, health and diagnostics, and photovoltaics and fuel cells [3–6].

Recently, nanocomposites synthesised using organic molecules and metal ions as inorganic components have been investigated for their various activities. It has been observed that the resulting nanocomposites form due to chelation with Cu^{2+} ions, which occurs through bonds formed between the C, N, Cu, P and O elements [7]. In a study conducted by Dr Zare and his team, hybrid nanocomposites consisting of two main components (organic and inorganic) were synthesised. Using a new immobilisation technique, Dr Zare and his team first employed bovine serum albumin flower-shaped hybrid nanocomposites. The organic component is bovine serum albumin and the inorganic component is Cu^{2+} ions. They synthesised flower-shaped hybrid nanocomposites using a phosphate buffer as the synthesis medium. This synthesis method was also applied to enzymes, various biomolecules and proteins by modifying the organic structure. Due to their resemblance to flowers, structures consisting of two basic components (organic and inorganic) were named 'nanoflowers'. An increase in the activity and stability of proteins in nanoflower structures was observed compared to their free forms [8].

Herein, DNA hybrid nanocomposites (DNA Hybrid NCs) were synthesized for the first time. These contained DNA sequences with different lengths of cytosine nucleotides. Their peroxidase mimic reaction activity was investigated. Additionally, the effects of DNA sequence concentration and medium pH on nanocomposite production were systematically examined. DNA containing cytosine nucleotides is considered suitable for hybrid nanocomposite synthesis as an organic component for two main reasons. When we examine the chemistry of cytosine DNA, we observe that the phosphodiester bond, which links nucleotides end-to-end in a chain, contains O atoms bearing free electrons in the bond between the 3'-OH group of the first nucleotide's sugar and the 5'-phosphate group of the next nucleotide. Furthermore, the nitrogen (N) in the amine group attached to the fourth carbon (C) of the cytosine base and the oxygen (O) in the group attached to the second carbon both have free electrons. This suggests that DNA containing cytosine nucleotides is suitable for hybrid nanocomposite synthesis as an organic component. These DNA-containing nanocomposites are expected to introduce a new approach to DNA-drug combinations in future studies and contribute to the field of targeted drug delivery. Peroxidase mimic activity (the Fenton reaction) involves oxidation sequences that occur in the presence of Fe^{2+} or Cu^{2+} ions and hydrogen peroxide (H_2O_2). In this process, hydroxyl radicals (OH•) are produced to oxidise toxic organic molecules. For example, AY36 (acid yellow) is an organic dye that causes water pollution and is directly toxic to aquatic life, leading to fish deaths. Fenton oxidation is used to reduce the toxicity of this organic dye [9–11].

2. Materials and methods

2.1. DNA hybrid NC synthesis

Various DNA molecules (C10, C20, C40, C20A and C20AA), produced from different lengths of cytosine nucleotides, were used as the organic component in the synthesis of DNA Hybrid NCs. Copper (II) ions was used as the inorganic component. Firstly, a $CuSO_4$ stock solution (120 mM) was prepared using deionised water. C10, C20, and C40 DNA solutions, prepared at 1 mg/mL stock concentrations, were added to the synthesis medium. The synthesis medium is a 10 mM phosphate buffer at different pH values (3.0, 7.0, 10.0). The DNA sequence was added at a concentration of 0.02 mg/mL and vortexed. After mixing, a DNA suspension was observed. Thus, it was concluded that the DNA sequences were not completely soluble in pH 7.4 phosphate buffer. To these suspensions, we added 0.333 mL (0.8 mM) of $CuSO_4$ stock solution, and we brought the mixtures to 50 mL with pH 7.4 phosphate buffer and vortexed them for approximately 30 seconds. The mixture was then left to incubate at +4 °C for 72 hours without intervention. After the incubation period, the mixture was centrifuged to stop the reaction and the resulting blue precipitate (DNA hybrid NCs) was dried in a 37 °C incubator.

2.2. Characterization of DNA hybrid NCs

A Scanning Electron Microscope (SEM) system can be used to examine materials in three dimensions using high-energy electrons. The studies resulted in the synthesis of hybrid nanocomposites using DNA sequences as organic components and Cu^{2+} ions as inorganic components. These were then dripped onto a copper grid and dried. The DNA hybrid NCs adhering to the copper grid were imaged using SEM [12,13].

2.3. **Peroxidase mimic activity of DNA hybrid NCs**

For measurement of peroxidase mimic activity, DNA Hibrit NCs (3 mg) were added to the solution containing H_2O_2 (22.5 mM), guaiacol (45 mM) and PBS (pH 6.8). The reaction volume was adjusted so that the final concentrations of 7.5 mM H_2O_2 and 15 mM guaiacol. The oxidation of guaiacol molecule (2-methoxyphenol) to the colored 3,3-dimethoxy-4,4-diphenoquinone molecule was recorded by measuring absorbance values at with a UV-Vis. spectrophotometer in a time-dependent manner [13,14].

3. Results

Figure 1 shows SEM images of the dried blue-coloured precipitate prepared in the first stage. Upon examining the results, it was observed that the expected flower-like morphology of the DNA Hybrid NCs did not form.

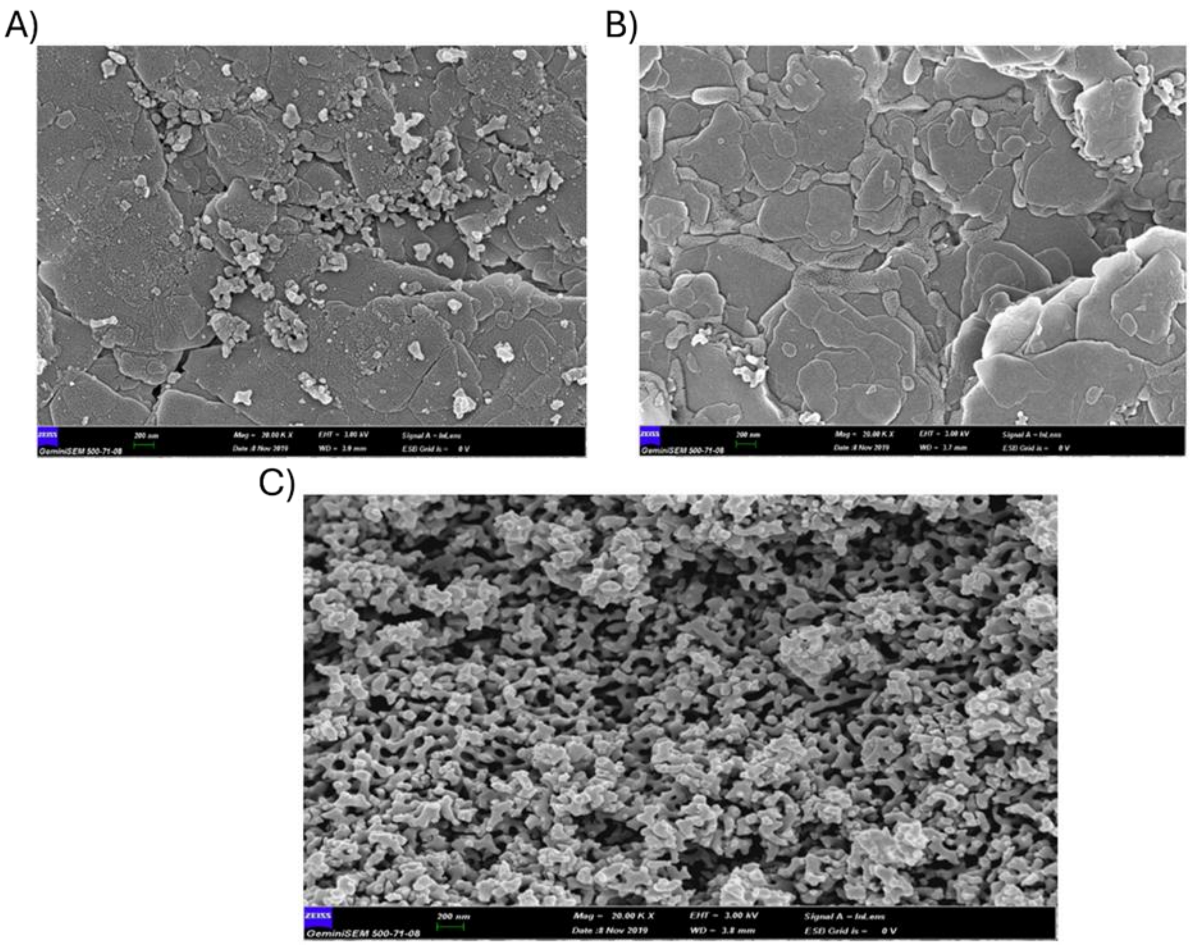

Figure 1. SEM images of DNA Hybrid NCs A) C40 DNA Hybrid NCs, B) C20 DNA Hybrid NCs, C) C10 DNA Hybrid NCs

Due to the inability to achieve the desired morphology, DNA sequences of different lengths coded as C20, C20A, and C20AA were used as the organic component. The solvent medium was a pH 7.4 phosphate buffer prepared using distilled water. However, the 0.02 mg/mL concentrations of the DNA sequences C20, C20A and C20AA did not dissolve completely in this medium, resulting in a cloudy appearance. Equal volumes of 0.333 mL each of a 120 mM $CuSO_4$ stock solution were added to the mixtures, which were then adjusted to 50 mL with a pH 7.4 phosphate buffer solution. The mixtures were vortexed for approximately 30 seconds and then incubated at +4 °C for 72 hours. After incubation, the resulting precipitates were filtered and dried in an incubator at 37 °C. SEM images of the obtained samples are shown in Figure 2.

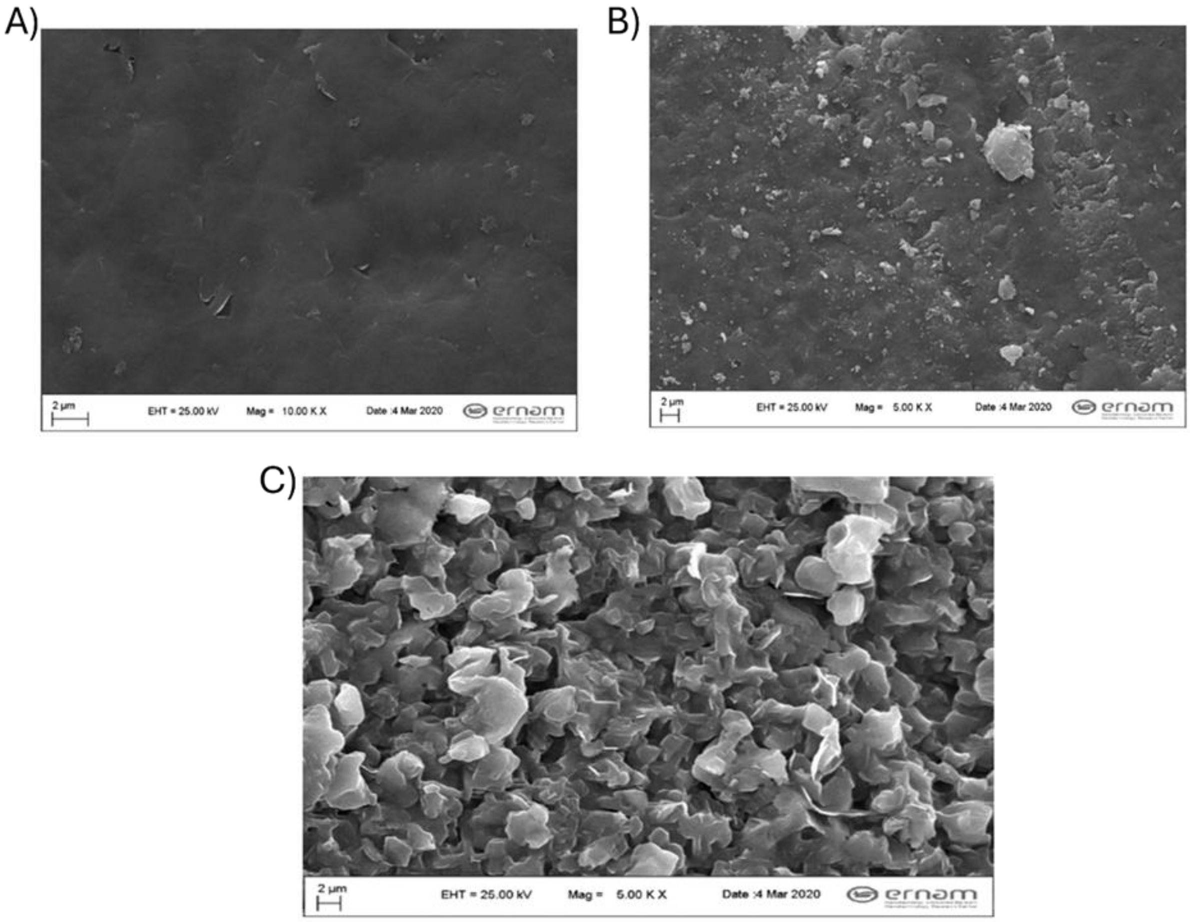

Figure 2. SEM images of DNA Hybrid NCs A) C20 DNA Hybrid NCs, B) C20A DNA Hybrid NCs, C) C20AA DNA Hybrid NCs

In the first two experiments, the failure to synthesize nanocomposites under the synthesis conditions was thought to be due to the inability of Cu^{2+} ions to form coordinate covalent bonds with DNA molecules. These molecules were not completely dissolved in distilled water and pH 7.4 phosphate buffer. This resulted in the failure to form flower-shaped nanocomposite structures. For this reason, the solvent system was changed. To investigate the effect of different pH values on synthesis, three different pH values (pH 3.0, pH 7.4 and pH 10.0) were prepared. To investigate the effect of concentration, two different DNA concentrations (0.02 mg/mL and 0.1 mg/mL) were prepared, establishing a third experimental environment. Because it has been previously demonstrated that the ideal morphology is at concentrations of 0.02 mg/mL and 0.1 mg/mL [13]. The results of these parameters, indicating whether flower-like morphology formed, are shown in Table 1.

Table 1. The effect of various synthesis conditions on the formation of DNA Hybrid NCs.

DNA sequences of different lengths	**Concentration of DNA (mg/mL)**	**pH 3.0**	**pH 7.4**	**pH 10.0**
C20	0.1	-	+	+
	0.02	-	-	+
C20A	0.1	-	+	-
	0.02	-	-	-
C20AA	0.1	-	+	+
	0.02	-	-	+

A 5:1 ratio of dimethyl sulfoxide (DMSO): Phosphate Buffer (PBS) was used as the solvent medium. The C20, C20A and C20AA DNA solutions are now clear, meaning that the solubility of the DNA sequences has increased in the new solvent system. An equal volume of 120 mM stock $CuSO_4$ (0.333 mL) was added to the mixtures to achieve a concentration of 0.8 mM in the synthesis medium, and the pH was adjusted using appropriate phosphate buffers to 50 mL. The mixtures were vortexed for approximately 30 seconds and then incubated at +4 °C for 72 hours. After incubation, the resulting precipitates were filtered and dried in an oven at 37 °C. Images of the DNA Hybrid NCs are shown in Figures 3 and 4. According to Table 1, it was observed that flower-like structures are formed depending on different pH and different concentrations, whereas structures were not formed at both concentrations at pH 3.0. In addition, the only successful synthesis for the C20A sample was seen at a concentration of 0.1 mg/mL and pH 7.4.

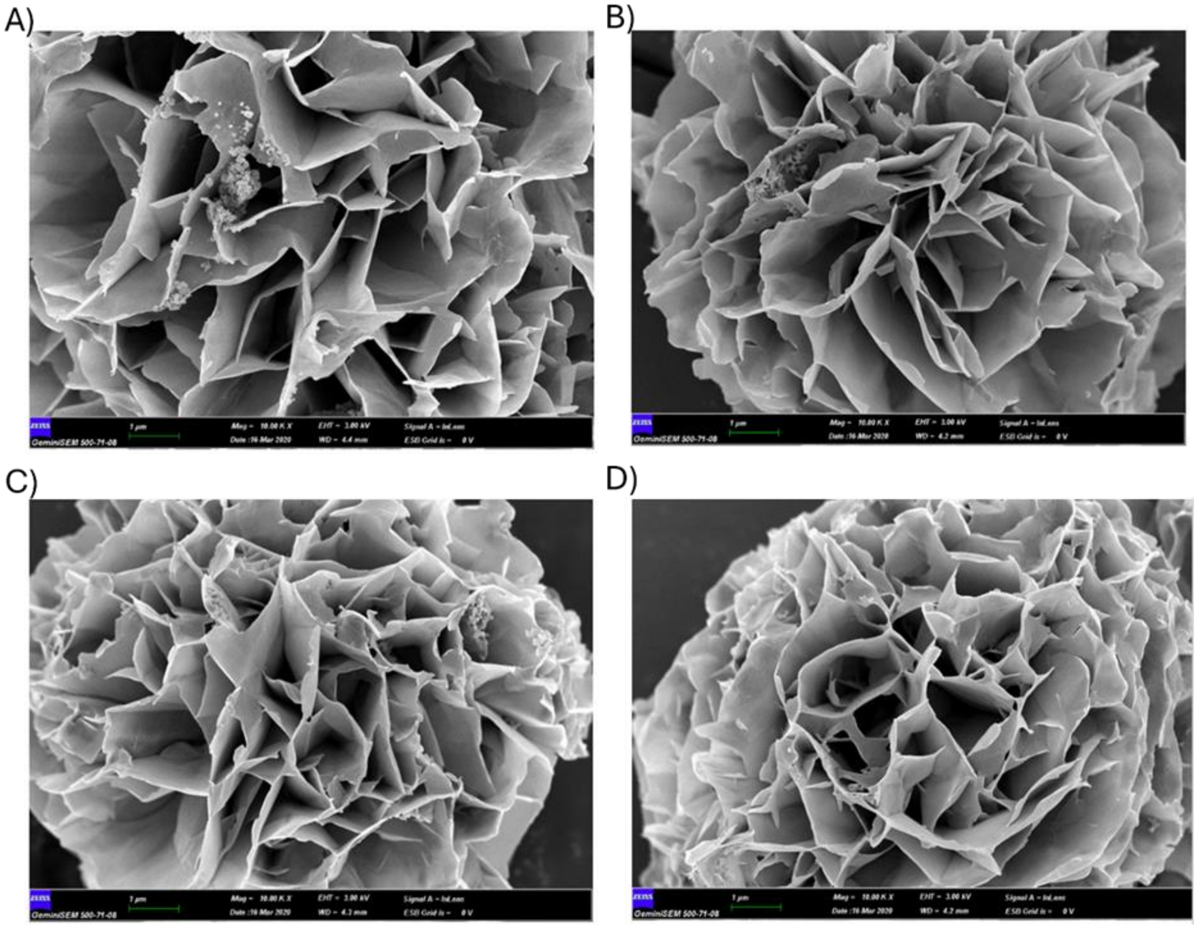

Figure 3. SEM images of DNA Hybrid NCs A) 0,02 mg/mL C20 DNA Hybrid NCs (pH 10.0), B) 0,1 mg/mL C20 DNA Hybrid NCs (pH 10.0), C) 0,1 mg/mL C20 DNA Hybrid NCs (pH 7.4), D) 0,1 mg/mL C20A DNA Hybrid NCs (pH 7.4)

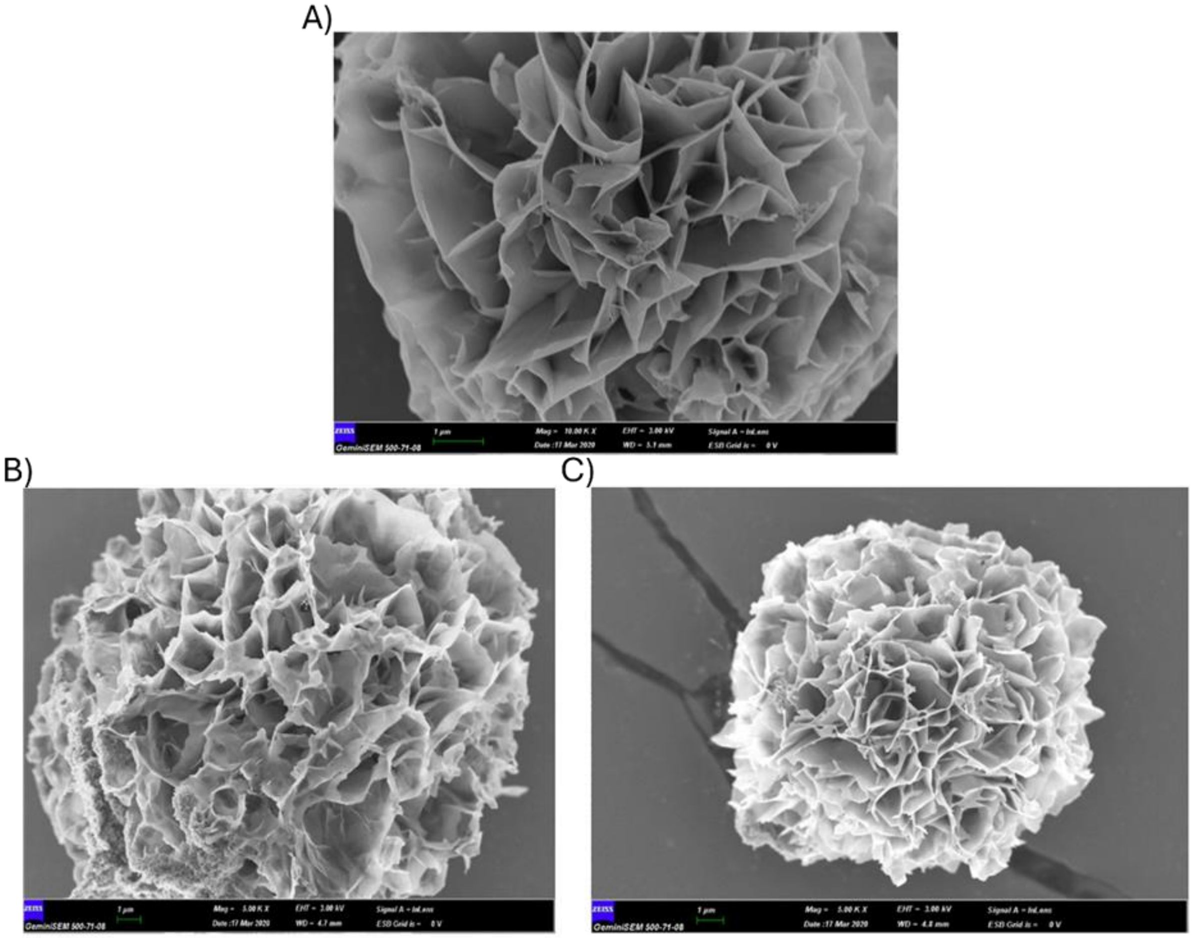

Figure 4. SEM images of DNA Hybrid NCs A) 0,02 mg/mL C20AA DNA Hybrid NCs (pH 10.0), B) 0,1 mg/mL C20AA DNA Hybrid NCs (pH 7.4), C) 0,1 mg/mL C20AA DNA Hybrid NCs (pH 10.0).

After the desired nanoflower morphology was obtained by completely scanning the synthesis conditions, the Fenton-like reaction activity was investigated. DNA Hybrid NCs were dissolved in 1 mL of a phosphate buffer solution at pH 6.8 and 10 mM, to which 1 mL of 22.5 mM H_2O_2 and 1 mL of 45 mM guaiacol were then added and vortexed. The absorbance of the supernatant was determined at 470 nm wavelength using a UV-Visible spectrophotometer over time. Figure 5 presents the Fenton-like activity results for C20 DNA Hybrid NCs, C20A DNA Hybrid NCs and C20AA DNA Hybrid NCs. Time-dependent measurements showed that the DNA Hybrid NC structures exhibited effective and similar enzymatic activity.

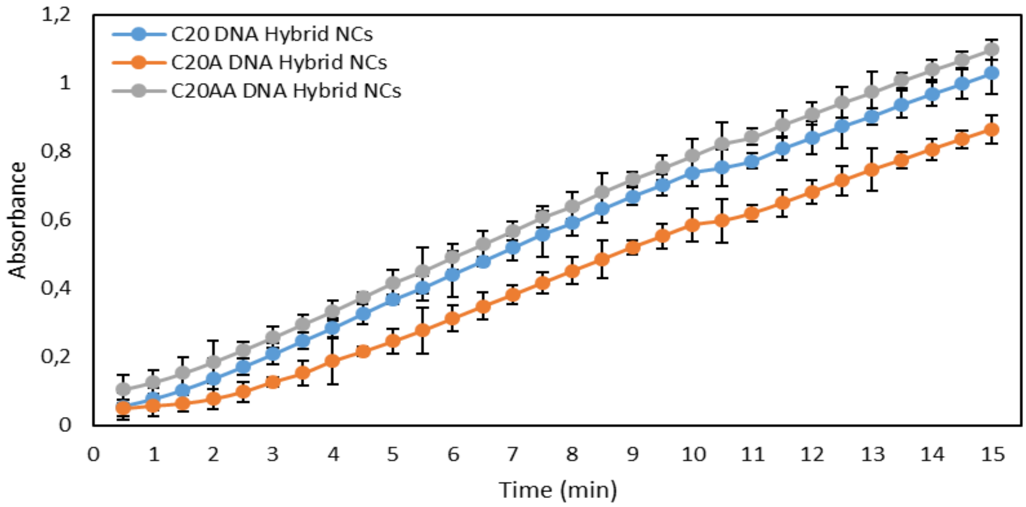

Figure 5. Peroxidase mimic (Fenton-like) activity results of DNA Hybrid NCs

4. Conclusions and discussion

DNA molecules are not only fundamental to the transfer of information across generations, they are also biological materials that play an important role in producing various biomaterials [15]. Thanks to the unique property of Watson–Crick base pairing, different DNA sequences can be synthesised, thereby altering intermolecular interactions [16,17]. DNA is a molecule with unique nanoscale properties and biocompatibility [18,19]. Among metal ions, copper ions (Cu^{2+}) in particular form complexes with various biological materials and play an important role in some metabolic pathways [20]. In this study, we synthesised hybrid nanocomposites from different DNA sequences and examined the formation of DNA hybrid nanocomposites with possible mechanistic theories. We also analyzed the effect of nanocomposite synthesis parameters on flower-like structural form. Typically, nanocomposite formation relies on the interaction of accessible amide groups in protein or enzyme backbones with Cu^{2+} ions in a phosphate buffer environment. Drawing inspiration from this, we used DNA sequences as organic ligands and investigated the formation of DNA hybrid nanocomposites through their reaction with Cu^{2+} via the amide group.

This study evaluated the effect of various factors, including pH, organic component concentration and DNA sequences, on the morphology of DNA Hybrid NCs. SEM images were used to investigate the morphology of DNA Hybrid NCs and the effects of environmental pH on morphology. According to these images, the desired structure was successfully synthesised at pH 7.4 and pH 10.0 when DNA sequences coded as C20, C20A and C20AA were used as the organic component. A flower-like morphology composed of petals was observed in the C20 DNA DNA Hybrid NCs at both pH 7.4 and pH 10.0 at a concentration of 0.1 mg/mL. However, the desired structure only synthesized at pH 10.0 at a concentration of 0.02 mg/mL. Additionally, synthesis of the C20A DNA Hybrid NCs occurred only at a concentration of 0.1 mg/mL at pH 7.4 (Figure 3). Similar to C20, flower-like structures formed in the C20AA DNA Hybrid NCs at pH 7.4 and pH 10.0 at a concentration of 0.1 mg/mL. At a concentration of 0.02 mg/mL, the desired structure only formed at pH 10.0 (Figure 4). These data clearly demonstrate the significant effect of the pH level of the synthesis solution on the structural properties like as shape and size of copper-based nanocomposites. In addition, earlier research have shown that the concentration of organic/inorganic materials is important in nanocomposite synthesis [21]. Baldemir et al. described the nanoflower formation mechanism resulting from the reaction of amino groups in plant extracts with Cu^{2+} ions. They defined this mechanism as having three phases: nucleation, where amino groups bind with phosphate-buffered Cu^{2+} ions; growth, where the crown petals form as the copper (II) ions and protein grow; and completion, where flower formation is completed through anisotropic growth [22]. Furthermore, the formation mechanism of hybrid nanostructures has shown that the metal-binding ability of amine groups depends on the pH of the medium [23, 24].

The peroxidase enzyme activities of the DNA Hybrid NCs were measured using guaiacol as the target compound, with the absorbance measured at a wavelength of 470 nm using a UV-visible spectrophotometer (Figure 5). The C20, C20A and C20AA DNA Hybrid NCs exhibited very similar peroxidase mimic activity, which Dadi and colleagues characterised as a Fenton-like reaction. In another work, researchers demonstrate that Cu-hNFs synthesised from *C. sinensis* oxidise the substrate molecule (guaiacol) by mimicking peroxidase activity and forming free radicals [22]. Ildiz et al. demonstrate that the copper (II) ions and other negatively charged groups present in Cu-NFs synthesised using a plant extract have catalytic properties, oxidising the substrate molecules with free radicals via a Fenton-like reaction [25]. In summary, Cu^{2+} ions are reduced to Cu^{1+} ions in the existence of H_2O_2 . The resulting hydroxyl radicals then cause the oxidation of the substrate in a reaction with H_2O_2. According to the results obtained, our study is consistent with previous research.

Herein, we attempted to synthesise DNA Hybrid NCs using DNA sequences and copper (II) ions as the organic and inorganic components, respectively. Also, we systematically demonstrated the effects of synthesis parameters on the flower-shape and peroxidase-like activity of the nanocomposites. Structures with ideal morphology were formed using C20 and C20AA DNA sequences and Cu^{2+} ions under conditions where the pH of the PBS solution was 7 or 10. Below pH 7.4, protonation of the amide group in the DNA sequences, coupled with the high negative charge of the DNA molecules, prevented nanocomposite formation. Experimental results demonstrated how pH values of the phosphate buffer forming the synthesis medium, as well as various DNA sequences containing cytosine nucleotides of different lengths, affect the morphology of HNCs. The DNA Hybrid NCs exhibit peroxidase mimic activity based on the Fenton reaction mechanism, generating highly reactive hydroxyl radicals existing of H_2O_2. DNA Hybrid NCs exhibited significant catalytic activity by oxidising guaiacol. Using this approach, various other metal-DNA nanomaterials suitable for biomedical and biotechnological applications can be synthesised. These nanocomposites are expected to be an effective candidate in DNA-based drug delivery systems and biosensor applications.

Conflicts of interest: No Conflict of Interest.

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Ethical statement: This study does not require ethical approval.

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