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Research Article

In-Silico Analysis of Mn_3O_4 Nanoparticles Interaction with GDP-Mannose 6-Dehydrogenase: Potential for Inhibiting Biofilm Formation in Pseudomonas aeruginosa

Sara Mohammed Alsaigh, Reem Hamoud Alrashoudi and Ayesha Mateen*

Clinical Laboratory Sciences Department, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

***Corresponding Author:** Ayesha Mateen, Clinical Laboratory Sciences Department, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia.

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Abstract

The *algD* gene encodes GDP-mannose dehydrogenase, a key enzyme involved in the biosynthesis of alginate, a major exopolysaccharide produced by *P. aeruginosa* and other bacteria.

The aim of the study is to analyze molecular interaction of Mn_3O_4NPs and GDP-mannose dehydrogenase using *In-silico* approaches.

The molecular docking studies were conducted using Autodock 4.2 software and the protein structures were retrieved from UniProtKB servers.

In-silico molecular docking, analysis reveals insights into the binding efficacy of Mn_3O_4NPs with GDP-mannose 6-dehydrogenase protein exhibited highest binding energy (-6.42 kcal/mol), suggesting a potent inhibitory effect on biofilm formation.

In conclusion, Mn_3O_4NPs were found to possess the potential to disrupt biofilm integrity by interaction with GDP-mannose 6-dehydrogenase biofilm-associated protein.

Keywords: GDP-Mannose Dehydrogenase; Mn_3O_4NPs; Autodock 4.2 Software and *algD* Gene

Abbreviations

Mn_3O_4NPs: Manganese Oxide Nanoparticles; RMSD: Root Mean Square Deviation; KI: Inhibition Constant; THR: Threonine; CYS: Cysteine; TRP: Tryptophan; HIS: Histidine; VAL: Valine; TYR: Tryptophan

Introduction

Biofilms are complex, surface-attached microbial communities encased in a self-produced extracellular matrix, which provides structural stability and protection to the constituent cells [1]. These biofilms are of particular interest due to their role in persistent infections and resistance to antimicrobial treatments [2]. One of the key components of the biofilm matrix in many bacteria, including *Pseudomonas aeruginosa* (*P. aeruginosa*), is alginate, a high-molecular-weight polysaccharide that significantly contributes to the physical and functional characteristics of biofilms [3].

The alginate produced due to the action of the *algD* gene enhances the structural integrity of biofilms, making them more robust and difficult to disrupt. This is particularly important in chronic infections, where *P. aeruginosa* biofilms are known to be highly resistant to treatment [4,5].

The gene algD encodes GDP-mannose dehydrogenase protein that catalyzes the production of GDP-mannuronic acid from

GDP-mannose and is particularly vital for producing alginic acid, which creates a gel-like substance necessary for biofilm maturation and stability [6,7].

In recent years, nanotechnology has emerged as a promising avenue for developing innovative strategies to combat bacterial biofilm formation [8]. Manganese oxide nanoparticles (Mn_3O_4NPs) have unique properties and are promising in preventing bacterial biofilm formation. Previous studies have shown that chemically synthesized Mn_3O_4-MnO_2 nanocomposites are effective against *P. aeruginosa* bacteria. Mn_3O_4NPs have potential antibacterial effects, but more research is needed to understand their impact on biofilm formation at the genetic and molecular levels [9-11].

The present study has been conducted to analyze *In-silico* molecular interaction of Mn_3O_4NPs and GDP-mannose dehydrogenase protein binding efficacy which encodes biofilm formation genes. This research study may provide valuable information for developing personalized and environmentally friendly nanotherapeutics. We aim to contribute innovative biofilm control strategies in clinical and environmental settings.

Methodology

Molecular docking analysis

Molecular docking studies were conducted to determine the binding mode and interactions between Mn_3O_4NPs and the protein as GDP-mannose 6-dehydrogenase protein (algD gene) (ID:P11759), belongs to *P. aeruginosa*, using Autodock 4.2 software [12]. The protein structures were obtained from UniProtKB servers [13].

The Molecular docking was performed using the protein structure of biofilm-formation genes of *P. aeruginosa* as receptors and Mn_3O_4NPs as ligands. The search grid of the GDP-mannose 6-dehydrogenase protein was identified as coordinates of central grid Point_x = -1.885, center_y = -0.038, and at a spacing of 0.375 Å. Coordinates of the central grid point of the pelF protein were identified as center x = -1.781, center y = -1.365, and center z = 2.903 at a spacing of 0.375 Å. Coordinates of the central grid point of the pslD protein were identified as center_x = 2.666, center_y = 0.294, and center z = -4.200 at a spacing of 0.375 Å. The analog Mn_3O_4NPs have been retrieved from the chemspider website [14].

All other parameters were set to the default values for the Auto Dock software program and are not mentioned herein. The compound with the least binding affinity value was the best-scoring compound. Discovery Studio Visualizer v24.1.0.23298 software and PyMOL Molecular Graphic System v2.5.8 [15] were used to analyze all results visually.

Results

Molecular docking analysis of biofilm-formation proteins and Mn_3O_4NPs

The interaction between GDP-mannose 6-dehydrogenase protein and Mn_3O_4NPs (Figure 1). was characterized using molecular docking techniques. The binding energy of the interaction was calculated to be -6.42 kcal/mol. This negative value indicates a thermodynamically favorable interaction between GDP-mannose 6-dehydrogenase and Mn_3O_4 NPs. The root mean square deviation (RMSD) of the protein upon binding to Mn_3O_4 NPs was found to be 7.14 Å. This significant RMSD value implies substantial conformational changes in the protein structure. The inhibition constant (KI) was determined to be 0.51 mM, indicating that Mn_3O_4 NPs are potent inhibitors of GDP-mannose dehydrogenase. A total of 11 hydrogen bonds were identified between GDP-mannose 6-dehydrogenase and Mn_3O_4 NPs, with bond distances ranging from 2.591 to 3.437 Å. The hydrogen bonds involved the following amino acid residues: THR212, CYS213, TRP216, HIS217, VAL215, and TYR211. These residues are located near the enzyme's active site, indicating that Mn_3O_4 NPs may interact with and potentially disrupt the enzyme's catalytic function (Table 1) (Figure 2).

Discussion

The *In-silico* molecular docking study of Mn_3O_4NPs with GDP-mannose 6-dehydrogenase biofilm-formation protein in *P. aeruginosa* reveals insights into Mn_3O_4NPs potential as biofilm formation inhibitors.

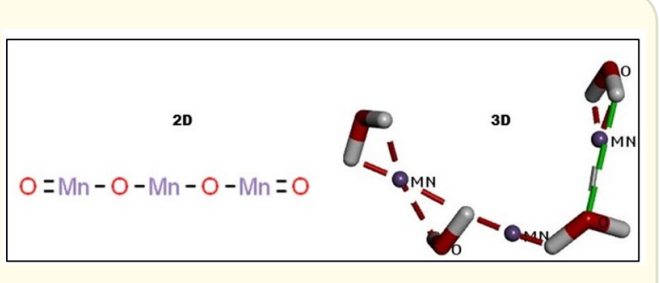

Figure 1: Structure of Mn_3O_4 NPs.

Protein(receptor) and Mn_3O_4 NPs (Ligand)	Binding energy (kcal/mol)	Reference RMSD (A)	Inhibition Constant (KI) (mM)	No. of H bonds	Distance of H bonds range	Amino acids involved in the interaction
GDP-mannose 6-dehydrogenase protein and Mn_3O_4 NPs	-6.42	7.14	0.51	11	2.591-3.437	THR212, CYS213, TRP216, HIS217, VAL215, TYR211.

Table 1: Molecular docking analysis of Biofilm-formation proteins and Mn_3O_4 NPs.
GDP-mannose 6-dehydrogenase protein (algD gene); pelF protein (pelF gene); pslD protein (pslD gene).

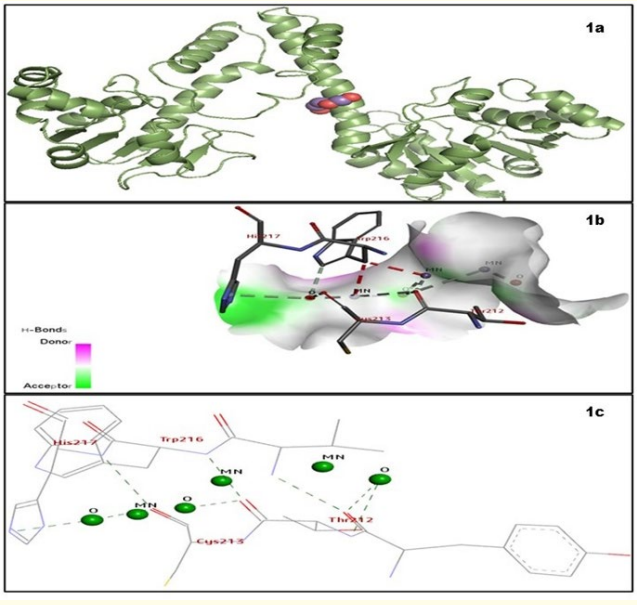

Figure 2: The Molecular docking 2D and 3D images of Biofilm-formation proteins (receptor) with Mn_3O_4 NPs (Ligand).

[Figures 1a, 1b, and 1c represent the molecular docking complex of GDP-mannose 6-dehydrogenase protein (algD gene) (Receptor) and Mn_3O_4 NPs (Ligand), 1b represents the 3D structure and 1c represents the 2D structure].

The interaction between GDP-mannose 6-dehydrogenase, a key enzyme in alginate biosynthesis encoded by the *algD* gene, and Mn_3O_4NPs was investigated to assess the potential impact on the enzyme's function and, consequently, on biofilm formation in *P. aeruginosa* [16]. The binding energy of -6.42 kcal/mol indicates a relatively strong and favorable interaction between GDP-mannose dehydrogenase and Mn_3O_4NPs. This suggests that the nanoparticles have a significant affinity for the enzyme, which could potentially interfere with its activity [17].

The root mean square deviation (RMSD) value of 7.14 Å suggests substantial conformational changes in the protein upon binding to Mn_3O_4 NPs. Such a high RMSD indicates that the binding of nanoparticles induces significant structural alterations in the enzyme, which could affect its stability, folding, and catalytic efficiency. This level of structural deviation suggests that the Mn_3O_4 NPs might disrupt the enzyme's normal function by altering its three-dimensional structure, particularly around the active site [18].

The inhibition constant (KI) of 0.51 mM further supports the notion that Mn_3O_4NPs are potent inhibitors of GDP-mannose dehydrogenase. The low KI value indicates a strong inhibitory effect, implying that even at low concentrations, Mn_3O_4 NPs can significantly reduce the enzyme's activity. Given the enzyme's critical role in alginate biosynthesis, such inhibition could lead to a decrease in alginate production, thereby affecting the formation and maintenance of biofilms, which are essential for *Pseudomonas aeruginosa* survival and pathogenicity.

The interaction analysis revealed the formation of 11 hydrogen bonds between GDP-mannose dehydrogenase and Mn_3O_4 NPs, with bond distances ranging from 2.591 to 3.437 Å. These hydrogen bonds involve key amino acid residues—THR212, CYS213, TRP216, HIS217, VAL215, and TYR211—that are located near the enzyme's active site. The involvement of these residues suggests that Mn_3O_4 NPs may interfere with the enzyme's catalytic activity by disrupting essential interactions within the active site, potentially leading to a reduction in substrate binding or catalytic efficiency.

Overall, the data suggest that Mn_3O_4NPs have a significant impact on the structure and function of GDP-mannose dehydrogenase. The strong binding affinity, coupled with the substantial conformational changes and potent inhibitory effect, indicates that these nanoparticles could effectively inhibit the enzyme's activity. This inhibition could result in reduced alginate production, thereby impairing biofilm formation in *P. aeruginosa*. Considering the critical role of biofilms in bacterial resistance to antibiotics and host immune responses [19]. Mn_3O_4NPs could be explored as a potential therapeutic agent for controlling biofilm-associated infections [20,21].

Further studies, particularly in vivo experiments, are needed to confirm these findings and to explore the therapeutic potential of Mn_3O_4NPs. These investigations would provide valuable insights into the feasibility of using nanoparticles to target key enzymes in biofilm formation, offering a novel approach to combat persistent bacterial infections.

Conclusion

To conclude, Mn_3O_4NPs exhibited as valuable inhibitor of biofilm formation in *P. aeruginosa* by targeting the GDP-mannose 6-dehydrogenase enzyme. As the bacterial biofilms plays a critical role in antibiotics resistance, Mn_3O_4 NPs could be useful as a novel therapeutic agent against biofilm-associated infections. However, further in vivo studies are necessary to confirm their efficacy and safety, paving the way for new treatments against persistent bacterial infections.

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Conflict of Interest

The authors have no conflict of interest.

Authors Contribution

Conception and design of the study was carried out by Sara Mohammed Alsaigh acquisition of data, analyses, and interpretation was Ayesha Mateen and critical revision of the manuscript was done Reem Hamoud Alrashoud.

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