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Title: A Molecular Docking Study Repurposes FDA Approved Iron Oxide Nanoparticles to Treat and Control COVID-19 Infection

Yasmin Abo-zeid[1], Nasser S. Ismail[2], Gary R. McLean[3,4], Nadia M. Hamdy[5]

[1] Pharmaceutics Dept., Faculty of Pharmacy, Helwan University, Cairo, Egypt,

[2] Pharmaceutical Chemistry Dept., Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt, Cairo 12311, Egypt,

[3] Cellular and Molecular Immunology Research Centre, London Metropolitan University, 166-220 Holloway Road, London, N7 8DB, UK

[4] National Heart and Lung Institute, Imperial College London, Norfolk Place, London W2 1PG UK

[5] Biochemistry Dept., Faculty of Pharmacy, Ain shams University, Cairo, 11566, Egypt

Corresponding Author: Yasmin Abo-zeid [1]

E-mail: yasmin.abozeid@pharm.helwan.edu.eg

Mobile: +201092892746

Co-Authors:

Nasser S. Ismail[2]

E-mail: nasser.saad@fue.edu.eg

Gary R. McLean[3,4]

E-mail: g.mclean@londonmet.ac.uk

Nadia M. Hamdy[5]

E-mail: nadia_hamdy@pharma.asu.edu.eg

Abstract

COVID-19, is a disease resulting from the SARS-CoV-2 global pandemic. Due to the current global emergency and the length of time required to develop specific antiviral agent(s) and a vaccine for SARS-CoV-2, the world health organization (WHO) adopted the strategy of repurposing existing medications to treat COVID-19. Iron oxide nanoparticles (IONPs) were previously approved by the US food and drug administration (FDA) for anemia treatment and studies have also demonstrated its antiviral activity *in vitro*. Therefore, we performed a docking study to explore the interaction of IONPs (Fe_2O_3 and Fe_3O_4) with the spike protein receptor binding domain (S1-RBD) of SARS-CoV-2 that is required for virus attachment to the host cell receptors. A similar docking analysis was also performed with hepatitis C virus (HCV) glycoproteins E1 and E2. These studies revealed that both Fe_2O_3 and Fe_3O_4 interacted efficiently with the SARS-CoV-2 S1-RBD and to HCV glycoproteins, E1 and E2. Fe_3O_4 formed a more stable complex with S1-RBD whereas Fe_2O_3 favored HCV E1 and E2. These interactions of IONPs are expected to be associated with viral proteins conformational changes and hence, viral inactivation. Therefore, we recommend FDA-approved-IONPs to proceed for COVID-19 treatment clinical trials.

Key Words: Iron oxide nanoparticles (IONPs); COVID-19; repurposing medication; molecular docking, SARS-CoV-2; HCV glycoproteins E1 and E2; reactive oxygen species (ROS)

1.Introduction

COVID-19 is a pandemic disease caused by the SARS-CoV-2 respiratory virus (Gorbalenya, 2020) that originated in Wuhan, China in late December 2019 (Gautret *et al.*, 2020). The virus has spread to 188 countries by travelers with a total number of 10,896,029 confirmed cases and 521,862 deaths by July 3rd 2020 according to the COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). The incubation period of the virus ranges from 7 to 14 days (Lai, 2020; Symptoms of Coronavirus Disease 2019, 2020) and is estimated to remain on solid surfaces for up to 9 days (Kampf *et al.*, 2020). These features allow for efficient person to person transmission (Chan *et al.*, 2020) and self-inoculation via mucus membranes of the eyes, nose, and mouth (Dowell *et al.*, 2004; Otter *et al.*, 2016). During this pandemic, healthcare providers (HCPs) have been at high risk of infection, due to a large number of admitted patients overwhelming hospital capacities and the associated shortages of protective personal equipment (PPE) making HCPs extremely vulnerable. For example, in Wuhan, China, the number of infected HCPs was 3,300 with 22 deaths, as recorded by February 24th 2020 (Wang, Zhou and Liu, 2020). Numerous reasons account for this high infection rate;(1) shortages of PPE e.g. gowns, gloves, head nets, overshoes, googles, and masks; (2) the sheer number of patients requiring hospitalization plus shortages in HCPs numbers available, forcing extended working hours ($\geq$ 10 h shifts), adding stress that affects their immune systems and increases risk of infection; (3) mobilization of HCPs from different medical departments who lack the knowledge of proper sequence of use, replacement, and disposal of personal protective equipment (PPE), further contributing to the spread of infections (Zhang *et al.*, 2020). To combat the COVID-19 pandemic, several approaches such as vaccine and antiviral development, as well as social control measures to limit infections are underway to protect HCPs and minimize infection spread in the

community. Because vaccine and new antiviral development can take years (Wang *et al.*, 2020), the WHO adopted the strategy of repurposing medications of known safety profile to be quickly applied for COVID-19 treatment protocols (Kai and Cohen, 2014).

We previously applied nanoparticles (NPs) for the treatment of viral infection(s) with promising results (Abo-zeid *et al.*, 2018). Therefore, we decided to investigate the repurposing of metal oxide nanoparticles (MONPs) for the treatment of COVID-19 and control of SARS-CoV-2 infections as well as nosocomial hospital infections. The antimicrobial activity of MONPs was recently reported (Abo-zeid and Williams, 2019). Importantly these were able to overcome bacterial resistance and control nosocomial bacterial infections in hospitals, especially when incorporated into textiles (Imai et al., 2012; Issa M. El Nahhal and Amara, 2016). MONPs antimicrobial efficiency likely results from several mechanisms of action but the principle mechanism involves the production of reactive oxygen species (ROS) which are potently antimicrobial. Microorganisms do not readily develop resistance to ROS production because ROS oxidizes multiple sites and biomolecules in the microorganism, resulting in cell death (Raghunath and Perumal, 2017). The application of MONPs as antiviral agents has also been recently investigated (Aderibigbe, 2017; Raghunath and Perumal, 2017; Abo-zeid and Williams, 2019), due to the fact that many viral strains become resistant to the current treatment approaches (Rai *et al.*, 2014a; Ghaffari *et al.*, 2019).

The antimicrobial activity of iron oxides NPs (IONPs) has been frequently reported (Pessan *et al.*, 2018; Abo-zeid and Williams, 2019). The antiviral activity of IONPs has previously been investigated against Dengue virus (Murugan *et al.*, 2017), influenza virus (H1N1)(Kumar *et al.*, 2019) and rotavirus (Gutierrez *et al.*, 2009). IONPs are biocompatible and have been approved by the FDA for treatment of anemia (Coyne, 2009). Based on these findings, we hypothesize that IONPs antiviral activity is via interaction with the viral surface proteins and interference with virus

attachment and/or entry into the host cell, resulting in neutralization. Therefore, IONPs could be a promising and safe candidate for rapid application in the treatment of COVID-19 patients.

Here we performed a docking model study to understand and track the interactions of IONPs ($Fe2O_3$ and $Fe3O_4$) with the spike protein of SARS-CoV2 that is responsible for its attachment and entry into host cells. The docking model was also applied to hepatitis C virus (HCV) glycoproteins, E1 and E2 to investigate the utility of this concept for other viruses and to ascertain the potential application of IONPs in the treatment and control of diverse viral infections.

2. Methods

2.1.Software and databases

2.1.1. Protein Data Bank archive-information containing solved structures of the 3D shapes of proteins; www.rcsb.org,

2.1.2. Molecular Operating Environment (MOE); https://www.chemcomp.com/index.htm,

2.1.3. American Mineralogist Crystal Structure Database; http://www.minsocam.org/MSA/Crystal_Database.html

2.1.4. Discovery Studio 4.1,

2.2. Molecular docking studies

The HCV envelope glycoprotein structure of E1 (PDB ID: 4uoi) (Pink *et al.*, 2005) and E2 (PDB ID: 4mwf) (Kong *et al.*, 2013), and the structure of the chimeric S-receptor-binding domain(RBD) of SARS-CoV-2 (PDB ID: 6vw1) (Shang *et al.*, 2020) were obtained from the Protein Data Bank (www.rcsb.org). The protein structure was minimized using the steepest descent minimization algorithm. Coordinates of Fe_2O_3 and Fe_3O_4 were obtained from the American Mineralogist Crystal Structure Database (Jeong *et al.*, 2010; Xu, Lee and Xu, 2017) (Figure 1) and were selected as a

model of NPs. These were converted to three-dimensional structures using Discovery studio 4.1. The energy minimization of Fe_2O_3 and Fe_3O_4 was calculated using "Ligand Preparation Protocol" of Accelry's Discovery Studio 4.1. The ionization pH was adjusted to 7.4 to be relevant to the physiological pH as we expect IONPs to interact with virus particles present in the physiological fluids.

Docking studies were performed by MOE 2010.10 release of Chemical Computing Group, Canada. The Triangle Matcher Placement Method and London dG Scoring Function were used for evaluation of the binding patterns and binding affinity of the ligands.

Protein structures of HCV E1/E2 and RBD of SARS-CoV-2 were prepared for docking studies by removal of water molecules. The protein structures were then prepared using Protonate 3D Protocol in MOE with default options. This was accomplished by adding hydrogen atoms to the amino acid residues, completing the missing residues and applying Force Field Parameters by using CHARMm Force Field. The docking protocol was first validated and then used to study the IONPs–receptor interactions in the active site to predict their binding modes and binding affinities. The selected docking pose among the 10 retrieved possible docks was chosen based on interactions with the essential amino acids in binding pocket.

The molecular docking approach for IONPs was used to support the rational design of this study. IONPs interaction with the viruses target shells (SARS-CoV-2 and HCV) was studied using MOE. Necessary hydrogens and charges were added to the protein and the active site was determined. The essential amino acids in each determined active site were compared with that reported previously and used to validate the selection of the correct binding pocket.

3. Results

3.1 Docking studies of Fe_2O_3 and Fe_3O_4NPs with S1-RBD of SARS-CoV-2

Compounds that interact with the SARS-CoV-2 S1-RBD or the HCV glycoprotein E1 and E2 are hypothesized to interfere with virus attachment to host receptors and consequently inhibit viral infection. These interactions might also be associated with irreversible changes to the virus structure and reduction of infection. Therefore, we performed molecular docking studies to identify and understand the interaction and binding affinity of Fe_2O_3 and Fe_3O_4 with SARS-CoV-2 S1-RBD and HCV E1 and E2.

The outcome of the docking studies of Fe_2O_3 and Fe_3O_4 with the S1-RBD of SARS-CoV-2 are presented inTable1 and Figures 2 and 3.The binding free energy of Fe_3O_4 (-10.66 Kcal/mol) is lower than Fe_2O_3 (-8.97 Kcal/mol) indicating the higher stability of the Fe_3O_4 S1-RBD complex (Table 1). Thus, S1-RBD favors interaction with Fe_3O_4 over Fe_2O_3. The interaction of Fe_3O_4 with S1-RBD involved the formation of four hydrogen bonds, with a total intermolecular energy of -11.40Kcal/mol (Table 1). In addition, hydrophobic interactions of Fe_3O_4 were detected with Leu455, Ser494 and Phe497 (Table 1). In contrast, Fe_2O_3 interactions involved the formation of three hydrogen bonds with a total intermolecular energy of -7.55 Kcal/mol and hydrophobic interactions were identified with Tyr495, Phe497, Tyr505 (Table 1).

The essential amino acids in each determined active site were compared with that reported before the docking study to validate the selection of correct binding pocket. The docked structures (Figures 2 and 3) show the binding region of the S1-RBD SARS-CoV-2-IONPs complex is surrounded by amino acid residues Leu455, Phe486, Asn487, Gln493, Ser494, Tyr495 and Gly496 as reported recently (Choudhary, Malik and Tomar, 2020).

Table 1: The Docking Interaction Parameters of Both Fe2O3 and Fe3O4 with S1-RDB of SARS-CoV-2

Ligands	Binding free energy (Kcal/mol)	Total Intermolecular energy (Kcal/mol)	Interacting amino acids	Hydrogen bonds	Hydrophobic interactions
Fe_2O_3	-8.97	-7.55	Gly496, Gln493, Tyr 453	3	Tyr495, Phe497, Tyr505
Fe_3O_4	-10.66	-11.40	Gly496, Gln493, Tyr 453	4	Leu455, Ser494, Phe 497

3.2 Docking studies of Fe_2O_3 and Fe_3O_4NPs with E1, E2 of HCV

The docking studies of Fe_2O_3 and Fe_3O_4 interactions with HCV E1 and E2 are presented in Table 2 and Figures 4 to 7. As shown, the binding free energy recorded with HCV E2 is lower than HCV E1 for both Fe_2O_3 and Fe_3O_4 (Table 2). In addition, the binding free energy of Fe_3O_4, -8.46 and -8.55 kcal/mol is higher than Fe_2O_3, -9.31 and -9.82 kcal/mol for both HCV E1 and E2 respectively (Table 2). Thus, the Fe_2O_3 have stronger interactions than Fe_3O_4 with HCV E1 and E2. The interactions of Fe_2O_3 with HCV E1 and E2 involved the formation of one and two hydrogen bonds, respectively. With HCV E1, the hydrogen bond formed with one amino acid (Ser77), whereas for HCV E2, the hydrogen bonds formed with the amino acids Gly523 and Phe537 (Table 2). Fe_3O_4 interactions with HCV E1 involved the formation of two hydrogen bonds bounds with amino acids Ser45 and Ser77 whereas with HCV E2 just one hydrogen bond to Gly523 was found (Table 2).

Total intermolecular free energy recorded for Fe_2O_3 interactions with HCV E1 and HCV E2 were identical at -7.45 Kcal/mol, whereas the total intermolecular free energy recorded for Fe_3O_4 was slightly higher for HCV E1 at -11.40 Kcal/mol compared with -11.55 Kcal/mol for HCV E2 (Table

2). Fe_2O_3 and Fe_3O_4 hydrophobic interactions with HCV E1 were observed with both Val75 and Gly76 and additionally with Ala78 for Fe_2O_3. For HCV E2, both Fe_2O_3 and Fe_3O_4 showed hydrophobic interactions with Thr519, Ala524, and Pro525 (Table 2).

The binding regions of the E1 glycoprotein-IONPs complex (Figures 4 and 5) are surrounded by amino acid residues Val75, Gly76, Ser77, Ala78 and Gly97 as reported previously (Chang *et al.*, 2017). This differed from the binding region for E2 glycoprotein-IONPs complex (Figures 6 and 7), which was surrounded by amino acid residues Gly523, Ala524, Pro525, Y527 and Gly530 (Chang *et al.*, 2017).

Table 2: The docking interaction parameters of both Fe2O3 and Fe3O4 with HCV glycoproteins

Ligands	Binding free energy (Kcal/mol)	Total Intermolecular energy (Kcal/mol)	Interacting amino acids	Hydrogen bonds	Hydrophobic interactions
HCV glycoprotein E1					
Fe_2O_3	-9.31	-7.45	Ser77	1	Val75, Gly76 and Ala78
Fe_3O_4	-8.46	-11.40	Ser45, Ser77	2	Val75, Gly76
HCV glycoprotein E2					
Fe_2O_3	-9.82	-7.45	Gly523, Phe537	2	Thr519 Ala524, Pro525
Fe_3O_4	-8.55	-11.55	Gly523	1	Gly523, Ala524, Pro525

4. Discussion

SARS-CoV-2, a pandemic infectious disease resulting in COVID-19, is causing numerous health and economic problems to the global population. Its rapid spread in the communities and among HCPs is due to the relatively efficient transmission between people and length of the incubation

period, resulting in a high number of infected individuals that is now over ten million globally. More than half million have died due to COVID-19. This necessitates finding a promising strategy for treatment of infected patients and efficient protection of HCPs and moreover, controlling the virus spread within hospitals.

MONPs, as described earlier, have been investigated as antimicrobial agents (Abo-zeid and Williams, 2019). Many MONPs are approved by the FDA for diverse biological purposes such as…..and….. (Bobo *et al.*, 2016; Ventola, 2017). In this context, we propose the repurposing IONPs to be used for treatment of patients suffering from COVID-19 and for infection control, based on IONPs reported antiviral activity. Importantly, IONPs have been approved by the FDA for the treatment of anemia therefore safety profiles have been established (Coyne, 2009). In the current study, a molecular docking model was performed to investigate the potential interaction of IONPs with SARS-CoV-2 and HCV structural proteins that are responsible for viral attachment and host cell entry.

SARS-CoV2 and HCV must bind to specific receptors on host cells surface to allow their entry to begin replication and continue the spread of infection. SARS-CoV-2 attaches to angiotensin converting enzyme-2 (ACE2) receptors, allocated on the surface of host cells, by anchoring the virus S-proteins, S1 subunit. S1 subunit has the RBD that is responsible for the high affinity viral binding to ACE2 receptor (Andersen *et al.*, 2020; Choudhary, Malik and Tomar, 2020; Engineering *et al.*, 2020). For HCV to infect cells, it is required to attach to host cell surface receptors; CD81, SR-B1, Claudin-1, and Occludin through its glycoproteins ligands, E1 and E2 (Pileri *et al.*, 1998). Therefore, compounds that interact with these two structural proteins of HCV have the potential to stop or reduce infection.

As revealed from our studies, IONPs, Fe_2O_3 and Fe_3O_4 interact efficiently with SARS-CoV-2 S1-RBD and HCV E1 and E2. Fe_3O_4 formed the most stable complex with S1-RDB of COVID-19 as indicated by its lower free energy. This was not the case for HCV E1 and E2, where Fe_2O_3 formed the most stable complex with E1 and E2 as revealed by the lower value of free energy recorded for formed complexes. These interactions are expected to be associated with conformational changes of the viral structural proteins and subsequently to inhibit virus entry into host cells, limiting virus replication and further infection. Several reported studies are in agreement with our findings, with Cu_2O NPs reported to interact with the HCV surface, inhibiting its entry into Huh7.5.1 cells and limiting viral replication (Hang *et al.*, 2015). Furthermore, sialic acid functionalized gold NPs (Papp *et al.*, 2010) and Gold NPs coated with mercaptoethane sulfonate (Baram-pinto *et al.*, 2010) have also been reported to interfere with influenza virus and herpes simplex virus binding to host cells plasma membranes.

The binding of IONPs with S1-RBD and HCV E1 and E2 could also initiate virus destruction through generation of ROS, a process previously reported with other metal containing NPs (Rai *et al.*, 2014b; Abo-zeid and Williams, 2019). For example, copper ions of CuI NPs were reported to oxidize the influenza virus lipid envelop, resulting in the loss of viral ability to infect cells (Fujimori *et al.*, 2012). CuI NPs was also confirmed to be effective against feline calicivirus, inactivating the virus by causing capsid protein oxidation via ROS that was generated by Cu^{+1} released from NPs (Shionoiri *et al.*, 2012).

Our results reveal that IONPs could be a promising candidate to be considered either for antiviral therapy or for infection prevention and control. To be used in antiviral therapy a major challenge is their large-scale manufacture and their safety profile *in vivo*. Fortunately, IONPs manufacturing

233 at industrial scale has been established and these have been FDA approved for treatment of anemia.
234 Several other parameters should also be addressed during the IONPs antiviral clinical trials such
235 as; (1) identification of the minimum dose and frequency of administration required to achieve
236 maximum antiviral activity (2) confirming the established safety profile of IONPs (3) clarifying
237 contraindications for co-administered medicines and identification of patients who should not take
238 IONPs (4) determination of any short-term and long-term side effects that might develop from
239 administration of IONPs.

240 For infection prevention and control in healthcare settings, we suggest the preparation of fabrics
241 incorporating IONPs to be used in manufacturing PPE such as gowns, masks, gloves, head nets,
242 and overshoes. Other fabric products used in hospitals could be also manufactured using these
243 novel fabrics, for example bed sheets, pillow covers and curtains. The use of these could limit the
244 spread of infections among HCPs as well as patients within hospitals. Moreover, these novel
245 fabrics would be multiple use and therefore considerably more economic and environmentally
246 friendly than the currently single use PPE. However, the question remains: would the incorporation
247 of IONPs into fabrics be associated with any changes of its reported antiviral activity?

248 Prior studies have investigated the antiviral activity of fabrics incorporating metal containing NPs
249 and the results are supportive. The antiviral activity of CuI incorporated in zeolite-textile (the
250 CuZeo-textile) has been compared to $CuCl_2$ solution against the avian influenza viruses H5N1 and
251 H5N3 (Imai *et al.*, 2012) . Zeolite is a microporous aluminosilicate mineral consisting of three-
252 dimensionally constructed tetrahedrons of SiO4 and AlO4 with ion exchange and adsorption
253 capabilities allowing binding to CuI. H5N1 was more sensitive to CuZeo-textile than H5N3.
254 Electron microscopy analysis revealed a small number of H5N3 viral particles with morphological
255 abnormalities in samples recovered immediately from the CuZeo-textile and no viral particles were

detectable from samples treated for 10 minutes. This suggested a rapid destruction of virions by the Cu^{2+} in the CuZeo-textile. Conversely, direct viral application of $CuCl_2$ solution (500 and 5000 µM) did not display antiviral effects on either virus, even after 48 hours of incubation (Imai *et al.*, 2012).

Another study (Gutierrez *et al.*, 2009) investigated the anti-rotavirus activity of IONPs (Fe_2O_3) loaded on glass fibers. This study revealed that an electrostatic interaction between the glass fiber coated with IONPs and the viral capsid proteins resulted in virus destruction and loss of infection properties. Furthermore, Ditta and colleagues (Ditta *et al.*, 2008) demonstrated antiviral activity of glass coated with thin films of hybrid CuO/ TiO2 NPs against bacteriophage T4, a virus that attacks *E coli*.

Taken together, the results obtained from the docking model used in our study demonstrates an efficient interaction between IONPs and two viruses, SARS-CoV-2, via S1-RDB and HCV, via glycoproteins E1 and E2. We speculate that these interactions will interfere with the virus binding and entry to the host cells. Additionally, the interactions of IONPs could initiate further reactions with the viral lipid envelopes, due to ROS release, rendering the virus inactive. Therefore, we propose the application of IONPs as therapeutic agents in COVID-19 clinical studies and a further application in the production of antimicrobial fabrics for manufacture of PPE for HCPs and fabric products that are used in hospitals for the control of infections in healthcare settings.

5.Conclusion:

Viral infections represent a major public health issue, with negative impacts not only on healthcare but also numerous socioeconomic costs. This is clearly evidenced by the COVID-19 outbreak with its progression being the biggest pandemic and public health crisis of the modern era. Although

there are many efficient antiviral agents in use, they still have drawbacks due to the development of viral resistance and the accumulation within off-target organs leading to adverse effects. Therefore, there is a high demand for discovery of novel strategies to improve the antiviral therapies to control or limit the spread of viral infections. In this work, we investigated the potential antiviral activity of IONPs on SARS-CoV-2 and HCV by molecular docking studies. Our models revealed that both Fe_2O_3 and Fe_3O_4 interacted efficiently with SARS-CoV-2 S1-RBD and HCV glycoproteins, E1 and E2. We found that Fe_3O_4 formed a more stable complex with S1-RBD whereas for HCV E1 and E2, a more stable complex was formed with Fe_2O_3. We expect these revealed interactions to be associated with conformational changes in viral structural proteins and subsequent inactivation of the virus.

Future prospective. We recommend for FDA-approved-IONPs to proceed into clinical trials for COVID-19. Additionally, due to their ability to produce ROS, we also recommend IONPs for synthesis of antimicrobial fabrics to be used in the manufacturing of lab coats, gloves, masks, head nets, overshoes, bedsheets and pillow covers. These applications are proposed to be an advanced measure to control viral and nosocomial infections in hospitals.

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Authors contribution. All authors contributed equally to the study.

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Figures Legends:

Figure1: The structure of nano-mineral representing NPs of (A) Fe_2O_3 and (B)Fe_3O_4.

Figure 2: 3D interaction diagram showing Fe_2O_3 docking interactions with the key amino acids in the S-RBD of SARS-COV-2.

Figure 3: 3D interaction diagram showing Fe_3O_4 docking interactions with the key amino acids in the S-RBD of SARS-COV-2

Figure 4: 3D interaction diagram showing Fe_2O_3 docking interactions with the key amino acids in the HCV E1 glycoprotein.

Figure 5: 3D interaction diagram showing Fe_3O_4 docking interactions with the key amino acids in the HCV E1 glycoprotein

Figure 6: 3D interaction diagram showing Fe_2O_3 docking interactions with the key amino acids in the HCV E2 glycoprotein

Figure 7: 3D interaction diagram showing Fe_3O_4 docking interactions with the key amino acids in the HCV E2 glycoprotein