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RESEARCH ARTICLE

# Azadirachtin-A a bioactive compound from *Azadiracta indica* is a potential inhibitor of SARS-CoV-2 main protease

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## ABSTRACT

Despite the growing scientific interest in finding effective treatment, SARS-CoV-2 virus remains a global major health burden and public health emergency. SARS-CoV main protease (Mpro) also known as chymotrypsin-like protease (3CLpro) is an important protein identified to be vital for SARS-CoV-2 survival. However, to date, there are no clinically approved drugs or antibodies specific for SARS-CoV-2. In the present study, we evaluated the interaction of 3CLpro with azadirachtin-A a bioactive compound from *Azadiracta indica* using in silico molecular docking study. Our results revealed that Azadiractin A docked well into the binding cavity of 3CLpro-SARS-CoV-2 with binding affinities ranges between -6.3 and -5.20 kcal/mol, and Pkd of 5.82~6.10 for the ten best binding modes. Azadiractin interacted with the active site of 3CLpro-SARS-CoV-2 by 2 conventional hydrogen bonding to HIS163 and GLU166, C-H interactions with HIS127, and alkyl interaction with PRO168 of the 3CLpro-SARS-CoV-2. We also found that the Azadiractin-A_3CLpro-SARS-CoV-2 complex is stabilized by various Vander wall forces with ASN142, LEU141, PHE140, MET165, GLN189, LEU167, THR190, and ALA191. In conclusion, our results suggested that Azadirachtin-A could be a potential inhibitor of SARS-CoV-2 main protease, thus worthy of further preclinical study.

**Keywords:** Azadirachtin-A; *Azadiracta indica;* SARS-CoV-2 main protease; molecular docking

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## 1.0 Introduction

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the order Nidovirales and Coronaviridae family widely distributed in humans and other mammals [1]. Generally, coronaviruses (CoVs) are categorized into four major genera including Betacoronavirus, Alphacoronavirus, Deltacoronavirus, and Gammacoronavirus [2]. In humans, CoVs usually cause mild to moderate upper-respiratory-tract infection, such as the common cold, however, the rarer forms of CoVs can be lethal. In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia [3]. However, recently, six groups of human CoV have been reported including HCoV-229E and HCoV-NL63 belonging to Alphacoronavirus genera, severe acute respiratory syndrome SARS-CoV, HCoVHKU1, HCoV-OC43, and Middle East respiratory syndrome MERS-CoV, belonging to genera of Betacoronavirus [4] . However, of the six CoVs, SARS-CoV, and MERS-CoV, are the most infective and lethal and are associated with the

outbreak of two epidemics at the beginning of the 21st century [5] .

There is a rapid ongoing search for therapeutics against SARS-CoV-2 [6]. Drugs targeting either the S protein or main protease have been screened. These approaches have led to the discovery of small molecules with high binding affinities to the aforementioned proteins [7]. SARS-CoV main protease (Mpro) also known as chymotrypsin-like protease (3CLpro). Mpro cleaves most of the sites in the polyproteins and the products are nonstructural proteins (nsps) which assemble into the replicase-transcriptase complex (RTC). However, to date, there are no clinically approved drugs or antibodies specific for SARS-CoV-2.

African natural products are generally known to be therapeutically effective in the management of diseases including parasitic, antiviral, antimicrobial, anticancer, antioxidants, and several other diseases [8-11]. In addition, natural products are bio-friendly and exhibited no or minimal side effects as compared to conventional therapies [12-14]. Azadirachta indica A. Juss is a medicinal plant commonly known as neem, has been extensively used in Ayurvedic medicine by the Nigerian population for treatments of several diseases including virus infections. It has been scientifically reported for anti-viral activity against several serotypes of coxsackievirus B [15], poliovirus [16], dengue virus type 2 [17] showed the inhibitory effect of neem leaves aqueous extract on dengue virus and HSV-1 virus [18], BoHV-1[19] . The traditional use as antiviral is described for the treatment of animals suffering from bovine and avian poxvirus infections by applying a paste of neem leaves directly on the infected skin [20]. In addition, Neem is considered harmless to animals, insects, humans, birds, and earthworms and has also been approved by the United States Environmental Protection Agency for use as a food crop [21].

Major chemical constituents of neem are terpenes and limonoids. The major active components in the limonoids are azadirachtin, 3-deacetyl-3-cinnamoylazadirachtin, 1-tygloyl-3-acetyl-2-methoxyazadirachtin, 22,23-dihydro-23β-methoxyazadirachtin, nimbanal, 3-tigloylazadirachtol, 3-acetyl-salannoV nimbidioV margocin, margocinin, margocilin, and others [21]. Azadirachtin A is a member of the family of azadirachtins. Structurally, azadirachtin is an organic heterotetracyclic compound, an epoxide, an enoate ester, an acetate ester, methyl ester, a cyclic hemiketal, and tertiary alcohol.

The process of drug discovery and development entails series of stages that include target identification and validation, lead identification, optimization, pre-clinical evaluation of pharmacology and toxicology, and clinical studies [22,23]. Today in silico drug target identification has become an essential tool in drug discovery and development and has been widely employed in identifying a reliable target in preclinical and clinical settings [24-26].

The availability of crystalized protein structure, ligands structures, and ligand database made it easier to simulate the possible interactions of drug candidates with potential targets and hence enable the identification of therapeutic implications and possible biological processes regulated by the drug candidate. In the present study, we demonstrate the drug-likeness and structural based evidence for its potential to be a novel SARS-CoV-2 inhibitor via targeting the main protease (Mpro) of the virus.

## 2. Material and methods

### 2.1 Source of Azadiractin A with SARS-CoV-2 main protease structure

The three-dimensional (3D) structure of Azadiractin A, a bioactive compound from *Azadiracta indica* (Compound CID: 5281303) and the canonical smiles of Azadiractin A (CC=C(C)C(=O)OC1CC(C2(COC3C2C14COC(C4C(C3O)(C)C56C7CC(C5(O6)C)C8(C=COC8O7)O)(C(=O)OC)O)C(=O)OC)OC(=O)C) were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov). The PDB file formats of the crystal structure of Mpro (PDB; 6LU7) was downloaded from the PDB database (https://www.rcsb.org/).

### 2.2 In-silico Pharmacokinetics and Drug-likeness Analysis

The Pharmacokinetics, drug-likeness, and ADMET properties of Azadiractin A were evaluated using the SwissADME algorithm. The canonical smiles of Azadiractin A were used as a query ID on the SwissADME algorithm.

### 2.3 molecular docking analyses of Azadiractin A with SARS-CoV-2 main protease.

For molecular docking, the three-dimensional (3D) structure of Azadiractin A (Compound CID: 5281303) was retrieved in SDF file format from the PubChem database and were subsequently transformed into the protein data bank (PDB) format using the PyMOL Molecular Graphics System. The PDB file formats of the crystal structure of Mpro (PDB; 6LU7)was downloaded from the PDB database (https://www.rcsb.org/). The Azadiractin A and and the receptor were subsequently converted into the Auto Dock Pdbqt format using AutoDock Vina [27].

Pre-docking preparation of the receptors followed the removal of water molecules, while hydrogen atoms and Kolmman charges were added accordingly. Molecular docking studies were performed using Autodock VINA software and by following the protocols described in our previous study [24,28]. PyMOL software was used to visualize H-bond interactions, binding affinities, interacting amino acid residues, binding atoms on the ligands and receptors, and 3D graphical representations of ligand-receptor complexes, while 2D graphical illustrations of ligand-binding interactions were further visualized using Discovery studio visualizer [29].

### 3.0 Results and Discussion

The chemical structure of Azadiractin A is shown in Figure 1A. The six physicochemical properties displayed by the bioavailability radar indicated that Azadiractin A exhibited good physicochemical properties (Figure 1B). However, physicochemical analysis of Azadiractin A revealed low passive gastrointestinal absorption (GIA) and brain permeability (Figure 1C). The in silico Pharmacokinetics, drug likeness and ADMET properties of Azadiractin A is shown in table 1.

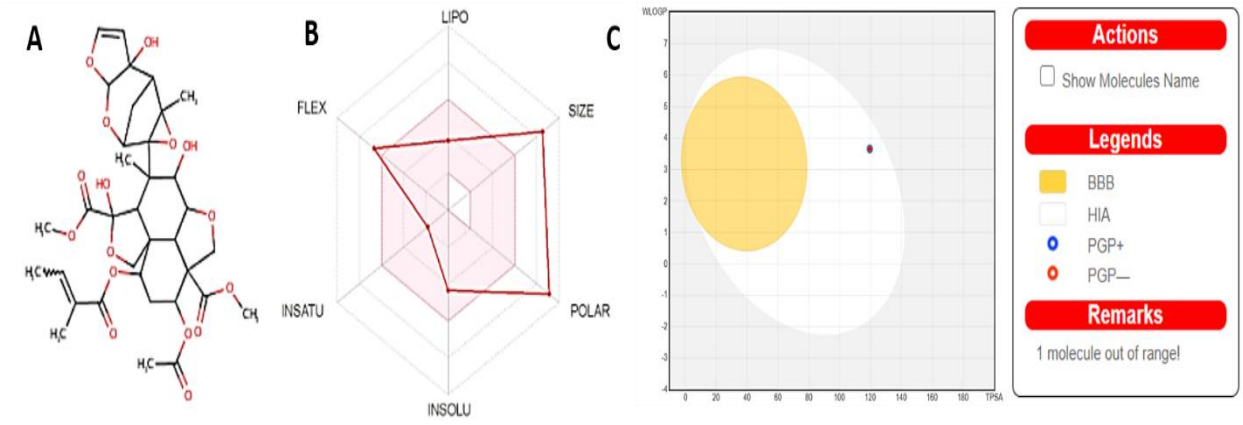
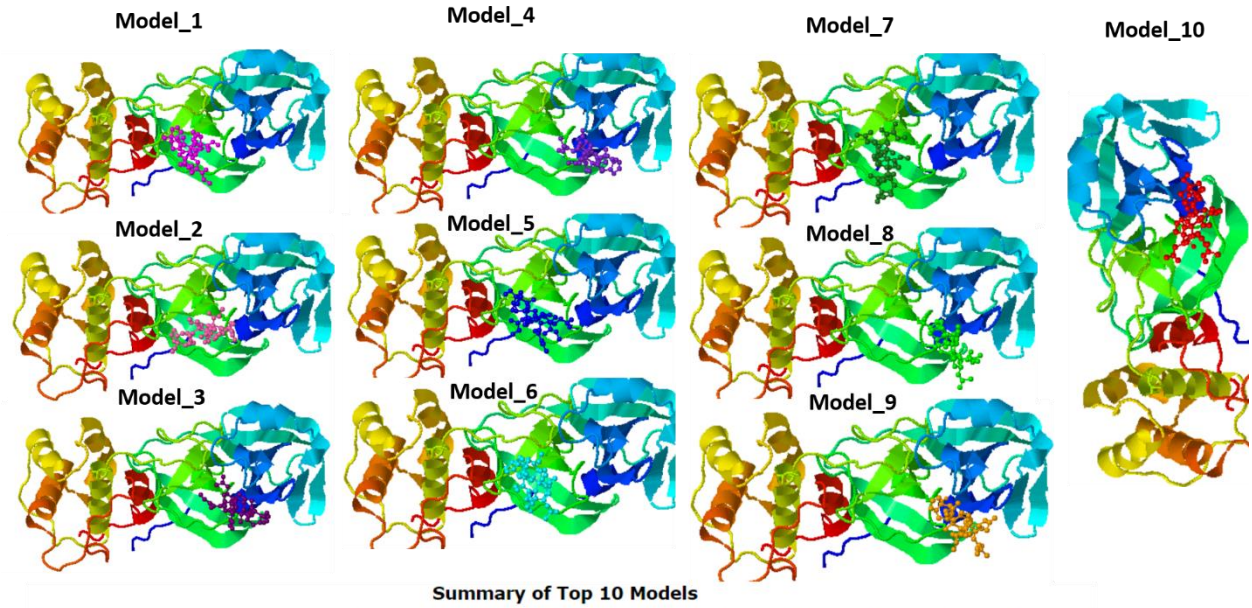



**Figure 1:** Azadiractin-A (A) Chemical Structure, (B) bioavailability radar and Boiled egg model for blood brain barrier permeation and intestinal absorption property of Azadiractin A.




Summary of Top 10 Models

| Rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Score Value (kcal/mol) | -6.30 | -5.60 | -5.60 | -5.50 | -5.50 | -5.40 | -5.30 | -5.30 | -5.20 | -5.20 |
| RF Score Value (pKd) | 5.82 | 5.90 | 5.97 | 5.78 | 5.77 | 5.77 | 5.82 | 5.62 | 5.68 | 6.10 |

**Figure 2:** The top ten (10) binding affinities and models of Azadiractin interactions with chymotrypsin-like protease (3CLpro) of covid 19

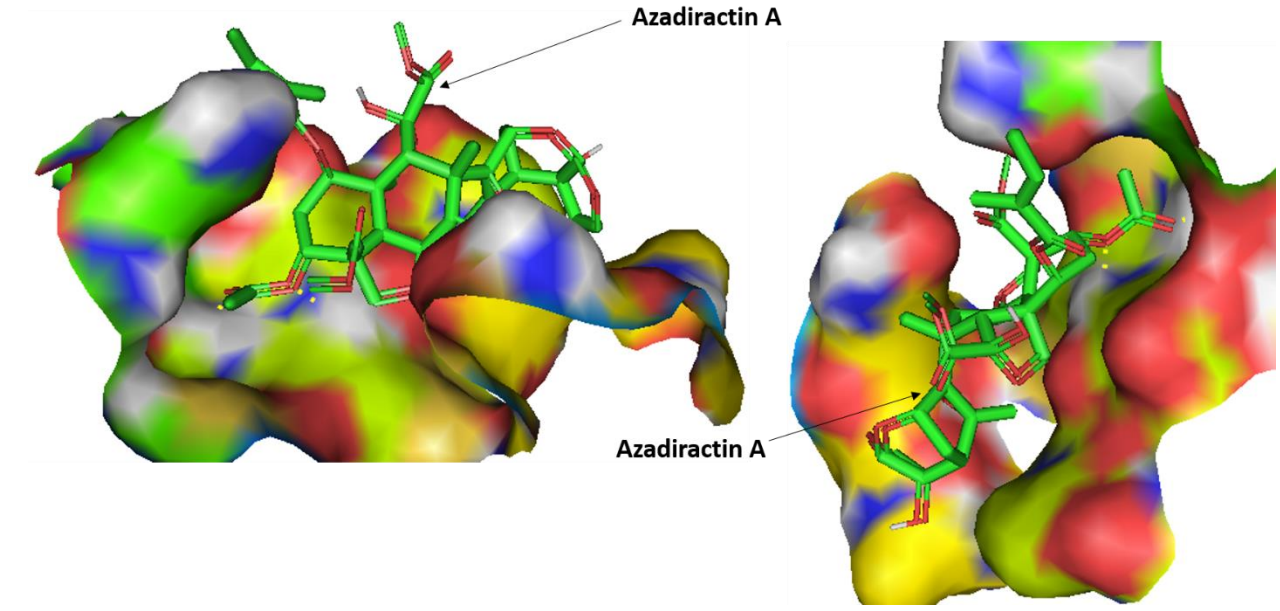



**Figure 3:** The three dimensional solid srurface representation of Azadiractin A in the binding pocket of the receptor (3CLpro-SARS-CoV-2)

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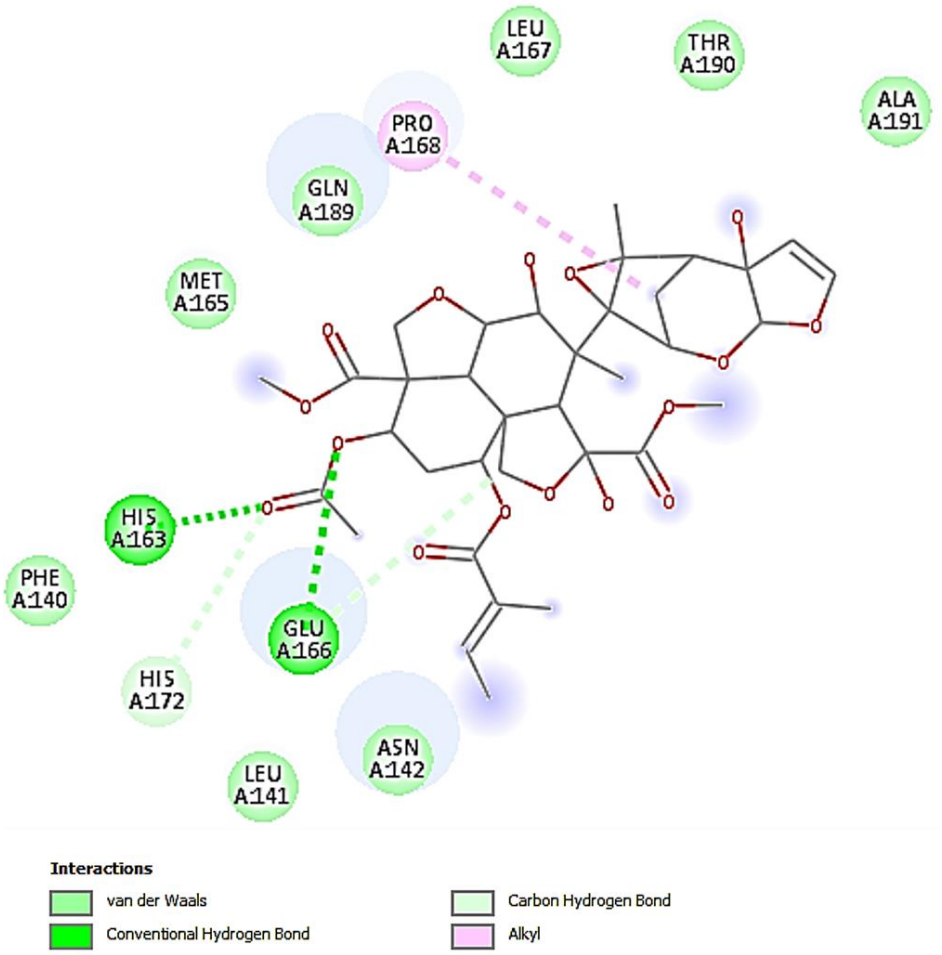


**Figure 4:** The two dimensional representation of ligand-receptor interaction of Azadiractin-A_3CLpro-SARS-CoV-2 complex showing the amino acid interaction in the active site of the 3CLpro-SARS-CoV-2.

Receptor-ligand interactions play useful roles in structure-based drug discovery and development. We analyzed protein-ligand binding complex interactions of Azadiractin A with 3CLpro-SARS-CoV-2 using molecular docking studies. Interestingly, we found that Azadiractin A interacted with 3CLpro-SARS-CoV-2 with binding affinities ranges between -6.3 and -5.20 kcal/mol, and Pkd of 5.82~6.10 for the ten best binding mode (Figure 2).

We found that Azadiractin A docked well into the binding cavity of 3CLpro-SARS-CoV-2 (Figure 3) by 2 conventional hydrogen bonding to HIS163 and GLU166, C-H interactions with HIS127 and alkyl interaction with PRO168 of the 3CLpro-SARS-CoV-2. We also found that the Azadiractin-A_3CLpro-SARS-CoV-2 complex is stabilized by various Vander wall forces with ASN142, LEU141, PHE140, MET165, GLN189, LEU167, THR190 and ALA191

Table 1: In silico Pharmacokinetics, drug likeness and ADMET properties of Azadiractin A.

| Parameters | Values |
|---|---|
| **Physicochemical Properties** | |
| Formula | C35H44O16 |
| Molecular weight | 720.71 g/mol |
| Num. heavy atoms | 51 |
| Num. arom. heavy atoms | 0 |
| Fraction Csp3 | 0.77 |
| Num. rotatable bonds | 10 |
| Num. H-bond acceptors | 16 |
| Num. H-bond donors | 3 |
| Molar Refractivity | 165.92 |
| TPSA | 215.34 Å² |
| **Lipophilicity** | |
| Log Po/w (iLOGP) | 3.9 |
| Log Po/w (XLOGP3) | 1.09 |
| Log Po/w (WLOGP) | -0.2 |
| Log Po/w (MLOGP) | -0.47 |
| Log Po/w (SILICOS-IT) | 1.07 |
| Consensus Log Po/w | 1.08 |
| **Water Solubility** | |
| Log S (ESOL) | -4.34 |
| Solubility | 3.33e-02 mg/ml; 4.62e-05 mol/l |
| Class | Moderately soluble |
| **Pharmacokinetics** | |
| GI absorption | Low |
| BBB permeant | No |
| P-gp substrate | Yes |
| CYP1A2 inhibitor | No |
| CYP2C19 inhibitor | No |
| CYP2C9 inhibitor | No |
| Log Kp (skin permeation) | -9.92 cm/s |

The unique stability of Azadiractin A in the binding site of the 3CLpro-SARS-CoV-2 could be attributed to the H-bond and. The high affinity of Azadiractin A was also associated with the presence of larger number of Van der waal forces created on it backbone the respective amino acids ASN142, LEU141, PHE140, MET165, GLN189, LEU167, THR190 and ALA191 which undoubtedly created a strong cohesive environment, thereby stabilizing the complex formed [30]. These high number of interactions undoubtedly contributed to high affinity that Azadiractin A has for 3CLpro-SARS-CoV-2.

### 4.0 Conclusion

In conclusion, our results suggested that Azadirachtin-A demonstrated a robust interaction with the main protease of SARS-CoV-2 and thus could be consider as a potential inhibitor of SARS-CoV-2 main protease, worthy of further preclinical study

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