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COMPUTED QUANTUM CHEMICAL MODELING OF THE EFFECT OF NANOSILVER ON CORONAVIRUS COVID-19

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ABSTRACT

This article presents an analysis of available scientific data on the morphology and nanostructure of the COVID-19 coronavirus. Possible mechanisms of influence of nanosilver particles on the coronavirus are considered. Models of nanosilver complexes with spike protein of coronavirus amino acids were constructed using computer quantum-chemical modeling. The values of electron density distribution, highest occupied molecular orbital, lowest unoccupied molecular orbital, and electron density distribution gradient for each constructed model are obtained. As a result of quantum chemical modeling, it was found that silver nanoparticles can interact with the following amino acids: Proline, glutamine, lysine, arginine, asparagine, histidine, glutamic and aspartic acids, tryptophan, and cysteine, which is due to the presence of additional –NH2, –NH, –SH and –COOH groups in these amino acids that are not involved in the formation of a peptide bond. The freedom of additional groups makes it possible to interact with nanosilver. Analysis of the obtained data showed that the most energy-efficient interaction is the formation of the "tryptophan–nanosilver" complex (E= - 5856.83 kcal/mol). Based on the findings of quantum chemical calculations, the most stable complex is the "cysteine– nanosilver" (ΔE = 0.16 a.u).

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Introduction

2020 was a real epic of medical feats and testing of our research and development [1-6]. However, the most important news

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of this year was the pandemic caused by the coronavirus.

Coronavirus disease (COVID-19) is a worldwide pandemic influencing more than 60 million people and has immensely affected healthcare networks globally [7-10]. On March 11, 2020, the World Health Organization (WHO) officially identified this public health problem as a global crisis [11]. Due to the massive redirection of medical care and priority towards the COVID-19 infected patients, the surgical arena has been affected. The economic requirements of the mentioned universal problem are rising, and they are being intensified by the demand for surgical proceedings [12].

The COVID-19 pandemic has forced the scientific world to expand its knowledge of this type of virus. Coronaviruses are a set of viruses covered with an unsegmented genome consisting of a single plus-chain RNA. Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) coronaviruses are highly pathogenic zoonotic coronaviruses that have caused zonal and universal prevalence at different times [13, 14].

Currently, coronavirus infection has become the number one target for scientific and medical research in the world because of its very fast distribution. Most authors are inclined to develop effective antiviral agents. In general, many interesting areas have been covered in recent years. Some scientists suggest using active phytopreparations in food to prevent viruses [15-17]. There are works on the study of the venom activity of migalamorphic spiders [18], which concluded that the polypeptide combinations of the studied poisons have strong antiviral activity. The effect of other biologically active substances on antiviral activity has also been studied [19-21]. Of particular importance for the formation of a significant immune response to various viral particles is also the normalization of the intake of essential nutrients into the body. The most important of which is the essential trace element zinc. The most noteworthy is the highly biologically active colloidal hellate forms presented in the following works [1, 22-25]. It is also worth noting the development of digitalization of medical wards [3, 26] of computer simulation of operations and the use of an electronic pharmacologist in postoperative therapy [2]. The development of special antiseptics and disinfectants is also an important factor in the fight against new types of viruses [27-29].

A large number of works indicates a serious study of the issue of combating COVID-19. However, there is no definitive solution yet. To understand which of the areas of the fight against coronavirus has great prospects, it is necessary to analyze its morphology and microstructure.

Based on the International Committee on Taxonomy of Viruses coronavirus is a *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae* [30]. According to primary serological and subsequent genomic researches, representatives of *Coronavirinae* are classified into 4 genera: α -, β -, γ - and δ-coronaviruses [31]. Four types of viruses (A, B, C, and D) belong to the genus β-coronaviruses [32]. Among the 6 familiar human coronaviruses (HCoV), HCoV-229E and HCoV-NL63 are included in the genus α-coronaviruses, while HCoVOC43 and HCoV-HKU1 are included in type A, SARS-CoV in type B, and MERS-CoV in type C of the genus β-coronaviruses [33].

The illustrative diagram indicating the genome composition of 6 familiar HCoV (not at scale) shows the 5'-cap composition and 3'-end polyadenylation (AnAOH-3'). Open reading frames (ORF1a and ORF1b) are indicated as short red rectangles. Genes encoding structural spike proteins (S), envelope (E), membrane (M), nucleocapsid (N), and hemagglutinin esterase (HE) are presented as blue rectangles. Genes encoding auxiliary proteins are indicated as grey rectangles [34].

Having a diameter of 80-120 nm., coronaviruses are spherical or pleomorphic. The surface of the virion is dotted with club-shaped protrusions formed by triangular spines (S) made of glycoprotein. Shorter protrusions consisting of the dimeric hemagglutinin esterase (HE) protein are seen in a number of β-coronaviruses, including HCoV-OC43 and HCoV-HKU1 [35]. S and HE are types I transmembrane proteins with a long extracellular domain and a short intracellular domain. The coating of the virus is formed by a membrane glycoprotein (M), a structural protein that is embedded in the coating and includes 3 transmembrane areas [36]. In addition, the nucleocapsid (N) contains a small amount of a transmembrane protein with a relatively small molecular weight, known as envelope protein (E). Eventually, the nucleocapsid (N) protein binds to the RNA genome as "beads on a string", forming a helically symmetric structure [36].

The coronavirus genome is an unsegmented genome consisting of a single plus-chain RNA of an astonishingly big size (from 27 to 32 thousand base pairs). Genomic RNA that has a 5 'cap and a poly (A) tail at the 3' end includes many Open Reading Frames (ORF). The genes are arranged in the following order: 5 '- replicase-S-E-M-N-3' with various little ORF (encoding auxiliary proteins) scattered among the structural genes. The coronavirus replicase is encoded by two large overlapping ORF (ORF1a and ORF1b), which occupy about two-thirds of the genome and are straightly translated from genomic RNA. However, structural and auxiliary genes are translated from subgenomic RNAs (sgRNA) that are synthesized while genome transcription/replication, as explained below. The coronavirus replication cycle is classified into various stages:

* Attaching and embedding in the cell;
* Broadcast of viral replicase;
• Transcription and replication of the genome;
* Translation of structural proteins;
* Virion assembly and release.

Coronavirus duplication is started by the binding of the S-protein to the cell membrane receptor(s). The S-protein consists of two functional subunits: S1 ("bulb") for binding to the receptor and S2 ("stem") for fusing to the membrane. The special

interplay between S1 and a special receptor causes a sharp structural alteration in the S2 subunit, resulting in the merger of the viral coating with the cell membrane and the penetration of the nucleocapsid into the cytoplasm [34, 36]. Interaction with the receptor is a determining factor in the tissue tropism of the coronavirus to human target cells. Some HCoV use cell membrane enzymes as receptors: HCoV-229E-aminopeptidase N, HCoV-NL63, and SARS-CoV-angiotensin-converting enzyme 2 (ACE-2), MERS-CoV-dipeptidyl peptidase 4; HCoV-OC43 and HCoV-HKU1 use 9-O-acetylated sialic acid as a receptor [37].

The S1 and S2 subunits of the coronavirus S-protein are cleaved by one or more host cell proteases. For example, activity of the SARS-CoV S-protein needs consecutive division by the endosomal cysteine protease cathepsin L and another trypsin-like serine protease [38]. However, the MERS-CoV S-protein includes two division areas for furin, which is a ubiquitously expressed protease. Surprisingly, the S1/S2 site is cleaved within MERS-CoV S-protein synthesis, while the other site (S2') is cleaved within virus penetration. Previously, researchers discovered a similar cleavage process in the Infectious Bronchitis Virus (IBV) or avian coronavirus and the typical gamma-coronavirus that infects chickens [39]. Moreover, type II transmembrane serine proteases (TMPRSS2 and TMPRSS11D) are involved in the activation of SARS-CoV and HCoV-229E S-proteins. In addition to S-protein activity, host cell elements can also be involved in next phases of virus entrance. For instance, a valosin-comprising protein promotes the release of coronavirus from early endosomes, since a decrease in the amount of this protein leads to a decrease in the duplication of both HCoV-229E and IBV [14].

Host cell factors can also limit the addition and penetration of HCoV. For instance, Interferon-Induced Transmembrane proteins (IFITM) have broad-spectrum antiviral effects against different RNA viruses. IFITM also restricts the entrance of SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-NL63 into the cell. In contrast, HCoV-OC43 uses IFITM2 or IFITM3 as an implementation element. A late research recognized many amino acid residuals in IFITM that control the intensity of HCoV introduction [40].

A detailed analysis of the morphology of the coronavirus, its structure, and microstructure of the nanocomposites RNA leads to the conclusion that the most effective tool in the fight against coronavirus may be the use of nanoscale silver particles exhibiting acute bactericidal **(Figure 1)** and antiviral activity [41, 42].

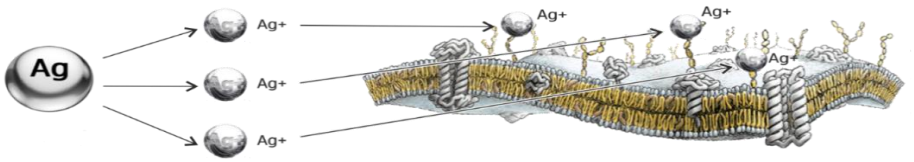


Figure 1. Mechanism of the Toxic Effect of Nanosilver on Bacterial Cells.

The mechanism of toxic action of nanosilver on bacterial cells and viruses is possible in several ways: interaction and damages to cell membranes, cellular uptake, reactive oxygen species (ROS) production, interaction with and damage to cellular proteins, binding and damages to cellular DNA and RNA repair [43]. In the case of coronavirus, there may be 3 directions of nanosilver exposure: membrane damage, RNA disintegration, and spike protein destruction [44]. The effectiveness of each type of toxic effect of nanosilver on coronavirus has yet to be determined in numerous experiments, which will be based on models of the mechanism of action.

The purpose of this work was to conduct computer quantum-chemical modeling of the mechanism of action of nanoscale silver particles on the morphology and micro-and nanostructure of coronavirus.

Materials and Methods

In the course of the work, integration with Protein Data Bank of Research Collaboratory for Structural Bioinformatics (RCSB PDB) was performed for accurate modeling of HCoV spike protein sections **(Figure 2)** and evaluation of the most affected nanosilver nodes.

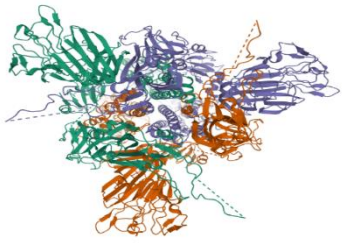
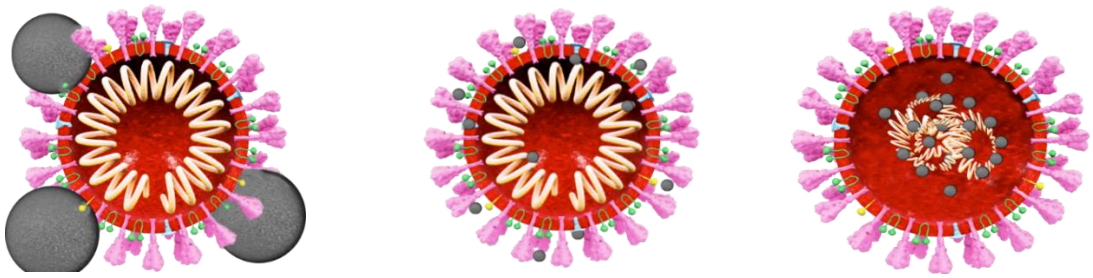


Figure 2. Prefusion Structure of a Human Coronavirus Spike Protein (Source RCSB PDB https://www.rcsb.org/3d-view/5I08).

Computer quantum-chemical modeling of the process of silver nanoparticle's effect on coronavirus was performed in the

QChem program using the IQmol molecular editor [45, 46]. The calculation was performed on the equipment of the Data Processing Center (Schneider Electric) of the North Caucasus Federal University. Calculation characteristics: Energy, method – B3LYP; basis – 3-21G, convergence-5, force field-Ghemic [47-49].

Amino acids were considered as the target of nanosilver. According to the research of Tok and Tatar (2017) and Masters (2006), the size of a coronavirus can vary from 80 to 120 nm, so the average size of a coronavirus is assumed to be 100 nm [36, 50]. In this regard, depending on the size of nanosilver particles, 3 types of interaction with coronavirus are possible: membrane damage (25-50 nm), spike protein destruction (10-25 nm), and RNA disintegration (<10 nm). The proposed types of influence of nanosilver on the coronavirus are shown in **Figure 3**.



a) b) c)

Figure 3. Schemes for the Effect of Nanosilver (Gray Particles) on Coronavirus at Different Particle Sizes: a) 25-50 nm, b) 10-25 nm, c) <10 nm

Since nanosilver can be very active with amino acids, it was suggested that the main target of nanosilver will be spike protein **(Figure 4)**.

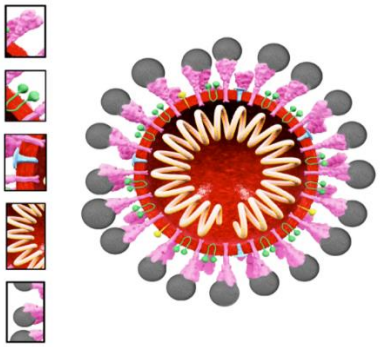


Figure 4. Mechanism of Nanosilver Effect on Spike Protein of HCoV.

The model of the effect of nanosilver on coronavirus presented in **Figure 4** is taken as the main one in this paper.

Results and Discussion

At the primer phase of study, quantum-chemical modeling of coronavirus's spike protein amino acids and nanosilver interaction was performed.

As a result of quantum chemical modeling, it was found that silver nanoparticles can interact with the following amino acids: Proline, glutamine, lysine, arginine, asparagine, histidine, glutamic and aspartic acids, tryptophan, and cysteine, which is due to the presence of additional –NH2, –NH, –SH and –COOH groups in these amino acids that are not involved in the formation of a peptide bond. These free additional groups make possible interaction with nanosilver [23, 47]. Thus, the interaction of silver nanoparticles with threonine, serine, and tyrosine is unlikely. Obtained data are confirmed by the results of quantum chemical calculations **(Table 1)**.

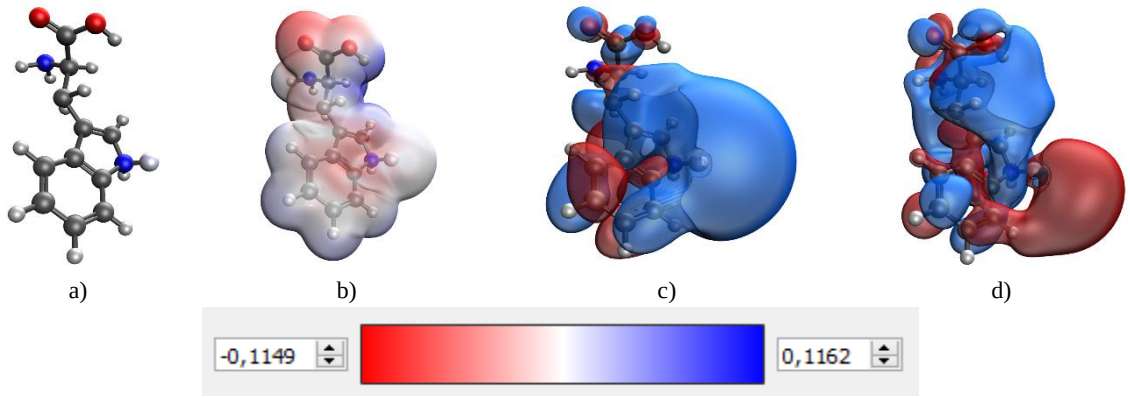
Table 1. The Results of Quantum-chemical Calculations.

Amino acid	E, kcal/mol	HOMO, a.u.	LUMO, a.u.	ΔE, a.u.
Proline	-398,553	-0,386	0,148	0,534
Proline+nanosilver	-5573,5	-0,085	-0,039	0,05
Serine	-396,703	-0,213	0,021	0,234
Serine+nanosilver	-5570,76	-0,173	-0,02	0,15

Threonine	-435,811	-0,211	0,017	0,228
Threonine+nanosilver	-5609,86	-0,167	-0,016	0,15
Cysteine	-718,033	-0,24	0,011	0,251
Cysteine+nanosilver	-5890,5	-0,199	-0,036	0,16
Tyrosine	-626,504	-0,214	-0,002	0,212
Tyrosine+nanosilver	-5800,53	-0,165	-0,031	0,13
Tryptophan	-682,279	-0,185	-0,033	0,152
Tryptophan+nanosilver	-5856,83	-0,115	-0,058	0,06
Aspartic Acid	-509,426	-0,223	-0,011	0,212
Aspartic Acid+ nanosilver	-5683,43	-0,196	-0,065	0,13
Glutamic Acid	-548,276	-0,2	-0,072	0,128
Glutamic Acid+nanosilver	-5722,28	-0,16	-0,095	0,07
Histidine	-545,675	-0,212	0,004	0,216
Histidine+nanosilver	-5720,21	-0,12	-0,03	0,09
Asparagine	-489,683	-0,229	0,004	0,233
Asparagine+nanosilver	-5664,23	-0,12	-0,037	0,08
Arginine	-603,07	-0,202	-0,004	0,198
Arginine+nanosilver	-5777,64	-0,09	-0,024	0,07
Lysine	-493,995	-0,168	-0,051	0,117
Lysine+nanosilver	-5668,58	-0,088	-0,054	0,03
Glutamine	-528,788	-0,227	0,006	0,233
Glutamine+nanosilver	-5703,33	-0,115	-0,038	0,08

Table 1 shows a decrease in the system when adding a nanosilver. i.e., the interaction of nanosilver with amino acids is an energetically beneficial process. The most energy-efficient interaction is the formation of the "tryptophan–nanosilver" complex (E= - 5856.83 kcal/mol), but the difference in the energy of interaction of nanosilver with other amino acids is not very significant. Based on the findings of quantum chemical calculations, the most stable complex is the "cysteine–nanosilver" (ΔE = 0.16 a. u.).

The obtained models of spike protein amino acids with nanosilver, electron density distributions, electron density distribution gradients, and molecular orbitals for "tryptophan–nanosilver" and "cysteine– nanosilver" are shown in **Figures 5 and 6**.



a) b) c) d)

e

Figure 5. a) Model of "Tryptophan-Nanosilver" Molecular Complex, b) Electron Density Distribution, c) Highest Occupied Molecular Orbital HOMO, d) Lowest Unoccupied Molecular Orbital LUMO, and e) Electron Density Distribution Gradient.

The formation of the "tryptophan– nanosilver" complex has a high probability, which is due to the presence of an additional NH group in the tryptophan structure.

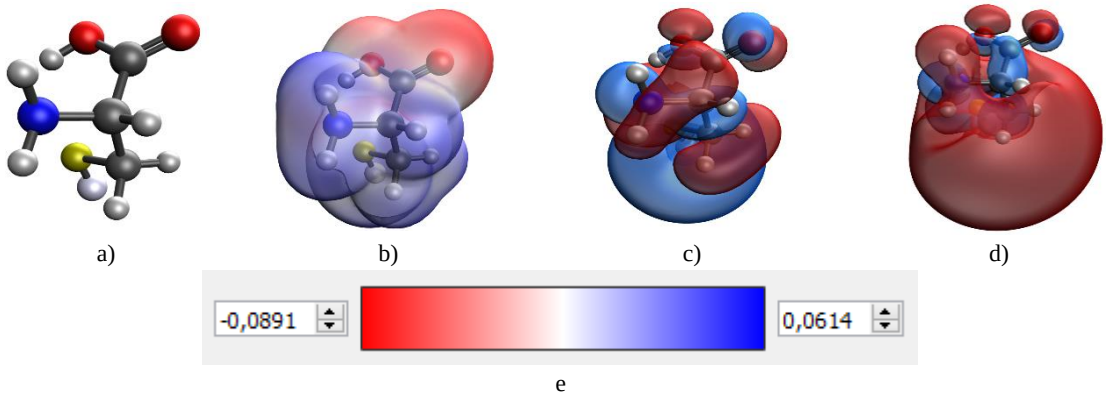


Figure 6. a) Model of "Cysteine-Nanosilver" Molecular Complex, b) Electron Density Distribution, c) Highest Occupied Molecular Orbital HOMO, d) Lowest Unoccupied Molecular Orbital LUMO, and e) Electron Density Distribution Gradient.

Silver nanoparticles can interact with cysteine, which is due to the presence of the SH group in the cysteine structure.

Conclusion

As a result of quantum chemical modeling, it was found that silver nanoparticles can interact with the following amino acids: Proline, glutamine, lysine, arginine, asparagine, histidine, glutamic and aspartic acids, tryptophan, and cysteine, which is due to the presence of additional –NH2, –NH, –SH and –COOH groups in these amino acids that are not involved in the formation of a peptide bond. The freedom of additional groups makes it possible to interact with nanosilver. Analysis of the obtained data showed that the most energy-efficient interaction is the formation of the "tryptophan–nanosilver" complex (E= - 5856.83 kcal/mol). Based on the findings of quantum chemical calculations, the most stable complex is the "cysteine–nanosilver" (ΔE = 0.16 a. u).

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Ethics statement: None

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