A Proposed Insight into the Anti-viral Potential of Silver Nanoparticles against Novel Coronavirus Disease (COVID-19)

Murad Anvarbekovich Magomedov¹, Nuri Ruslanovich Shebzukhov¹, Tabarik Rustamovna Timerbulatova², Elvin Makhir ogly Amrakhov³, Madina Elbrusovna Adzhieva⁴, Rizvan Abdievich Murdalov⁵, Rustem Khamidovich Ilbekov⁶, Hava Ilyasovna Batalova², Makka Magomedovna Isaeva⁵, Alikhan Magomedgadzhievich Ibragimov⁷ and Sergey Nikolaevich Povetkin⁸

¹Stavropol State Medical University, Stavropol, Russia.
²North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia, Russia.
³I.M. Sechenov First Moscow State Medical University, Moscow, Russia.
⁴Dagestan State Medical University, Makhachkala, Dagestan, Russia.
⁵Chechen State University Medicine Institute, Russia.
⁶Stavropol Regional Clinical Consulting and Diagnostic Center, Stavropol, Russia.
⁷Stavropol Regional Clinical Hospital, Stavropol, Russia.
⁸North Caucasus Federal University, Stavropol, Russia.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i41B32347

Editor(s):
(1) Dr. Mohamed Fawzy Ramadan Hassanien, Zagazig University, Egypt.
(2) Dr. Rafik Karaman, Al-Quds University, Palestine.
(3) Prof. Ali Nokhodchi, University of Sussex, UK.

Reviewers:
(1) Darwin F. Reyes, Nueva Ecija University of Science and Technology, Philippines.
(2) King Dave G. Martin, Nueva Ecija University of Science and Technology, Philippines.
(3) Monika Gupta, Invertis University, India.
(4) Deepti S. Deshpande, St. Aloysius College, India.
(5) Rama Sharma, GLA University, India.

Complete Peer review History: https://www.sdiarticle4.com/review-history/72149

Received 25 June 2021
Accepted 20 August 2021
Published 20 August 2021

*Corresponding author: E-mail: ruslankalmykov777@yandex.ru;
ABSTRACT

This article presents a proposed insight into the anti-viral potential of silver nanoparticles against novel coronavirus disease (COVID-19). Possible mechanisms of influence of silver nanoparticles 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. 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). According to the results of quantum chemical calculations, the most stable complex is the "cysteine–Ag nanoparticles" complex (ΔE = 0.16 a. u.).

Keywords: Silver nanoparticles; COVID-19; quantum and chemical modeling; spike protein.

1. INTRODUCTION

The study of the biological properties of metal nanoparticles, associated with the intensive development of nanomedicine and nanopharmacology, is one of the priority modern directions [1-8]. Nanomedicine studies the possibility of using nanotechnologies in medical practice for the prevention, diagnosis and treatment of various diseases [9,10]. Of particular interest in this regard is the development and study of the mechanisms of action of drugs based on silver nanoparticles [11-13]. It should be noted that silver preparations, such as collargol and protargol, have been widely used for a long time as antiseptic and anti-inflammatory agents [14,15]. With the advent of nanotechnologies, new opportunities have appeared in terms of developing more effective drugs using silver nanoparticles [16,17]. It has been established that silver in the nanoscale range has a more pronounced bactericidal, antiviral, antifungal and antiseptic effect and serves as a highly effective antibacterial agent against a wide range of pathogenic microorganisms [18,19]. Due to the larger specific surface area of nanoparticles, the areas of contact of nanosilver with bacteria or viruses increase, which significantly increases its bactericidal properties [20,21]. Accordingly, the use of silver in the form of nanoparticles makes it possible to reduce the concentration of the metal hundreds of times while preserving all its bactericidal properties. Intensive studies of recent years have shown the anti-inflammatory effects of silver nanoparticles [22,23]. However, the possibilities of using silver nanoparticles require further detailed research due to their insufficiently studied effect on various tissues and body systems.

At the moment, the study of the prospects for the use of silver nanoparticles in the treatment of inflammatory processes, the study of possible toxicological effects and the pathogenetic justification of optimal approaches to the use of silver nanoparticles are relevant and require further in-depth study. Another promising direction of studying silver nanoparticles is the assessment of antiviral activity in relation to COVID-19 coronavirus infection [24,25].

Coronaviruses have a spherical shape or are pleomorphic, their diameter is 80-120 nm. (Fig. 1) [26].

A detailed analysis of the morphology of the coronavirus, its microstructural structure and RNA allows us to conclude that the most effective means in the fight against coronavirus can be the use of nanoscale silver particles exhibiting acute bactericidal (Fig. 2) and antiviral activity [27].

The mechanism of the toxic effect 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 [28]. In the case of coronavirus, there are 3 possible directions of nanosilver exposure: membrane destruction, RNA destruction and spike protein damage [29]. The effectiveness of each type of toxic effect of nanosilver on coronavirus has yet to be determined in the course of numerous experiments, the basis for which will be models of the mechanism of action.
The purpose of this work was to conduct computer quantum-chemical modeling of the mechanism of the effect of nanoscale silver particles on the morphology and micro-, nanostructure of the coronavirus.

2. MATERIALS AND METHODS

Computer quantum-chemical modeling of the process of silver nanoparticles effect on coronavirus was performed in the QChem program using the IQmol molecular editor. 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 [30,31].

We used the QChem program using the IQmol molecular editor, the description of the work is described below:

Changes to default behavior:

- Use of automatically generated superposition of atomic densities SCF guess for custom basis sets (Yuezhi Mao, Kevin Carter-Fenk)
- Use atomic size-corrected Becke weights for CDFT (Kevin Carter-Fenk)
- General features and improvements:
  - New methods to distort molecules using force and pressure: HCFF, X-HCFF, GOSTSHYP (Tim Stauch, Maximilian Scheurer)
  - Overhauled library of standard basis sets for consistency with Basis Set Exchange and extended support through element 118
  - Improved stability of ECP fitting and updated definitions of fitted ECPs (CRENBs, CRENBL, HWMB, LACVP, LANL2DZ, SBKJC)
  - Evaluation of electric field at nuclei (Yuezhi Mao)
Frequency calculations for rigid fixed-atom constraints (Saswata Dasgupta)
- Save additional calculation output files to unique folder
- Resolved issues with:
  * Inconsistent application of quadrupole field to resolve orbital degeneracies
  * Definition of jun-cc-pVDZ basis set (John Herbert)
  * Some jobs crashing with the FILE_SET_SYM_REP read error
  * Cleaning up in PES scan jobs on Windows
  * Unnecessary gradient evaluation at every point of frozen PES scan

Amino acids were considered as a target of nanosilver. According to the research of Mishunina et al. (2021), the size of the coronavirus can vary from 50 nm to 0.15 microns, and therefore the average size of the coronavirus is assumed to be 100 nm. In this regard, depending on the size of the nanosilver particles, 3 types of interaction with the coronavirus are possible: destruction of the membrane (25-50 nm), destruction of spike protein (10-25 nm), RNA dezintegration (<10 nm). The proposed types of influence of nanosilver on the coronavirus are shown in Fig. 3.

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

![Fig. 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](image-url)
The model of the effect of nanosilver on coronavirus presented in Fig. 4 is taken as the main one in this paper.

3. RESULTS AND DISCUSSION

At the first stage of research, quantum-chemical modeling of coronavirus’s spike protein amino acids and nanosilver interaction was performed. Silver nanoparticles can interact with proline, which is due to the presence of an additional amino group in the proline structure.
The carboxyl and amino groups in the serine structure participate in the formation of a peptide bond, so they do not participate in interaction with silver nanoparticles. The addition of silver nanoparticles to the hydroxyl group has a low probability, so the formation of the "serine–nanosilver" complex is improbable.

The carboxyl and amino groups in the threonine structure participate in the formation of a peptide bond, so they do not participate in interaction with silver nanoparticles. The formation of the "threonine–nanosilver" complex is improbable, due to the absence of additional amino and carboxyl groups in the threonine structure. The addition of silver nanoparticles to the hydroxyl group has a low probability.

Silver nanoparticles can interact with cysteine, which is due to the presence of the SH group in the cysteine structure.
Fig. 8. Model of “cysteine-nanosilver” molecular complex (A), electron density distribution (B), highest occupied molecular orbital HOMO (C), lowest unoccupied molecular orbital LUMO (D) and electron density distribution gradient (E).

The formation of the "tyrosine–nanosilver" complex is unlikely, due to the absence of additional amino and carboxyl groups in the tyrosine structure. The addition of silver nanoparticles to the hydroxy group has a low probability.
The formation of the complex "aspartic acid–nanosilver" has a high probability, which is due to the presence of an additional carboxyl group in the structure of aspartic acid.

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.
The formation of the complex "glutamic acid-nanosilver" has a high probability, due to the presence of an additional carboxyl group in the structure of glutamic acid. The formation of the "histidine-nanosilver" complex has a high probability, which is due to the presence of an additional NH group in the histidine structure.
Silver nanoparticles can interact with asparagine, which is due to the presence of an additional amino group in the structure of asparagine.

The formation of the "arginine-nanosilver" complex has a high probability, which is due to the presence of an additional amino group in the arginine structure.
The formation of the "lysine-nanosilver" complex has a high probability, which is due to the presence of an additional amino group in the histidine structure.

The formation of the "glutamine-nanosilver" complex has a high probability, which is due to the presence of an additional amino group in the glutamine structure.

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 \(-\text{NH}_2\), \(-\text{NH}\), \(-\text{SH}\) and \(-\text{COOH}\) 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. 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).
the proteins involved in the coronavirus. Checking the individual interaction between the nanosilver and the specific amino acids is a good result to provide insight about the silver nanoparticles. 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. According to the results of quantum chemical calculations, the most stable complex is the "cysteine–Ag nanoparticles" (ΔE = 0.16 a. u.). Molecular docking could be done to further strengthen the claim that the silver nanoparticle can be a potential anti-COVID drug.

Table 1 shows a decrease in the system when adding 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. According to the results of quantum chemical calculations, the most stable complex is the "cysteine–Ag nanoparticles" (ΔE = 0.16 a. u.).

Molecular docking could be done to further strengthen the claim that the silver nanoparticle can be a potential anti-COVID drug.

Checking the individual interaction between the nanosilver and the specific amino acids is a good result to provide insight about the silver nanoparticles, but the specific structure of the proteins in coronavirus could affect the system during inhibition. With this we suggest conducting molecular dynamics between the nanosilver and the proteins involved in the coronavirus.

| 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  | -557,35     | -0.085     | -0.039     | 0.05    |
| Serine              | -396,703    | -0.213     | 0.021      | 0.234   |
| Serine+nanosilver   | -557,076    | -0.173     | -0.02      | 0.15    |
| Threonine           | -435,811    | -0.211     | 0.017      | 0.228   |
| Threonine+nanosilver| -560,86     | -0.167     | -0.016     | 0.15    |
| Cysteine            | -718,033    | -0.24      | 0.011      | 0.251   |
| Cysteine+nanosilver | -589,0,5    | -0.199     | -0.036     | 0.16    |
| Tyrosine            | -626,504    | -0.214     | -0.002     | 0.212   |
| Tyrosine+nanosilver | -580,53     | -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    |

4. 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). According to the results of quantum chemical calculations, the most stable complex is the "cysteine–nanosilver" (ΔE = 0.16 a. u.).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely
no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES
1. Barabanov PV, Gerasimov AV, Blinov AV, Kravtsov AA, Kravtsov VA. Influence of nanosilver on the efficiency of Pisum sativum crops germination. Ecotoxicol Environ Saf. 2018;147:715-719. DOI: 10.1016/j.ecoenv.2017.09.024
2. Baklanov IS, Baklanova OA, Shmatko AA, Gubanova MA, Pokhilko AD. The Historical Past as a Factor of Sociocultural Transformations of Postmodernity. Journal of History Culture and Art Research. 2018; 7(1):373-378.
3. Blinov AV, Siddiqui SA, Nagdalian AA, Blinova AA, Gvozdenko AA, Raffa VV, et al. Investigation of the influence of Zinc-containing compounds on the components of the colloidal phase of milk. Arab J Chem. 2021;14(7):103229.
4. Demchenkov EL, Nagdalian AA, Budkevich RO, Oboturova NP, Okolelova AI. Usage of atomic force microscopy for detection of the damaging effect of CdCl2 on red blood cells membrane. Ecotoxicology and Environmental Safety. 2021;208:111683.
5. Lunin LS, Lunina ML, Kravtsov AA, Blinov AV. Effect of the Ag Nanoparticle Concentration in TiO2–Ag Functional Coatings on the Characteristics of GaInP / GaAs / Ge Photoconverters. Semiconductors. 2018;52:993–996. Available:https://doi.org/10.1134/S106378 2618080122
6. Nagdalian, Andrey Ashotovich, Pushkin, Sergey Viktorovich, Lodgyn Alexey Dmitrievich, Timchenko Lyudmila Dmitrievna, Rzhepakovskiy, Igor Vladimirovich, Trushov Pavel Andreевич. Bioconversion of nutrients and biological active substances in model systems chlorella-insect-livestock. Entomol Appl Sci Lett. 2018;5(1):103-110.
7. Blinov AV, Gvozdenko AA, Kravtsov AA, Krandievsky SO, Blinova AA, Maglakelidze DG, Vakalov DS, Remizov DM, Golik AB. Synthesis of nanosized manganese methahydroxide stabilized by cysteine. Materials Chemistry and Physics. 2021; 2651:124510.
8. Blinov AV, Kravtsov AA, Krandievskii SO, Timchenko V, Gvozdenko AA, Blinova A. Synthesis of MnO2 Nanoparticles Stabilized by Methionine. Russ J Gen Chem. 2020;90(2):283-6.
9. Razin MP, Minaev SV, Axelrov MA, Tarakanov VA, Svirsky AA, Trushin PV, Galanina AV, Barova NK, Gramsin AV, Smolentsev MM, Rakitina EN, Sklyar KE, Makhlin AM, Emelyanova VA, Sevkovsky IA. Diagnosis and treatment of the congenital diaphragmatic hernia in children: a multicenter research. Medical News of North Caucasus. 2019;14(2):302-308. (In Russ) DOI:http://dx.doi.org/10.14300/mnnc.2019.14073
10. Remizova AA, Dzgoeva MG, Tingaeva YI, Hubulov SA, Gutnov VM, Bitarov PA, et al. Tissue Dental Status and Features of Periodontal Microcirculation in Patients with New COVID-19 Coronavirus Infection. Pharmacophore. 2021;12(2):6-13. Available:https://doi.org/10.51847/5JIbnUbHkT
11. Morozov V. Yu, Kolesnikov RO, Chernikov AN. Effect from Aerosol Readjustment Air Environment on Productivity and Biochemical Blood Parameters of Young Sheep. Research Journal of Pharmaceutical Biological and Chemical Sciences. 2017;8(6):509-514.
12. Raevskaya AI, Belyalava AA, Shevchenko PP, Karpov SM, Mishvelov AE, Simonov AN, et al. Cognitive impairments in a range of somatic diseases diagnostics, modern approach to therapy. Pharmacophore. 2020;11(1):136-41.
13. Kotsoeva GA, Esiev RK, Toboev GV, Zakaeva RS, Kulova AA, Tsokova LV, et al. Phytoadaptogenic cocktail use...
"Biorithm-E" in the complex treatment of odontogenic inflammatory diseases of the maxillofacial region. Ann. Dent. Spec. 2021;9(2):52-57. Available:https://doi.org/10.51847/PyVv83 OTG

14. Lopteva MS, Povetkin SN, Pushkin SV, Nagdalian AA. 5% suspension of albenzazole echinacea magenta (Echinacea purpurea) Toxicometric Evaluation Entomology and Applied Science Letters. 2018;5(4):30-34.

15. Blinov AV, Yasnaya MA, Blinova AA, Shevchenko IM, Momot EV, Gvozdenko AA, Senkova AO. Computer quantum-chemical simulation of polymeric stabilization of silver nanoparticles. Physical and chemical aspects of the study of clusters nanostructures and nanomaterials. 2019;11:414-421.

16. Blinov AV, Kravtsov AA, Raffa VV, Kramarenko VN, Krandievsky SO, Maglakelidze DG, Blinova AA. Influence of synthesis conditions on aggregate stability of Ag aerosols. Physical and Chemical Aspects of the Study of Clusters Nanostructures and Nanomaterials. 2020;12:25-32.

17. Yasnaya MA, Blinov AV, Blinova AA, Shevchenko IM, Maglakelidze DG, Senkova AO. Determination of optimal modes for measuring the size of colloidal particles by photon-correlation spectroscopy and acoustic spectroscopy. Physical and Chemical Aspects of the Study of Clusters Nanostructures and Nanomaterials. 2020;12:232-242.

18. Markowska K, Grudniak AM, Wolska KI. Silver nanoparticles as an alternative strategy against bacterial biofilms. Acta Biochim Pol. 2013;60(4):523-30.

19. Zhang XF, Liu ZG, Shen W, Gurunathan S. Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci. 2016;17(9):1534. DOI: 10.3390/ijms17091534

20. Yin IX, Zhang J, Zhao IS, Mei ML, Li Q, Chu CH. The antibacterial mechanism of silver nanoparticles and its application in dentistry. Int J Nanomedicine. 2020 Apr 17;15:2555-2562. DOI: 10.2147/IJN.S246764

21. Mishununa VV, Chapanov MM, Gakaeva KI, Tsoroeva MB, Kazanova SA, Gorlova MI, et al. Computed Quantum Chemical Modeling of the Effect of Nanosilver on Coronavirus COVID-19. Pharmacophore. 2021;12(2):14-21. Available:https://doi.org/10.51847/LcTdy7p SqE

22. Tang S, Zheng J. Antibacterial Activity of Silver Nanoparticles: Structural Effects. Adv Healthc Mater. 2018;7(13):e1701503. DOI: 10.1002/adhm.201701503.

23. Franci G, Farlanga A, Galdiero S, Palomba L, Rai M, Morelli G, Galdiero M. Silver nanoparticles as potential antibacterial agents. Molecules. 2015;20(5):8856-74. DOI: 10.3390/molecules20058856

24. Zimmerman T, Siddiqui SA, Bischoff W, Ibrahim SA. Tackling Airborne Virus Threats in the Food Industry: A Proactive Approach. International Journal of Environmental Research and Public Health. 2021;18(8):4335. Available:https://doi.org/10.3390/ijerph18084335

25. Ayivi R, Ibrahim S, Colleran H, Silva R, Williams L, Galanakis C, Fidan H, Tomovska J and Siddiqui SA. COVID-19: human immune response and the influence of food ingredients and active compounds. Bioactive Compounds in Health and Disease. 2021;4(6):100. Available:https://ffhdj.com/index.php/BioactiveCompounds/article/view/802

26. Magomedova UG, Khadartseva ZA, Grechko VV, Polivanova MN, Mishvelov AE, Povetkin SN, et al. The role of Covid-19 in the acute respiratory pathology formation in children. Pharmacophore. 2020;11(5):61-65

27. Nagdalian AA, Rzhepakovsky IV, Siddiqui SA, Piskov SI, Oboturova NP, Timchenko LD, Lodygin A, Blinov AV, Ibrahim SA. Analysis of the content of mechanically separated poultry meat in sausage using computing microtomography. Journal of Food Composition and Analysis. 2021;103918.

28. Guo Z., Zeng G, Cui K. Toxicity of environmental nanosilver: mechanism and assessment. Environ Chem Lett. 2019;17:319–333. Available:https://doi.org/10.1007/s10311-018-0800-1

29. Qurat-Ul-Ain, Sarfraz RA, Qayyum A. Mechanism of action of bio-inspired nanosilver particles. Bioinspired, Biomimetic and Nanobiomaterials. 2018;7(3):174–186. Available:https://doi.org/10.1680/jbnn.17.00026
