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Investigation of the effect of Hydroxychloroquine, Remdesivir, Oseltamivir and some home remedies in the light of Molecular Dynamics Simulation

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ABSTRACT

Modeling and simulation is another way of finding the interaction between different drugs and chemical species with human cell. Preliminary studies before clinical trial involve computer simulation based on the physical modeling so that clinical trial can be made easier. In many aspects of drug developing, simulation is an essential tool. Here molecular dynamics simulation is performed for the interaction of the spike protein of Covid-19 virus and some of the recently used drugs. Also, the effect of caffeine, theanine, nicotine etc on the virus is found by simulation.

Keywords: COVID-19, Modeling and simulation, Molecular dynamics simulation

1 Introduction

As time advanced from January 2020, our normal life is continuously threatened by the outbreak of the highly contagious disease caused by the COVID-19 virus. Since then, it has rapidly spread over all the countries of the world and now it is of utmost necessity to find its proper treatment and vaccination. The pandemic outburst due to the COVID-19 virus has raised the need for extensive research involving experimental as well as simulation procedures.

The hunt for vaccines and proper medicine among the researchers and scientists is increasing day by day. Human receptor protein ACE2 in the upper respiratory tract is identified as the receptor of the virus in the human body [1]. At the onset, the spike protein (S-protein) loosely binds its receptor before replication [2]. The virus can be detected in the upper and lower respiratory tract [3]. Identified with many similar symptoms like the normal influenza virus, the highly virulent Cov-19 virus showed moderate to severe respiratory trouble and pneumonia in some cases [4]. Infection can also be transmitted by asymptomatic carriers in the incubation period [5, 6]. Almost all countries followed containment measures to reduce the spreading of the virus. The result of consecutive lockdown measures was little effective in some countries [7] but it could hardly reduce the spreading in India due to lack of awareness between people [8] and due to high density of population. Almost all countries are facing economic falls due to lockdown [9, 10] and the tremendous downfall of general health conditions and mental illness are

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increasing day by day. Lack of proper lockdown strategy is also responsible for less effectiveness of the same in controlling community spreading [11].

The reproductive number of the COVID -19 virus is higher compared to SARS Coronavirus and MARS Coronavirus. That means it generates a greater number of new infections from an infected person compared to the former two species [12]. Though respiratory trouble is the most severe symptom of this virus, cardiovascular damage is also observed in some patients. More clearly saying, patients with cardiovascular diseases are more likely to be affected by severe respiratory trouble [13] but there may not be any historical changes in the heart tissue after the SARS-Cov-2 attack and it may not directly damage the heart [14]. On the other hand, cases of virus affected patients with diarrhea are increasing [15] day by day.

In the present scenario, when vaccine and therapeutic are in urgent need and almost all countries are in a hurry to find a quick cure of this curse, modeling and simulation is an effective tool for finding the effectiveness of drugs and remedies before applying them on human being or animals directly [16, 17].

Until 19th May 2020, the total number of confirmed cases is 23,752,965 worldwide including 815,038 deaths, reported to WHO. The total mortality rate reported to WHO is 3.4% as far most current information. Several symptoms, basically for elderly persons including severe respiratory trouble, hyper inflammation, and hypercytokinaemia followed by multiorgan failure are proven fatal for the affected patients [18] Above 2115 clinical trials are ongoing which is listed in World Health Organization's International Clinical Trials Registry Platform. Of them, some trials are about to start that can be the potential medicine or process to combat COVID-19. These include normal medicine with a peripheral blood draw, nasal intake, hyperbaric oxygen therapy, plasma therapy, ultrasound, etc and deal with moderate to the highly critical condition of the patients. To date, hydroxychloroquine [19], remdesivir [20] oseltamivir [21] have been used in India and also in China and United States. Much debate is there about the effectiveness of the medicine. Some trials show that they don't have any usefulness in treating Covid-19 [22] whereas one much-cited research article talks about the joint use of Hydroxychloroquine with azithromycin in some cases that were more effective than the use of only hydroxychloroquine [23]. The most recent study says it is no better than a normal placebo with more side effects than later.

So, in this work, the fruitfulness of some of the home remedies and effectiveness of some currently used medicines is investigated by modeling and simulation. The process may lead future researchers to find the efficacy of the drug in the human body.

2 Research Methodology

All the simulations are done on the spike protein of the COVID -19 structure. The detailed information of SARS COV2 is obtained from the news released in Drug Target Review (Drug Target Review, 2020). The simulations are done with the spike protein (PDB Id 6CRV). As known, The Spike or S-protein of the SARS CoV-2 virus binds with the human ACE2 and gradually symptoms like cough, fever, short breathing, etc. appear within 2-4 days [24]. In this work, investigations are performed whether the S protein can be destroyed or made ineffective before multiplying at this stage. The method includes the binding the S-protein with the proposed drug or chemical and subjecting the combined system to molecular dynamics (MD) simulation of the optimized geometry.

The spike protein with PDB ID 6crv is downloaded [25]. The protein structure is allowed to interact with the test molecule by finding its adsorption at different surfaces. Adsorption locator in the materials studio helps to bind the required number of test molecules with the protein structure, mainly on its surface. It also gives the total energy, adsorption energy, deformation energy, etc. at the binding sites. In simulated annealing total number of MC simulation step is 100000. Before simulation 500 iterations of optimization is performed where the temperature is controlled automatically. After simulated annealing, the final structure is again optimized by the conjugate gradient method in the Forcite module. Molecular dynamics simulation is then performed for the optimized structure with the Universal force field for a

total time duration of 50 ps in the NVE ensemble. The time step is taken as 1 fs. Long-range interaction is modeled by van der Waals interaction with cut-off distance 12.5 Å. Simulations are repeatedly performed taking different test molecules like nicotine, theanine, and caffeine. The effect of drugs like remdesivir, hydroxychloroquine, oseltamivir are also investigated. The results are analyzed stepwise.

3 Theory and Calculation

In adsorption locator, simulation is run on a substrate with adsorbate. Low energy adsorption sites are found while the energy profile reveals the most possible site of adsorption. Simulated annealing method reduces the temperature slowly and Monte Carlo (MC) simulation tells the adsorption possibility of different sites in a canonical ensemble. In such ensemble the probability (p_m)of a specific configuration is given in terms of β (reciprocal of temperature) and E_m (total energy of mth configuration) as

$$p_m = C \exp[-\beta E_m] \tag{1}$$

where C is the normalisation constant. The total energy of the configuration is the sum of three terms

$$\mathrm{E}_T = E^A + E^S + E^{AS} \tag{2}$$

From left to right, the terms are the intramolecular energy of the adsorbed molecules, intramolecular energy of the sorbate molecules, and the intermolecular energy of the two different molecules. Monte Carlo simulation sets up random conformation for the substrate with the adsorbate by employing four canonical ensembles for conformation, rotation, translation, and regrowth. In simulated annealing by MC method, temperature decreases from a much higher value, and at each step energy is changed. acceptability of higher energy state is lesser than that of lower energy state, though it was accepted initially. Thereafter, lower energy states are preferred over the higher ones and the temperature is decreased to attain the state with local minimum. The process is repeated to have a global minimum for the system.

4 Results and Discussion

4.1 Preparation of model for simulation

The structure of hydroxychloroquine (HCQ) is imported from PubChem and energy minimized using COMPASS force field of Forcite module. Conjugate gradient method with 500 iterations is used for the purpose. The structure of the S-protein of Cov-19 virus is simulation annealed with 10 adsorbate molecules setting the surface of the protein as the site of adsorption. COMPASS force field of Adsorption Locator module finds the minimum energy configuration of the adsorbate loaded protein structure in atom based electrostatic and Van der Waals environment. In the process of simulated annealing, the system is free to acquire higher energy states initially at high temperature which is restricted slowly by lowering the temperature so that ultimately global minimum state can be reached in coarse of time. This is a good approximation to locate global minimum in an extended system space. **Fig 1** depicts the S-protein attached with HCQ molecules.

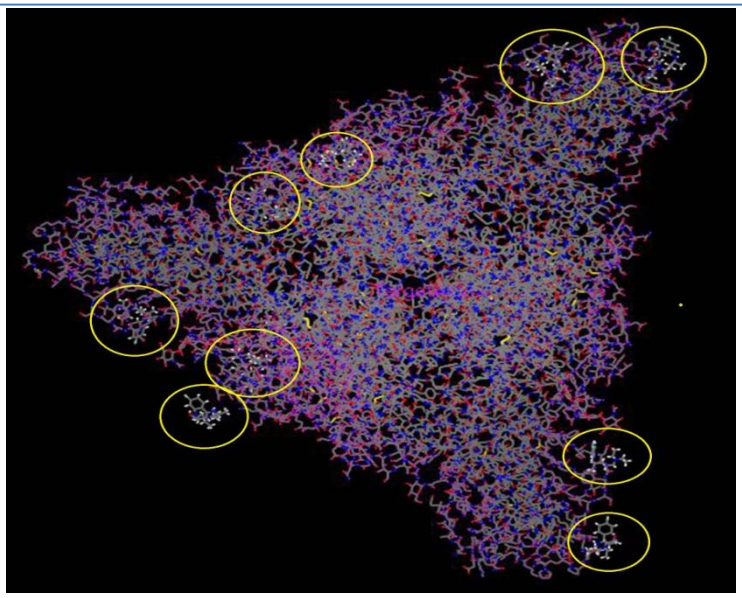


Fig 1: HCQ molecules attached to the S-protein structure. Yellow circles denote the HCQ molecules. Nine HCQ molecules are shown in the image. One molecule is detached from the structure which is confirmed from the energy profile of simulated annealing.

4.2 Simulation

After getting the final structure of the protein, it's structure is again optimized and then subjected to MD simulation. By doing this the system is allowed to interact among its own constituents. Total simulation time is 50 ps and time step is assumed as 1 fs. HCQ loaded S-protein shows deformation on simulation with distorted sharp edges. But the structure is not destroyed. The protein structure after simulation is shown in **Fig 2.** It can be said that the protein may become inactive after binding with HCQ.

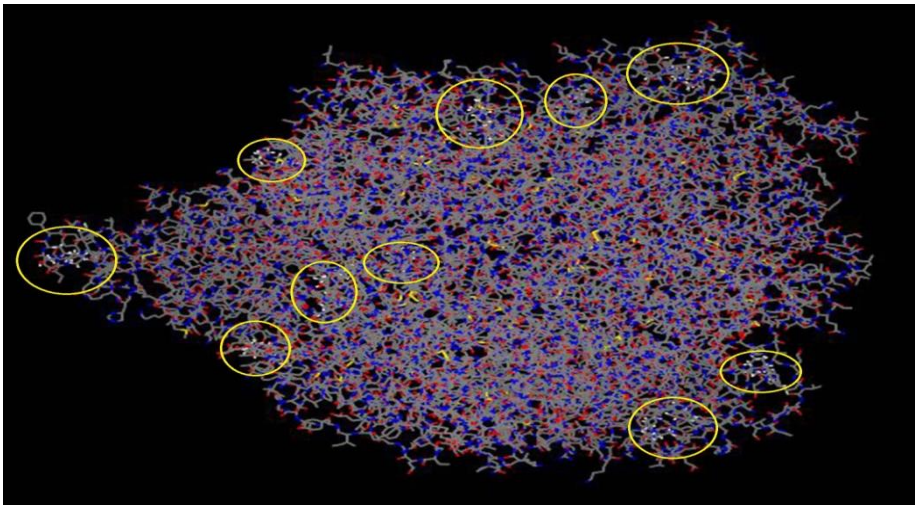
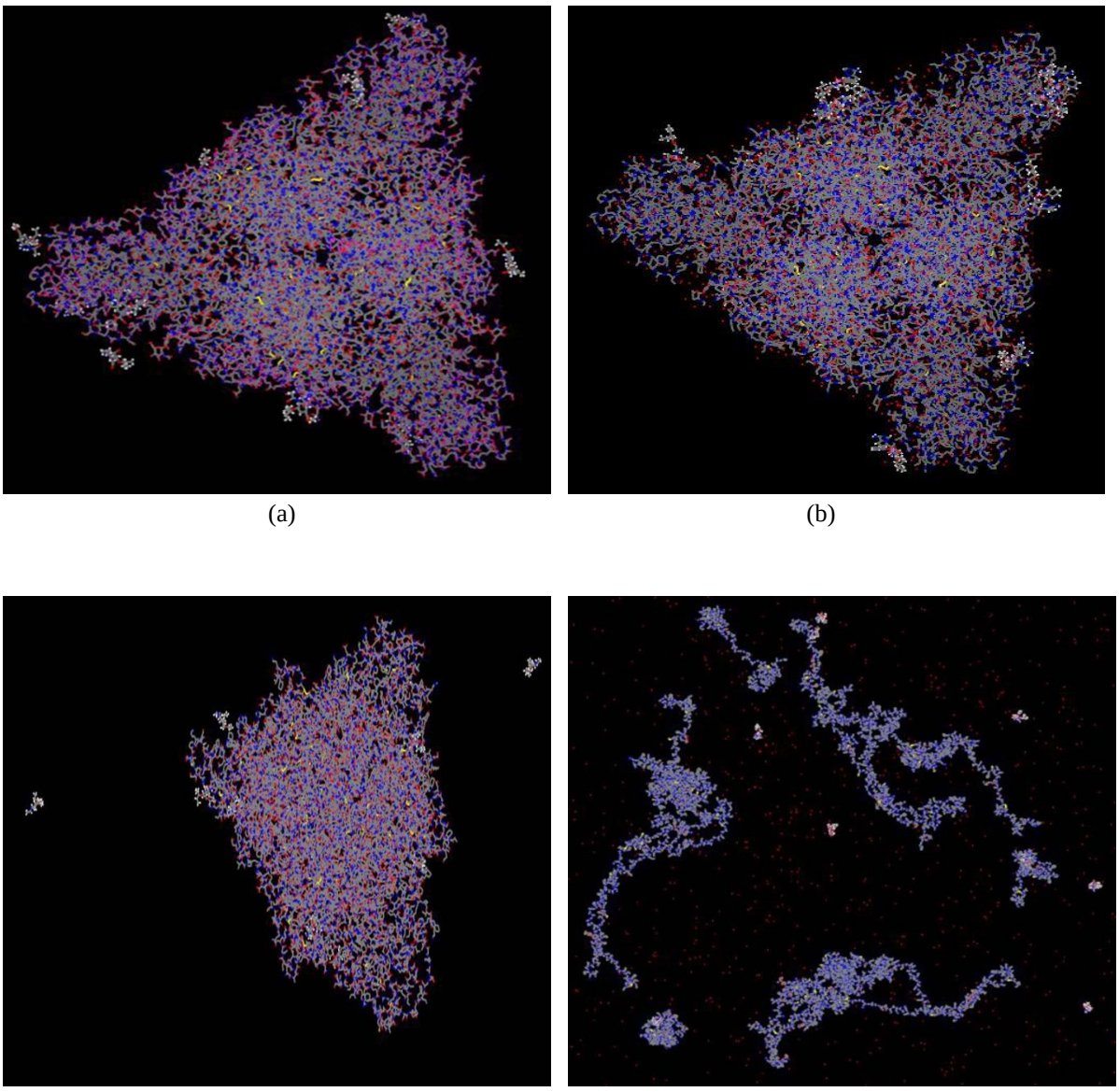


Fig 2: Simulated structure of HCQ loaded Covid-19 S-protein. HCQ molecules remain attached to the protein and the main structure is not broken but the structure is modified completely. Yellow circles identify the HCQ molecules.

The same process is repeated with oseltamivir (GS-4104) and remdesivir (GS-5734). Ten molecules of each species are bound with S-protein in the same manner as done with HCQ. But attachment of GS-4104 with the S-protein is not so stable in some sites. Binding energy is very low for two molecules to bind them with the protein. Fig 3 (a) is the picture of GS-4104 bound 6crv protein and Fig 3 (b) is the same protein with ten GS-5734 molecules attached with it. Fig 3(c) and 3(d) are the structure of the

protein after simulation with GS-4104 and GS-5734 respectively. That the later completely destroys the S-protein spike, is clear from the picture.



(a) (b)

(c) (d)

Fig 3: (a) S-protein loaded with ten molecules of oseltamivir (b) S-protein loaded with ten molecules of remdesivir (c) Oseltamivir loaded protein structure after simulation (d) remdesivir loaded protein structure after simulation

The energy profile of the remdesivir loaded S-protein is shown in figure 4. Non bond energy is very low which is given in Table 1.

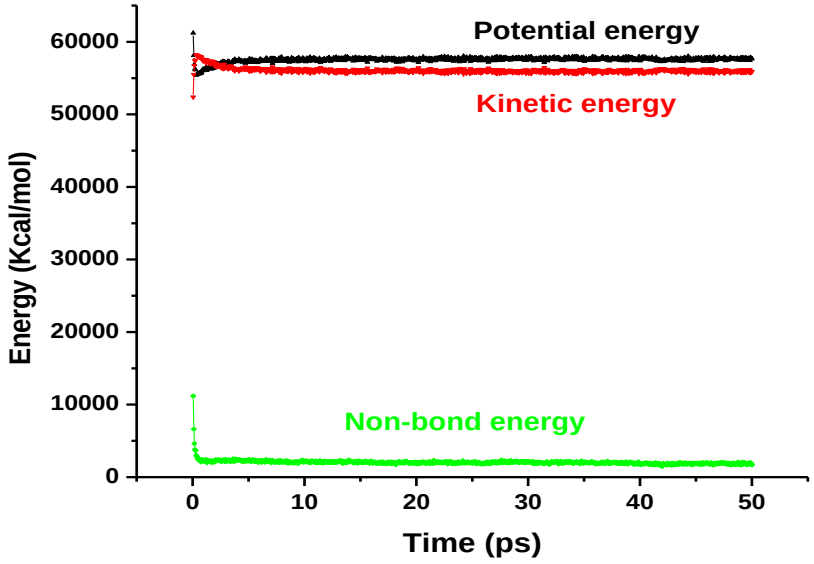


Fig 4: Energy profile of MD simulation for S-protein attached with remdesivir. Black-Potential energy, Red-Kinetic energy, Green-Non-bond energy.

The effect of chemicals like nicotine, caffeine, theanine etc. is then investigated following the same procedure. After interacting with theanine molecules, several bond breakings of the S-protein are observed. Though one of the ingredients of tea is theanine. But when the S-protein bound with tea is simulated, no such breaking of bonds in protein structure occurs. Caffeine also has such effect, i.e. it changes the S-protein structure considerably. While caffeine is capable to change the structure of the protein to bring it to an inactive stage, no such change is observed with nicotine. Fig 5 (a) and 5(b) depict the simulated structure of the protein bound with theanine and caffeine respectively.

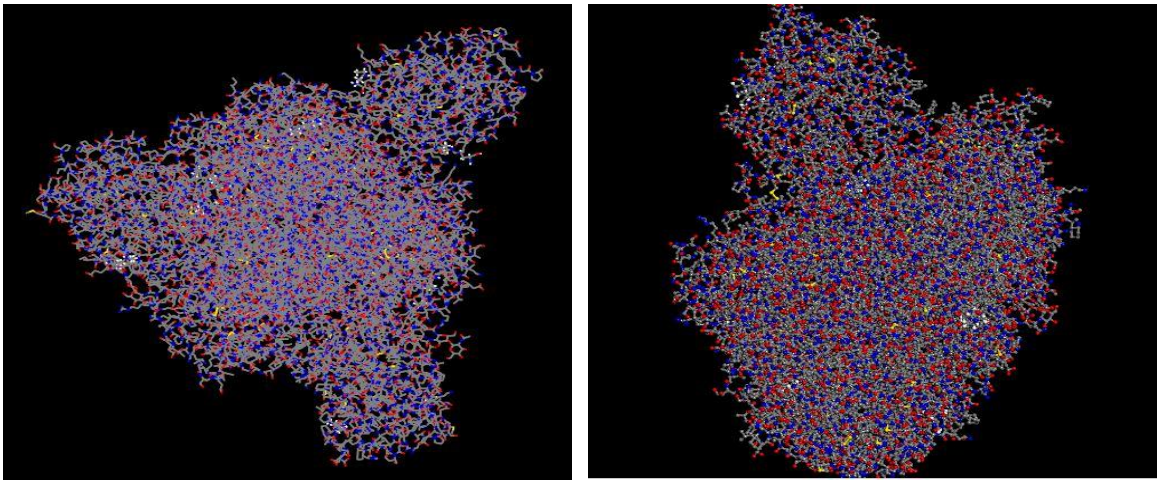
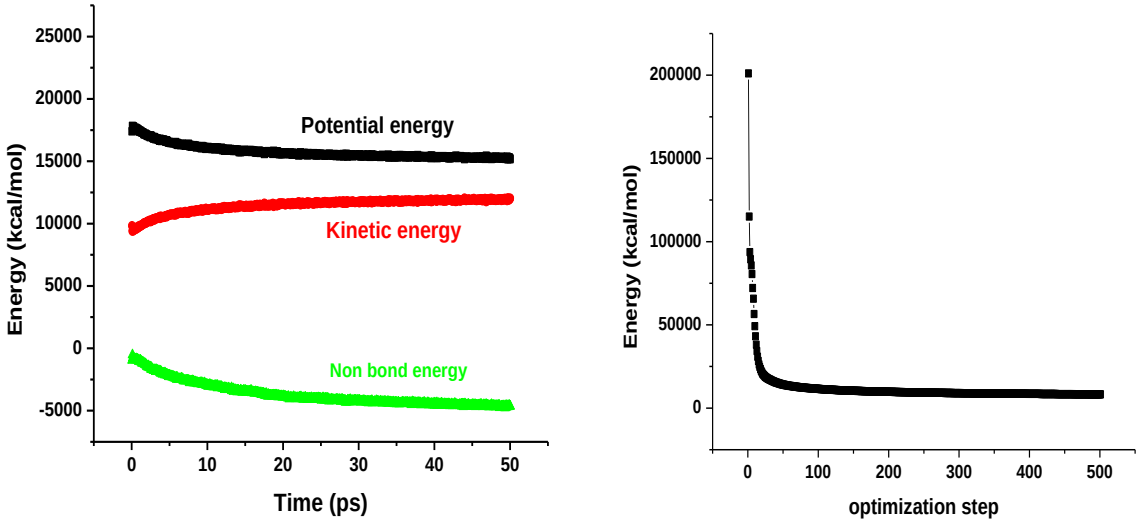


Fig5. (a) S-protein loaded with theanine after simulation (b) S-protein loaded with caffeine after simulation

The energy profile of MD simulation run for theanine loaded S-protein molecule is given in Fig 6 (a) where 6(b) gives the energy variation with energy optimization step.



(a) (b)

Fig 6: (a) Energy profile of MD simulation for theanine loaded S-protein. Black line indicates potential energy, red line-kinetic energy and green line, non-bond energy. (b) The energy variation in the optimization process is shown

Simulation energies like kinetic, potential, bond and non bond energies for all simulations are tabulated in Table 1

Table 1: *Simulation energies calculated for all simulations*

Name of the species	**MD Simulation energy (kcal/mol)**			
	Kinetic	**Potential**	**Bond**	**Non bond**
Hydroxychloroquine	29817.48	35599.39	11934.05	-861.89
Remdesivir	56046.60	57547.08	12664.29	1690.40
Oseltamivir	35150.56	41677.38	13225.84	219.33
Theanine	11461.46	15751.57	4876.41	-4644.81
Caffeine	18897.10	23424.14	7268.05	-3763.76
Nicotine	26647.32	30905.87	1977.83	3566.33

5 Conclusions

Modeling and simulation tells us the potential of a future medicine and possible remedies that may be used on Covid-19 virus attack. Three known medicines are taken for simulation of which remdesvir is found to be most effective among them to combat against COVID-19. HCQ and oseltamivir are effective to some extent to make its spike blunt but not capable of destroying the virus. Remdesivir can effectively break the S-protein contrary to the other two cases. Home remedy like tea, coffee etc are not so much effective. But theanine and caffeine have some potential as revealed in this study.

6 Declarations

6.1 Acknowledgements

The author acknowledges the contribution of NIT Durgapur for the commercial software Materials Studio

6.2 Competing Interests

The author declares that there is no potential conflict of interest in this publication.

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