International Journal of Traditional and Natural Medicines, 2020, 10(1): 13-23

Modern Scientific Press

International Journal of Traditional and Natural Medicines **ISSN: 2167-1141**

Journal homepage: www.ModernScientificPress.com/Journals/IJTNM.aspx *Florida, USA*

Article

In-vitro Investigation on Selected compounds in *Annona Muricata* Seed: A Potential SARS-CoV nsp12 Polymerase Inhibitors down Regulating 2019-nCoV

Oyebamiji Abel Kolawole[1,5*] Oladipo Elijah Kolawole*[2] , Olotu Titilayo Marbel[2], Awoyelu Hilda Elukunbi[3], Adamolekun Emmanuel[4] and Semire Banjo[5]

[1]*Department of Basic Sciences, Adeleke University, P.M.B. 250, Ede, Osun State, Nigeria* [2]*Department of Microbiology, Laboratory of Molecular of Biology, Immunology and Bioinformatics, Adeleke University, P.M.B. 250, Ede, Osun State, Nigeria*

[3]*Department of Natural Sciences, Precious Cornerstone University, P.M.B. 250, Ede, Osun State, Nigeria*

[4]*Department of Medical Laboratory Services, University of Medical Sciences, Teaching Complex, Akure, Ondo State, Nigeria*

[5]*Computational Chemistry Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria*

* Author to whom correspondence should be addressed; Email: abeloyebamiji@gmail.com and koladipo2k3@yahoo.co.uk

Article history: Received 30 January 2020, Revised 6 March 2020, Accepted 8 March 2020, Published 24 March 2020.

Abstract: Coronaviruses are dangerous micro-organism that attacks both the young and adults. Some are responsible for trifling diseases that occur in human respiratory organ while the famous ones (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)) are very dangerous and are capable of causing terrible respiratory disease. In a way to inhibit this life threatening virus, five molecular compounds obtained from *Annona Muricata* Seed which has been helpful to human being were studied via density functional theory method using Spartan, Discovery studio, AutoDock Tool, AutoDock Vina and Edupymol. In this study, the calculated descriptors (highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), dipole moment, energy band gap, area, volume, polarizability, polar

surface area, Log P, hydrogen bond donor, hydrogen bond acceptor) obtained from optimized compounds were observed to describe anti-SARS-CoV nsp12 polymerase. Also, the docking study exposed the inhibiting ability of the studied compounds. The calculated binding affinity are -5.1 kcal/mol, -4.5 kcal/mol, -4.4 kcal/mol, -5.6 kcal/mol, and -4.7 kcal/mol for compounds **A-E** and it was observed that the calculated binding affinity values were closer and this is sign that the selected compounds in *Annona Muricata* seed are promising anti-SARS-CoV nsp12 polymerase. Therefore, the selected compounds from *Annona Muricata* seed have a promising ability to inhibit SARS-CoV nsp12 polymerase thereby inhibiting 2019-nCoV.

Keywords: *Annona Muricata*, 2019-nCoV, SARS-CoV nsp12 polymerase, inhibitor, DFT

1. Introduction

Wide use of plant extracts either from leaves, back, seed, flowers and roots in treating various kinds of diseases have gained attention globally (Wang *et al*., 2004). Most of the drug-like molecules present in plants still remain one of the imperative means of support to human health worldwide (Sejal *et al*., 2016). Also, many researchers have confirmed plant products with proficient biological significance to be foundation for well-being conservation (Ana et al., 2016). Various anti-microbial agents that originated from plants have drawn the attention of several researchers and this could be due to their safety and elongated history of practice (Stohs and Hartman 2015).

Moreover, *Annona muricata L.* is a tropical fruit-bearing tree usually found in some parts of the world (Gajalakshmi *et al.*, 2012). Many information have been revealed by various scientists from different laboratories on the medicinal use of *Annona muricata L.* such as anticancer, anti-diabetes, anti-inflammation, anti-diarrhoea, anti-cold fever, anti-rheumatism, anti-neuralgia and anti-hypertensive agents etc. (Joseph *et al*., 2019; Yajid *et al.*, 2018).

The recent occurrence of coronavirus in some part of China and other parts of the world (Japan, United States of America, Thailand, Korea, Singapore and Vietnam) has been a serious challenge to scientists globally. It poses a grave threat to human life and various animals via infection of their respiratory organs as well as their central nervous system (Yu et al., 2020; Ge et al., 2013; Chen et al., 2016). Due to this fast spreading virus, over 100 patients have been reported to be infected and above 5 patients have been reportedly deceased (Zhang *et al*., 2020).

Therefore, this work is aimed at observing the molecular interactions between *Annona Muricata* Seed and SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur) (Robert et al., 2019) as well as probing in to the descriptors with anti-SARS-2019CoV nsp12 polymerase activities.

2. Computational Details

2.1. Quantum Chemical Method

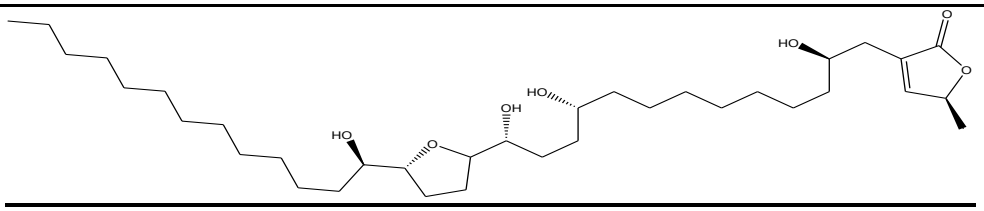
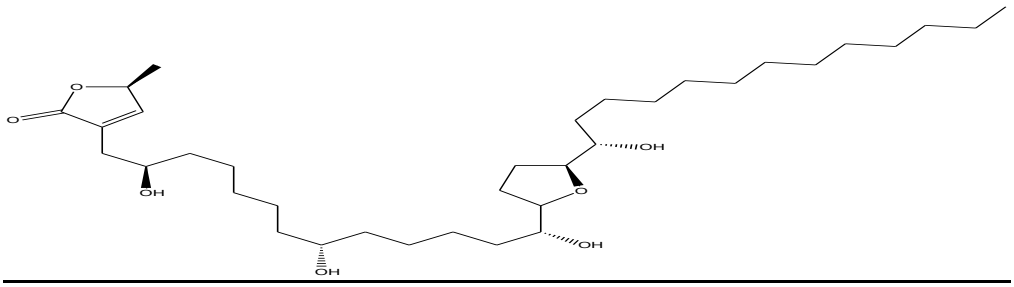
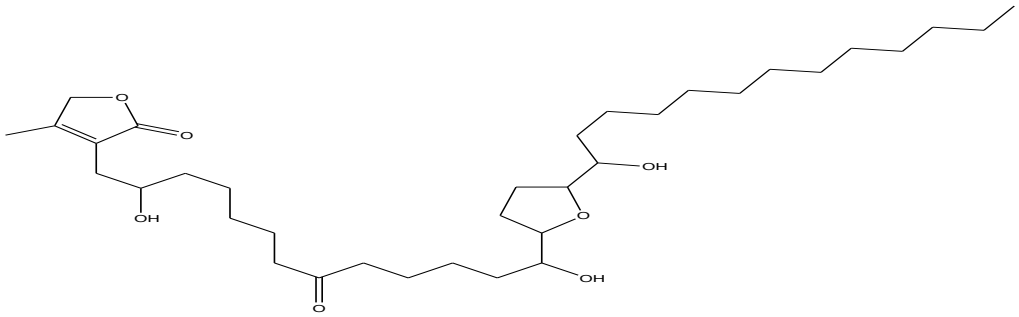
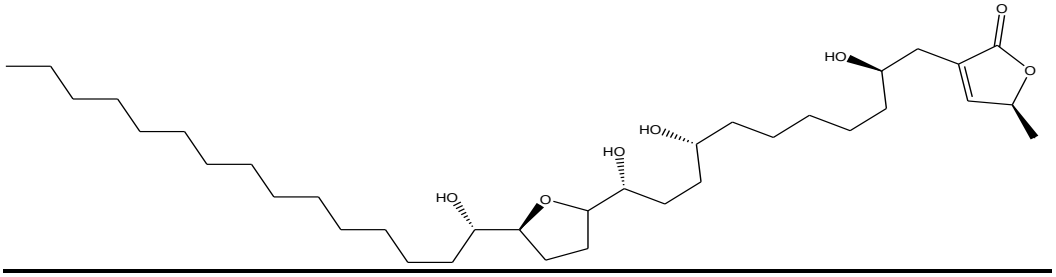
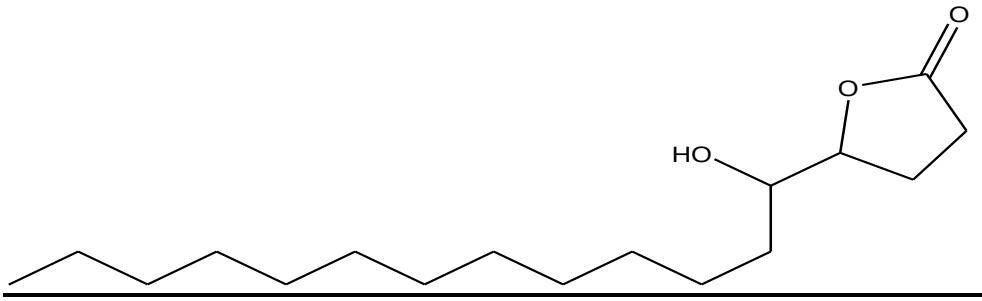
Selected compounds from *Annona Muricata* seed were optimized at density functional theory level using 6-31G* as basis set. Series of descriptors such highest occupied molecular orbital energy, lowest unoccupied molecular orbital energy, band-gap, dipole moment, log P, etc. were obtained from the optimized studied compounds. All the quantum chemical calculation was executed via Spartan 14 program (David et al., 2002).

2.2. Molecular Docking Study

The selected optimized compounds from *Annona Muricata* seed were docked against SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur) so as to examine the molecular interactions existing between the docked complexes. In this work, series of docking software (Discovery studio 2017, AutoDock Tool 1.5.6, AutoDock Vina 1.1.2 and Edupymol version 1.7.4.4) were used for effective docking investigation. The studied receptor (SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur)) was prepared using pymol. The binding site in SARS-2019 CoV nsp12 polymerase was located using AutoDock Tool for easy docking of the ligands into the active site of the receptor and the docking calculation was implemented via AutoDock Vina. The observed interactions were viewed using Discovery studio 2017. The observed grid box was as follows: center (X = 146.687, Y = 147.922, Z = 147.365) and size (X = 34, Y = 54, Z = 42).

The studied compounds obtained from *Annona Muricata* seed are (2*S*)-2-methyl-4-[(2*R*,10*R*,13*R*)-2,10,13-trihydroxy-13-[(2*R*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]oxolan-2-yl]tridecyl]-2*H*-furan-5-one (**A**), (2*S*)-2-methyl-4-[(2*R*,8*R*,13*R*)-2,8,13-trihydroxy-13-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]oxolan-2-yl]tridecyl]-2*H*-furan-5-one (**B**), 3-{2,13-dihydroxy-13-[5-(1-hydroxytridecyl)oxolan-2-yl]-8-oxotridecyl}-4-methyl-2,5-dihydrofuran-2-one (**C**), (2*S*)-2-methyl-4-[(2*R*,8*R*,11*R*)-2,8,11-trihydroxy-11-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxypentadecyl]oxolan-2-yl]undecyl]-2*H*-furan-5-one (**D)** and 5-(1-hydroxytridecyl)oxolan-2-one (**E**) (Table 1).

Table 1. The schematic structure of the studied compounds

	Structure
A	
B	
C	
D	
E	

3. Result and Discussion

3.1. Density Functional Theory Calculations

The studied compounds in this work were carefully selected and the contribution of each molecular descriptor obtained after optimization were investigated.

In this study, the investigated descriptors are highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), dipole moment, energy band gap, area, volume, polarizability, polar surface area, Log P, hydrogen bond donor, hydrogen bond acceptor (Table 2).

Table 2: Calculated molecular descriptors of the studied compounds

	E_{HOMO}(eV)	E_{LUMO}(eV)	BG	DM	MW	LOG P	OVA	PSA	POL	HBD	HBA
A	-6.74	-1.00	5.74	10.40	596.89	6.80	1.98	95.53	94.96	4	6
B	-6.69	-1.14	5.55	9.82	596.89	6.80	1.98	97.35	95.03	4	6
C	-6.66	-1.15	5.51	8.38	594.87	6.95	1.98	91.71	94.65	3	6
D	-6.75	-1.00	5.75	9.90	568.83	5.96	1.94	95.53	91.99	4	6
E	-7.17	-0.03	7.14	4.86	284.44	4.54	1.61	41.29	66.74	1	2

Note: BG: band-gap (E_{LUMO}-E_{HOMO}), DM: Dipole Moment, MW: molecular weight, OVA: Ovality, POL.: Polarizability, HBD: hydrogen bond donor, HBA: hydrogen bond acceptor.

The role played by dipole moment in drug compound-protein complex cannot be over emphasized [13]. The standard range for dipole moment of any drug-like molecule is 3-5 kJ/mol; therefore, compound **E** is expected to have a strong non-bonded interaction with SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur). Also, lipophilicity (Log P) exposes the dissolving ability of drug in lipophilic media (Khaled et al., 2011). The accepted standard for Log P is ≤5 and any drug-like molecule with greater Log P value may cause problems in oral absorption of such compounds (Meanwell 2011). Thus, compound **E** is expected to accurately dissolve in non-aqueous substance. Also, the calculated HBD and HBA shows that the studied compounds possess anti-SARS-2019 CoV nsp12 polymerase ability since the calculated value is lesser than the standard i.e. **≤ 5 and ≤ 10 respectively.**

Furthermore, E_{HOMO} define the propensity of molecules to donate electron to the nearby compounds. The calculated E_{HOMO} are -6.74 **(A)**, -6.69 **(B)**, -6.66 **(C)**, -6.75 **(D),** and -7.17 **(E)**. The calculated value for compound **C** revealed its ability to donate electron to the nearest compounds; therefore, it is expected to inhibit than other selected molecules (Oyebamiji and Semire 2016). The calculated E_{LUMO} shows the capability of molecules to receive electron from nearby molecules (Oyebamiji et al., 2018). Therefore, compound **E** with -1.15eV should possess greater ability to inhibit

the studied receptor than other studied compounds. Other studied calculated descriptors were displayed in Table 2. Moreover, band-gap (E_{LUMO} - E_{HOMO}) reveals the rate of reactivity of molecules. According to Semire *et al*., 2012, lower band-gap brings about easy excitation and thereby leads to better reactivity of molecules (Semire et al., 2012); thus, compound C with lower band-gap value is expected to react better than other studied compounds. Figure 1 show the E_{HOMO}-E_{LUMO} overlay.

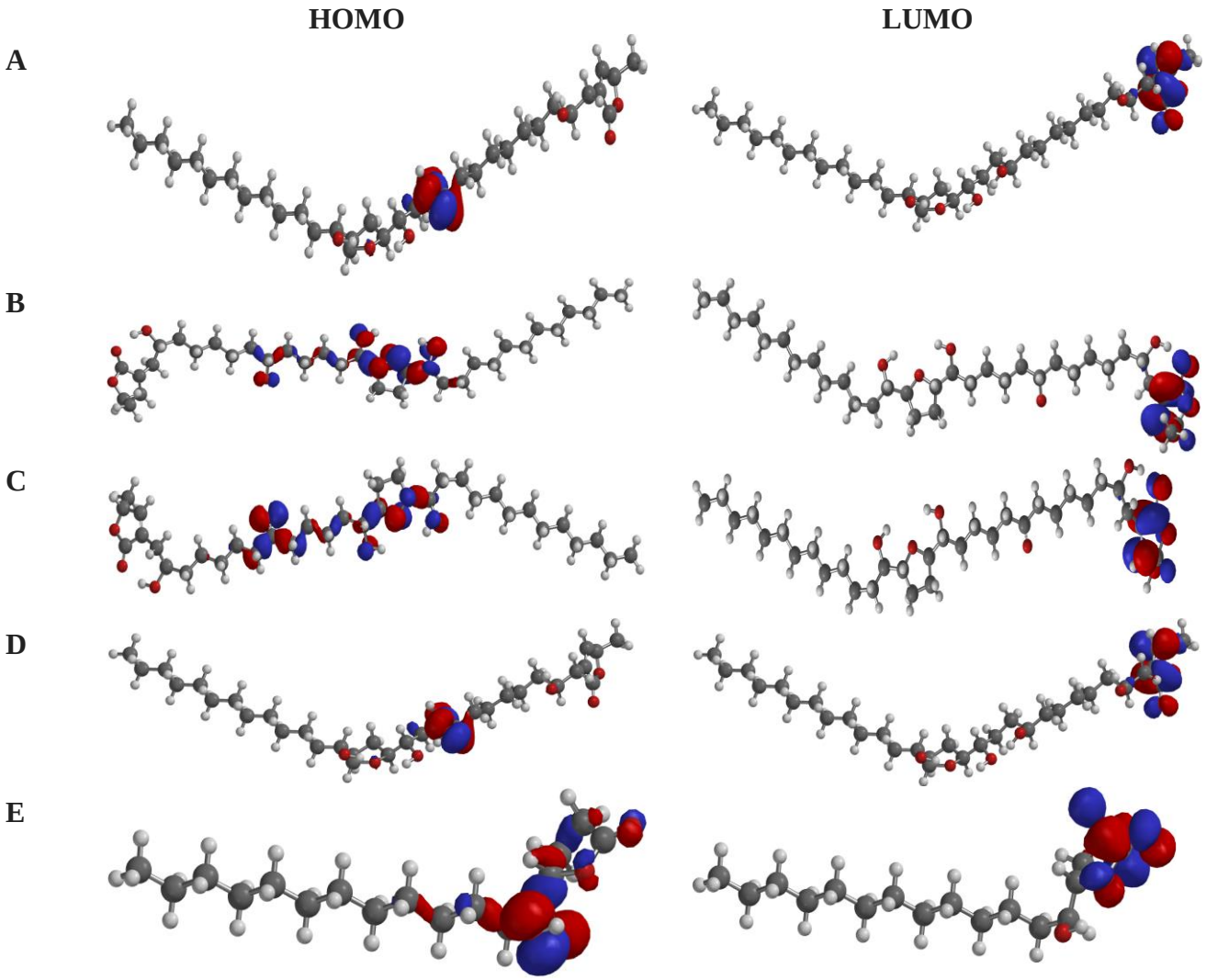


Figure 1: Studied E_{HOMO}-E_{LUMO} overlay

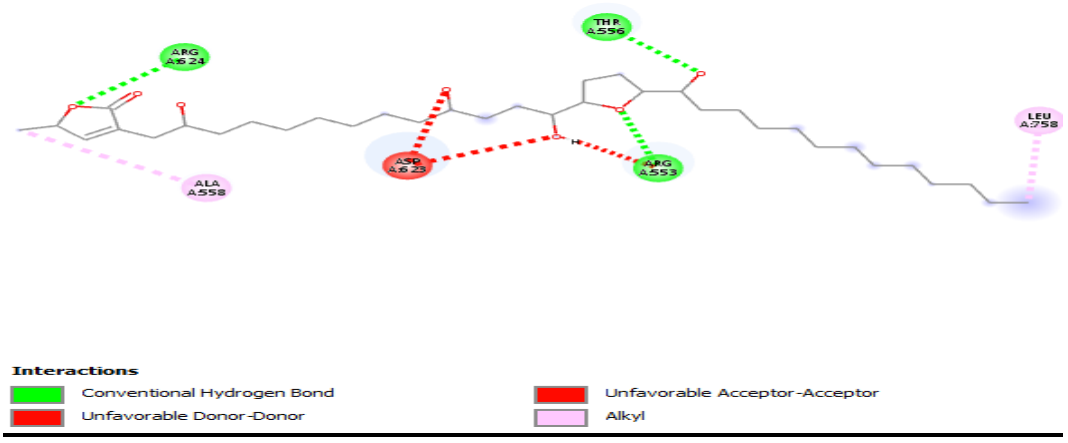
3.2. Molecular Docking Results

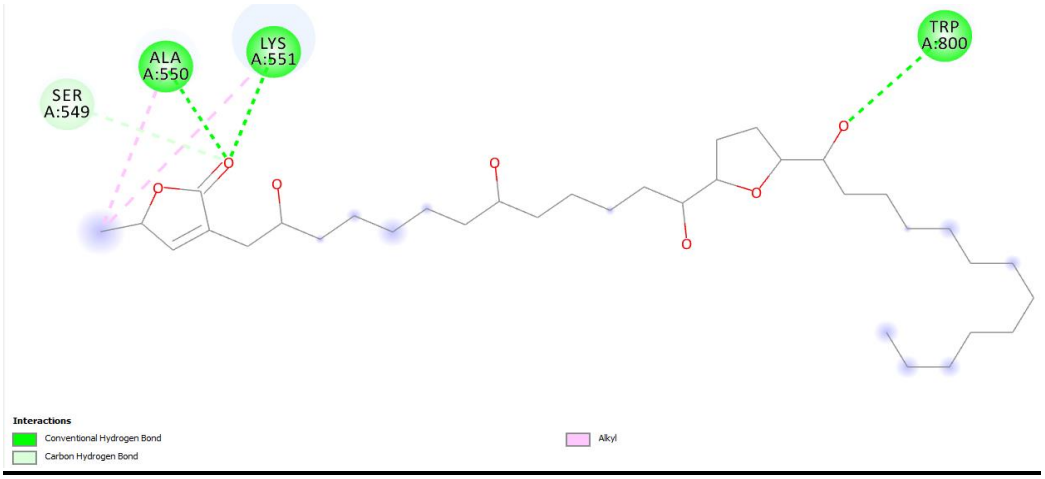
The selected molecular compounds from *Annona Muricata* seed were docked against SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur) in order to examine the non-bonding interaction present in the studied complex. The calculated binding affinity ranges from -5.6 to -4.4 kcal/mol and this

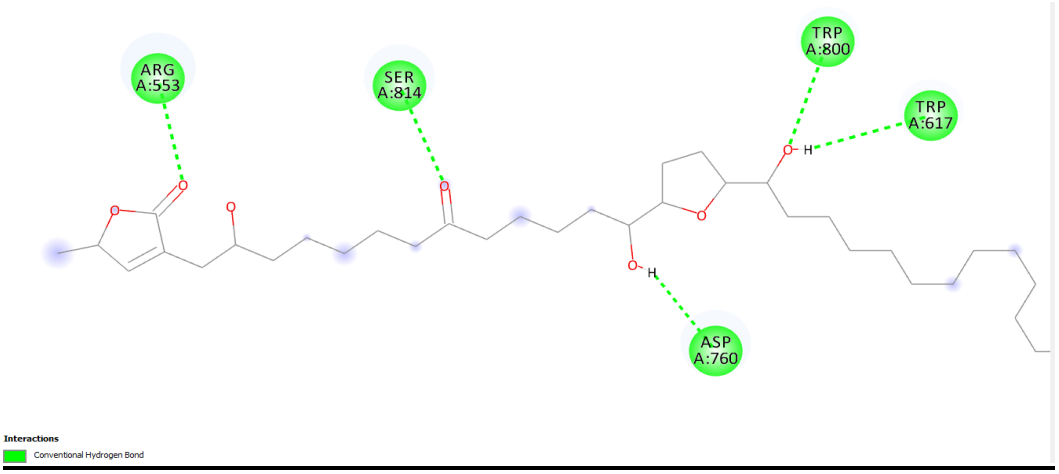
indicated that the studied compounds have a promising inhibiting activity. The calculated binding affinity from *Annona Muricata* seed - SARS-2019 CoV nsp12 polymerase complex were all negative and this indicated that the molecules understudy could serve as starting point for developing effective drugs targeting SARS-2019 CoV nsp12 polymerase thereby reducing coronavirus. The residue involve in each conformation are ARG-624, THR-556, LEU-758, ALA-558, ASP-623, ARG-553 for **A**; SER-549, ALA-550, LYS-551, TRP-800 for **B**; ARG-553, SER-814, TRP-800, TRP-617, ASP-760 for **C**; ALA-558, ARG-624, THR-556, TYR-455, LYS-621, ASP-452 for **D** and ARG-249, ASN-459, PHE-396 for **E** (Table 3) (Figure 2). Also, the common non-bonding interactions observed in this study is hydrogen bond and this confirms the inhibiting efficiency of the studied compounds against SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur).

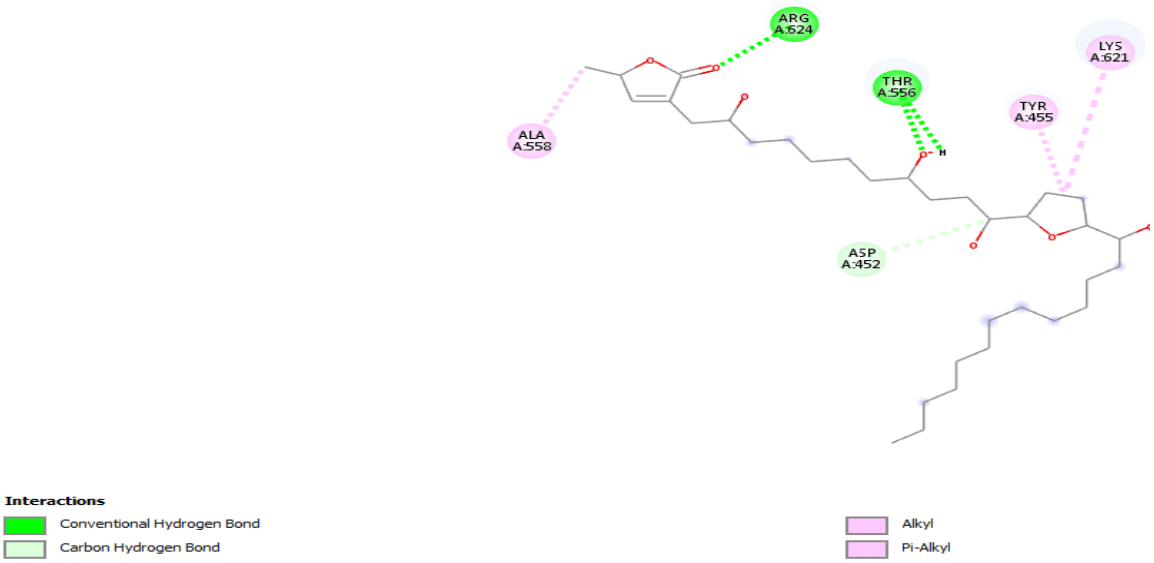
Table 3: Scoring of selected compounds in *Annona Muricata* seed with SARS-2019 CoV nsp12 polymerase (PDB ID: 6nur)

	Binding Affinity (kcal/mol)	**Amino Acid Residue**
A	-5.1	ARG-624, THR-556, LEU-758, ALA-558, ASP-623, ARG-553
B	-4.5	SER-549, ALA-550, LYS-551, TRP-800
C	-4.4	ARG-553, SER-814, TRP-800, TRP-617, ASP-760
D	-5.6	ALA-558, ARG-624, THR-556, TYR-455, LYS-621, ASP-452
E	-4.7	ARG-249, ASN-459, PHE-396









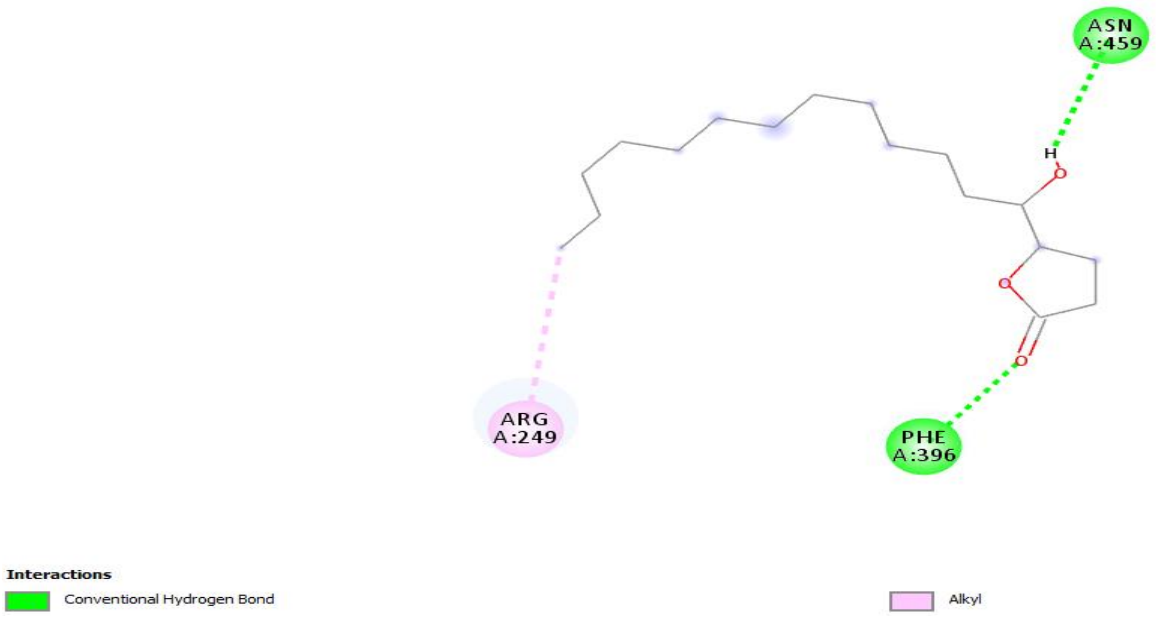


Figure 2: Binding interaction of compound A, B, C, D and E with 6nur respectively

4. Conclusion

In this work, anti-SARS-2019 CoV nsp12 polymerase activity of selected compounds obtained from *Annona Muricata* seed was investigated using density functional theory as well as docking method. The calculated descriptors described the anti-SARS-2019 CoV nsp12 polymerase activity and this was validated using docking method. The obtained binding affinity ranges from -5.6 to -4.4 kcal/mol and this showed that the selected compounds have a promising inhibiting activity.

References

Ana V. Coria-Te´ llez, Efigenia Montalvo-Go´ nzalez, Elhadi M. Yahia, Eva N. Obledo-Va´ zquez. Annona muricata (2016). A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. *Arabian Journal of Chemistry*, 11(5).

Chen, Y. and D. Guo (2016), Molecular mechanisms of coronavirus RNA capping and methylation. *Virol Sin*, 31(1): 3-11.

David, F.L.L. and Howard, B.B. (2002). Molecular binding interactions: their estimation and rationalization in QSARs in terms of theoretically derived parameters, *the sci world Journal* 2:1776 -1802.

Gajalakshmi S, Vijayalakshmi S, Rajeshwari Devi V. (2010). Phytochemical and Pharmacological Properties of *Annona muricata*: A Review, *Int J Pharm Sci.* 4(2): 3-6.

Ge, X.Y., et al. (2013). Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*, 503(7477): 535-8.

Joseph Nana Gyesi, Rita Opoku, and Lawrence Sheringham Borquaye (2019). Chemical Composition, Total Phenolic Content, and Antioxidant Activities of the Essential Oils of the Leaves and Fruit Pulp of *Annona muricata* L. (Soursop) from Ghana. *Biochemistry Research International*, Volume 2019, Article ID 4164576, 9 pages

Khaled, A., Petri, R., Sampo, M., Olavi, P. (2011). Metabolism of α-Thujone in human hepatic preparations in vitro. *Xenobiotica*, 41:101-111.

Meanwell, N. A (2011). Synopsis of some recent tactical application of biostereses in drug design. *Journal of medical chemistry*, 54(8): 2529 - 2591.

Oyebamiji Abel Kolawole and Semire Banjo (2016). Dft-Qsar Model and Docking Studies of Antiliver Cancer (Hepg-2) Activities Of 1, 4-Diydropyridine Based Derivatives. *Cancer Biology*, 6(2): 69-78.

Oyebamiji Abel Kolawole, Folashade O. Oyedeji, Isaiah A. Adejoro and Babatunde Benjamin Adeleke (2018). Anti-Fungal Activities Of 2,4-Dintrophenyl Hydrazones Derivatives: DFT and Docking Approaches. *Academia Arena*, 10(6): 2-16.

Robert N. Kirchdoerfer & Andrew B. Ward (2019). Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nature communications*, 10: 2342. https://doi.org/10.1038/s41467-019-10280-3.

Sejal P., Jayvadan K Patel (2016). A review on a miracle fruits of *Annona muricata*, *Journal of Pharmacognosy and Phytochemistry*, 5(1): 137-148.

Semire B., Oyebamiji A. and Ahmad M. (2012). Theoretical Study on Structure and Electronic Properties of 2, 5-Bis [4-N, N-Diethylaminostyryl] Thiophene and Its Furan and Pyrrole Derivatives Using Density Functional Theory (Dft). *Pak. J. Chem.* 2(4): 166-173.

Stohs, S.J. and Hartman, M.J. (2015). Review of the safety and efficacy of *Moringa oleifera*. *Phytother Res* 29: 796-804.

Wang W, Vinocur B, Shoseyov O, Altman A (2004). Role of plant heat-shock proteins and molecular chaperones in the abiotic stress response. *Trends Plant Sci.,* 9: 244-52.

Yajid AI, Ab Rahman HS, Wong MPK, et al (2018). Potential benefits of *Annona muricata* in combating cancer: A review. *The Malaysian journal of medical sciences*: *MJMS*, 25(1):5.

Yu Chen, Qianyun Liu, Deyin Guo (2020). Coronaviruses: genome structure, replication, and pathogenesis. *Journal of Medical virology*, 2020, 10.1002/jmv.25681

Zhang, N. *et al.* Recent advances in the detection of respiratory virus infection in humans. *J Med Virol,* doi:10.1002/jmv.25674 (2020).