Molecular Docking and Computational Exploration of Isolated Drugs from *Daphne* Species Against COVID-19

Irfan, Ahmad*[*+•]*; Imran, Muhammad***

Research Center for Advanced Materials Science (RCAMS), King Khalid University, P.O. Box 9004, Abha 61413, SAUDI ARABIA

Mumtaz, Muhammad Waseem

Department of Chemistry, University of Gujrat, Gujrat-50700, PAKISTAN

Raza Basra, Muhammad Asim

Center for Clinical and Nutritional Chemistry, School of Chemistry, University of Punjab, New Campus, Lahore, PAKISTAN

ABSTRACT: *The SARS-CoV-2 has initiated in Wuhan city of China and then extend all around the world as a health emergency. It begins a new research area to produce potential drugs using data-driven approaches to identify potential therapies for the treatment of the virus. This is the time to develop specific antiviral drugs using molecular docking, quantum chemical approaches, and natural products. The protease inhibitors that constitute plant derivatives may become highly efficient to cure virus-prompted illnesses. A systematic study of isolated phytochemicals was executed then frontier molecular orbitals, docking score, molecular descriptors, and active sites were compared with favipiravir, dexamethasone, redeliver, and hydroxychloroquine which are being used against COVID19 nowadays. This is the first study on the phytochemicals of Daphne species to explore their anti-SARS-CoV-2 behavior by molecular docking and quantum chemical methods.*

KEYWORDS: *COVID-19; Bio-guided isolation; Daphne; Molecular docking; Quantum chemical exploration; In-silico studies.*

INTRODUCTION

The coronaviruses belong to the genus Betacoronavirus, single-stranded ribonucleic acid (RNA) is a part of the virus's large family in order to common cold cause within the human beings. Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and recently SARS-CoV-2 are coronavirus family members that cause

***** *To whom correspondence should be addressed.*
+ E-mail: *irfaahmad@gmail.com*
● *Other Address: Department of Chemistry, College of Science, King Khalid University, P.O. Box 9004, Abha 61413, SAUDI ARABIA*
1021-9986/2021/6/2019-2027 9/$/5.09

life-threatening symptoms [1, 2]. The SARS-CoV-2 (COVID 19), which was discovered in humans, caused a pandemic due to its greater ability to inter-transfer with humans. The possible SARS-CoV-2 drug targets include papain related to protease (PLpro) related to protease (3CLpro), RNA-reliant on RNA polymerase, and spike (S) proteins [3]. The S proteins immediately bind to human angiotensin-converting enzyme 2 (ACE2), allowing the virus to enter the cells. Viruses' RNA polymerase is prepared for rapid mutation, as well as the ability to withstand clinically available antiviral drugs, resulting in global communal and economic consequences accompanying unexpected illnesses, deaths, and disturbing daily ordinary life activities. As a result, restraining SARS-CoV-2 protein is critical for reducing host receptor maneuverability. The study objectives include determining the inhibitory potential of isolated natural phytochemicals against the SARS-CoV-2 prime protease (6LU7) protein. The arrangement of SARS-CoV-2 6LU7 proteins has recently been tracked using the Worldwide Protein Data Bank [4].

Natural phytochemicals are rich in chemical diversity and antiviral activity, making them useful as therapeutic active ingredients against coronavirus disease. Bonducellpin D, a promising drug candidate isolated from *Caesalpinia bonduc*, demonstrated broad-spectrum inhibition potential against MERS-CoV (M^{pro}) and SARS-CoV (M^{pro}) [4]. Natural products psoralidin, tryptanthrin, quercetin, Silvestro L, myricetin, isobavachalcone, scutellarein, caffeic acid, and saikosaponin B_2 exhibited significant inhibition against coronavirus [5]. Plant extracts and isolated natural products were used to develop effective antiviral drugs based on their binding energy score against coronaviruses as determined by molecular docking [6]. Natural products derived from traditional herbal medicines may influence the development of novel antiviral drugs. Furthermore, during the COVID-19 pandemic in China, patients were treated with traditional Chinese medicinal therapies in addition to western medicine [7]. Natural products benzo-a-pyrone (coumarins) derivatives widely distributed in nature are considered as a novel agent that possesses large affinity as well as specificity to several molecular targets for antiviral agents based on unique characteristic protein-ligand binding designing [8]. The current study demonstrates coumarins' therapeutic potential against COVID-19 and summarizes the detailed Structure-Activity Relationship (SAR). Coumarins inhibit a wide range of target proteins and enzymes. Coumarins have cytotoxic, anti-Alzheimer, antitumor, anticancer, anti-inflammatory, antimicrobial, and antioxidant inhibitory activities. Coumarins are isolated from the *Daphne* genus of the Thymlelaeaceae family, which contains more than 15 genera and 500 species. The *Daphne* genus has well-known biological and enzymatic potential [9]. Phytochemical studies on *Daphne feddei* and *Daphne mucronata*, resulted in the isolation and structure elucidation of twelve (**1-12**) phytochemicals. These are named as 6-hydroxy-7-methoxycoumarin **(1)**, 6, 7-dihydroxycoumarin **(2)**, 6, 7, 8-trihydroxycoumarin **(3)**, 6-hydroxy-3-(4-hydroxyphenyl)-7-methoxy-2*H*-chromen-2-one **(4)**, 6-hydroxy-5-methoxy-7-methyl-3-(4-methoxyphenyl)-coumarin **(5)**, decursinol (**6**), 5, 5′-bi (6, 7- dihydroxycoumarin) (**7**), 6,6′,7,7′-tetrahydroxy-5,8′-bicoumarin (**8**), 9'-hydroxy (8'*S*)-3,4,3',4'-dimethylenedioxycoumarinlignan (**9**), 6,7-furanocoumarin (**10**), 8-isopent-2-enyloxy-6,7-furanocoumarin (**11**) and 5-hydroxy-8-(3'-methyl-2'-butenyl) furocoumarin (**12**), shown in Fig. 1. Preliminary *in silico* drug screening has proven to be useful to overcome challenges and identifying potential candidates.

As far as we know, inhibition impact of examined molecules from *Daphne feddei* and *Daphne mucronata* is the first report on COVID-19 by molecular docking. The exploration of active drugs against COVID-19 is important. We have explored active phytochemicals which can inhibit SARS-CoV-2. For this purpose, we have shed light on molecular descriptors, Electron Affinity (EA), Ionization Potential (IP), Molecular Electrostatic Potential (MEP), frontier molecular orbitals (FMO), molecular docking score, the interaction of the ligand with 6LU7 protein of SARS-CoV-2 and reactive sites of phytochemicals. The result of this study showed that these phytochemicals would be active which can prevent SARS-CoV-2.

EXPERIMENTAL SECTION

General

Silica gel (mesh size: 230-400), Sephadex LH-20 used for column chromatography, TLC: silica gel 60-F_{254} plates (0.25- and 0.50-mm thickness) followed by spot detection at 254 nm under UV lamp. Butanol fraction isolation was done through recycling HPLC (JAIGEL ODS-M 80 column) were used. JASCO DIP-360 digital polarimeter

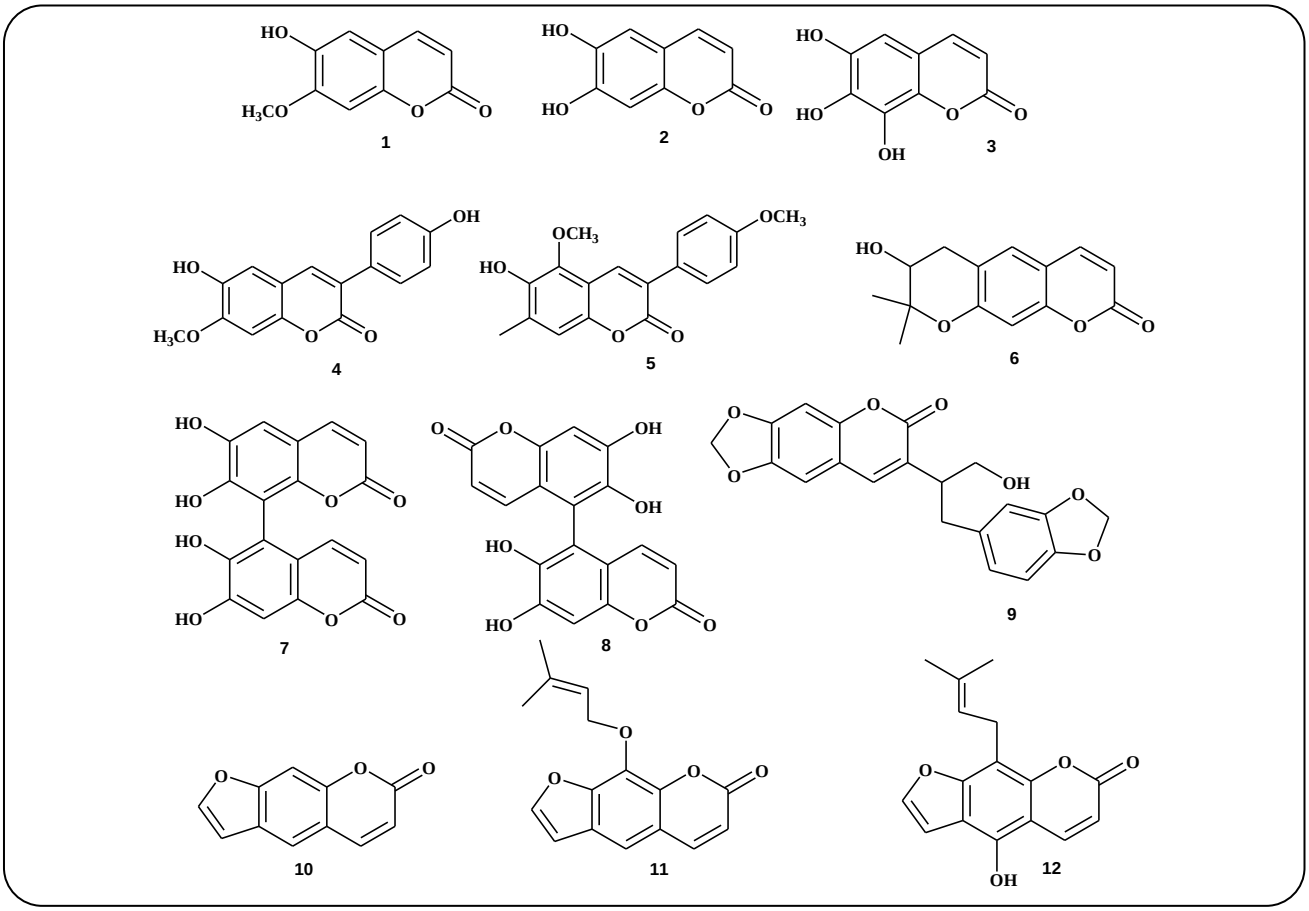


Fig. 1: Structures of isolated compounds 1-12.

used for optical rotations: *Hitachi UV-3200* spectrophotometer for UV spectra λ_{max} measured in nm: *JASCO 302-A* spectrometer for IR spectra with wavenumber in cm^{-1}. EI-MS with *Finnigan MAT 312* MS and HR-EI-MS noted with JEOL JMS-HX 110 MS. Bruker AM-400 spectrometer in deuterated solvents ($CDCl_3$) with TMS as internal standard was used for ^1H and ^{13}C NMR spectra.

Extraction and isolation

The withered *Daphne feddei* aerial parts (6 kg) were pulverized and extracted with CH_3OH thrice at room temperature (r.t.). The solvent was evaporated under reduced pressure to give CH_3OH extract, which was dissolved in H_2O and extracted with *n*-hexane, CH_2Cl_2, AcOEt, BuOH, and H_2O sub-fractions. The CH_2Cl_2 soluble sub-fraction was undergo CC using silica gel as adsorbent, elution with *n*-hexane-CH_2Cl_2-CH3OH gradient system to provide sub-fractions A–F. The separation of fraction B hexane:CH_2Cl_2 (5.0:5.0) with column chromatography using adsorbent silica gel, eluting with the same mobile phase, yielded compound **(1)**. The fraction C, obtained with *n*-hexane:CH_2Cl_2 (4.0:6.0) was re-chromatographed over silica gel, with the same mobile system to obtain compounds **(2)** and **(3**) respectively. The fraction D obtained with hexane:CH_2Cl_2 (4.0:6.0) was triturated with acetone to obtain bicoumarin (**7**) and (**8**). The fraction E, obtained with pure CH_2Cl_2, undergoes CC eluted with *n*-hexane:CH_2Cl_2 (0.5:9.5) to provide Furanocoumarin (**10**) along with decursinol (**6**). The dried, crushed aerial *Daphne mucronata* (5 kg) were extracted with 80 % CH_3OH (3 x 6 L, 5 days each) at r.t. The CH_3OH extract under reduced pressure within rotavapor was evaporated to yield green blackish residue and further divided into *n*-hexane, CH_2Cl_2, EtOAc, and BuOH after dissolved in H_2O. The *n*-BuOH sub-portion undergoes CC over silica gel (adsorbent) elution with CH_2Cl_2-CH_3OH in increasing order of polarity to acquire three main fractions (A-C). Fraction A (CH_2Cl_2:CH_3OH, 9.0:1.0) underwent reverse-phase CC over Sephadex LH-20 using

CH_3OH:H_2O (5.0:5.0) and H_2O as mobile phase affords two major fractions A and B. The fraction A that was eluted with CH_3OH, was subjected to reverse-phase CC over silica gel with the same H_2O-CH_3OH mobile system to give a crude mixture and pure compound coumarinlignan (**9**). The recycling HPLC (M-80 column) used to purify the obtained mixture through isocratic mode (eluent, CH_3OH:H_2O 5.0:5.0, flow rate;4 mL/min) provided compounds **(4)** and **(5)** respectively. Fraction B was subjected to reverse-phase flash CC over silica gel using H_2O-CH_3OH (4.0:6.0) and recycling HPLC (eluent, CH_3OH;H_2O 4.0:6.0, flow rate 4 mL/min) to give furanocoumarin (**11**) and (**12**) respectively.

Computational details

In biological sciences, Density Functional Theory (DFT) is a fascinating method to analyze numerous important properties [10, 11]. The DFT analysis is scientifically accustomed to investigating the electronic characteristic of molecules [12-16]. It's a persistent methodology in order to do geometries optimization within the ground state (S_0) [17, 18]. The B3LYP is a coherent functional for the S_0 geometries of numerous biologically active molecules. In current investigations regarding S_0 geometries optimizations as well as electronic characteristics, we adopted B3LYP/6-31G** within software Gaussian16 [19]. The calculations were done for a single molecule in the gas phase. Additionally, molecular docking was performed by Autodock version 4.2 [20] and MGL tools by deleting water molecules and adding polar hydrogen atoms. The compound was inserted in 6LU7 protein then an auto grid was developed in X, Y, and Z-axis directions.

RESULTS AND DISCUSSION

The CH_3OH extract of *Daphne feddei was* partitioned into hexane, CH_2Cl_2, EtOAc, and BuOH, H_2O sub-fractions. The CH_2Cl_2 fraction was subjected to chromatographic separations as described in the experimental part to obtain seven constituents. Isolation of compound focused only TLC spot detection under UV lamp with blue fluorescence at 254 nm along with UV absorption (max = 320 nm), suggesting coumarin phytochemicals. Based on spectral and literature data the isolated phytochemicals could be identified as 6-hydroxy 7-methoxycoumarin (M.F: $C_{10}H_8O_4$), 6, 7-dihydroxycoumarin (M.F: $C_9H_6O_4$), 6, 7, 8-trihydroxycoumarin (M.F: $C_9H_6O_5$), decursinol (M.F: $C_{14}H_{14}O_4$), 5, 5′-bi (6, 7- dihydroxycoumarin) (M.F: $C_{18}H_{10}O_8$), 6,6′,7,7′-tetrahydroxy-5,8′- bicoumarin (M.F: $C_{18}H_{10}O_8$) and 6,7-furanocoumarin (M.F: $C_{11}H_6O_4$). All these phytochemicals have been reported for the first time from this species. The 80 % CH_3OH *Daphne mucronata* extract was partitioned into *n*-hexane, DCM, EtOAc, and *n*-butanol. The *n*-BuOH fraction was subjected to chromatographic techniques as described in the experimental part to obtain five compounds first time from this plant. These could be identified as 6-hydroxy-3-(4-hydroxyphenyl)-7-methoxy-2*H*-chromen-2-one (M.F: $C_{16}H_{12}O_5$), 6-hydroxy-5-methoxy-7-methyl-3-(4-methoxyphenyl)- coumarin (M.F: $C_{18}H_{16}O_5$) 9'-hydroxy(8'*S*)-3,4,3',4'- dimethylenedioxycoumarinlignan (M.F: $C_{20}H_{16}O_7$), 8-Isopent-2-enyloxy-6,7-furanocoumarin (M.F: $C_{16}H_{14}O_4$) and 5-Hydroxy-8-(3'-methyl-2'-butenyl) furocoumarin (M.F: $C_{16}H_{14}O_4$), respectively.

Daphne feddei showed anti-HIV-1 inhibition comparison to cell line C8166 with (EC_{50} = 5.58 mg/mL) as well as potent cytotoxic cell lines (Hep-G2, KB, MDA-MB-231, and HL60) and anti-inflammatory inhibition. *Daphne mucronata* was found to have antimicrobial, TNF-α release (monocytes), anti-tumor (rats), cytotoxic, anti-tuberculosis and antioxidant properties [9]. Coumarins inhibited angiotensin-converting enzyme (ACE) with high potency (IC_{50} = 4.68-20.04 μM). The ACE inhibition of coumarins was confirmed further using molecular docking analysis. The hydrogen bond along with hydrophobic correlations with catalytic remains as well as zinc ion of N- and C-domain ACE obstructed its catalytic activity [21]. The coumarinlignan (**9**) possesses a unique lignan-containing coumarin skeleton whose synthetic pathway is derived from conferyl alcohol. It showed good anti-HBV activity against HBeAg (48%) and HBsAg (57 %) compared with positive control lamivudine (46 and 10 % respectively). Moderate anti-fibrotic inhibition (71%) was observed against HSC-T6 cells along with a significant neuroprotective effect [22]. Furanocoumarins showed neuroprotective effects and anti-oxidant potential compared with positive control as Neuron Growth Factor (NGF) and edaravone, a reactive oxygen species scavenger [23]. Furanocoumarins (**10**-**12**) also inhibit β-secretase (BACE1) activity in which C-7 substitution

with prenyloxy group seems to be very important. As psoralen (10), lacks benzene ring further replacement with polar moieties, established lower activity (>500 (19.3%) with IC_{50} = >500). The furocoumarin (**12**) showed significant inhibition (91.8 ± 8.2b with IC_{50} = 11.1) because of prenyloxy group substitution within C5 or C8 position [24]. The significant anti-TMV bioactivity through inhibition rate of 28.6% was observed within compounds **(4)** and **(5)** class compared with standard ningnanmycin (32.2% inhibition) whereas other coumarin showed anti-TMV inhibition rates (13.7–23.2%) [25]. The coumarins **1-12** were screened *insilico* using first-principles methods and molecular docking in comparison with standard FDA-approved drugs to see if they inhibited the coronavirus protease protein.

Electronic properties

The highest occupied and lowest unoccupied molecular orbitals (HOMOs/LUMOs) of phytochemicals and reference compounds remdesivir, dexamethasone, favipiravir, and hydroxychloroquine are shown in Fig. S1. The HOMO is at C=O while LUMO at phenanthren in dexamethasone. In remdesivir, pyrrolotriazin is involving in HOMO formation whilst LUMO is at triazin-7-yl aminopyrrolo moiety. In hydroxychloroquine, HOMO was found at $–NH_2$ of (ethyl)aminoethanol whereas LUMO at quinolin. In favipiravir, HOMO was noticed at 6-fluoro-3-hydroxypyrazine however the LUMO at pyrazine-2-carboxamide. The ICT was observed from HOMOs to LUMOs in all the studied phytochemicals and reference compounds. The phytochemical's activity is also sternly accompanying to HOMOs/LUMOs density that predicts the preferable sites to be attacked by reactive species. In the studied phytochemicals, HOMOs/LUMOs charge distribution is revealing that these compounds would be active compounds. The energies of HOMO (E_{HOMO}), LUMO (E_{LUMO}), and energy gaps (E_{gap}) are significant which help to explore the electronic properties and activity of the phytochemicals which are tabulated in Table S1.

The global chemical reactivity descriptors (GCRD) are important to shed light on the activity of phytochemicals. In current work, different GCRD is estimated, e.g., softness (S), chemical potential (μ), electronegativity (χ), chemical hardness (η), and electrophilicity index (ω) (see details in SI). The aromaticity of phytochemical is interlinked to the η [26, 27]. The ω showed the energy of stabilization of phytochemical from the external environment by electrons. The μ exhibited an electronic trend to predicate on the electronic cloud. The η revealed the prevention degree of electronic cloud to alteration. The good anti-oxidant aptitude of phytochemicals can obstruct viral infections [28]. In such a case phytochemicals gave electrons to free radicals resulting in radical cation that has to be stable for good anti-oxidant capability. In a one-electron transfer mechanism, IP is important to probe the antioxidant ability of phytochemicals (IP= $-E_{HOMO}$). Previous work exposed that a smaller IP value would be suitable to increase the anti-oxidant ability [29]. The IP values of the isolated compounds are smaller than reference drugs except for hydroxychloroquine. Among various isolated compounds IP of Comp4, Comp5, Comp7, Comp9, and Comp12 are smaller/alike than/ reference drugs which disclosed that isolated compounds might have the virtuous antioxidant ability.

Molecular electrostatic potential

The Molecular Electrostatic Potential (MEP) is critical to envisage charged vicinity in phytochemicals (see SI file). The MEP surfaces of reference compounds and phytochemicals have been established in color, see Fig. S2. The red and blue shades ascertain state-of-the-art –ive in addition to +ive potential regions that could be favorable to electrophilic and nucleophilic attack. In dexamethasone –ive potential is on –O atoms at the same time as +ive at -H atoms of –OH. In remdesivir, –ive potential can be visible on –O atoms whilst +ive at -H atoms of $–NH_3$. In hydroxychloroquine, –ive potential is visible on -O atom of quinoline and -O atom of ethanol even as +ive potential at -H atoms of –OH and -NH. In favipiravir, –ive potential may be visible on -O atom while +ive potential at -H atoms carboxamide. In studied phytochemicals, –ive potential was observed on –O atoms while +ive one on –H atoms of –OH. The –ive/+ive potential on –O/–H atoms is revealing that these sites would be suitable for electrophilic/nucleophilic attack, respectively.

Molecular docking

As far as we know, no results already computed accompanying SARS-CoV-2 resistance using theoretical

studies of these compounds (**1-12**). The structure of the 6LU7 proteins of SARS-CoV-2 has been determined recently by Worldwide Protein Data Bank [4,18,29,30]. The virus core protease crystal structure in the complex (6LU7) without water molecules and inhibitor are shown in Fig. 2. The 6LU7 protein structure was fabricated using Autodock and a model outlining the docking analysis of molecules (**1-12**) along with studied standards drugs. The obtained docking results were prosperous in all phytochemicals Comp1-SARS-CoV-2 to Comp12-SARS-CoV-2 along with reference compounds, *i.e.*, dexamethasone-SARS-CoV-2, remdesivir-SARS-CoV-2, hydroxychloroquine-SARS-CoV-2, and favipiravir-SARS-CoV-2. The binding energy values between ligands and protein (active sites in the title compounds along with amino acids) are displayed in Table 1 and Figs. 3 and S3. The anti-SARS-CoV-2 activity from isolated compounds (**1-12**) within 6LU7 protein of SARS-CoV-2 established accordance with following sequence: Comp9 > Comp12 > Comp6 > dexamethasone > Comp5 > Comp4 > Comp8 >Comp10 > Comp11 > Comp7 > hydroxychloroquine > Comp1 > Comp2 > Comp3 > favipiravir > remdesivir. The Comp9 provided better anti-SARS-CoV-2 activity, accompanied by the Comp12 and Comp 6. The computation outcomes indicated in order that such 12 compounds have a powerful 6LU7 inhibition of SARS-CoV-2. The -ive DS energy was observed, in the order of −4.35 to −7.39 Kcalmol^{-1}. From Table 1, it can be found that Compounds 9, 12, and 6 might be good candidates which can be used specifically against SARS-CoV-2 as these phytochemicals showed better DS energy values. The binding sequence of isolated drugs with various amino acids has been tabulated in Table 1. The docking results are illuminating that these phytochemicals might be a good choice that can inhibit SARS-CoV-2. Consequently, it is favorable to use isolated phytochemical(s) or extract of *Daphne* species to treat COVID-19 patients.

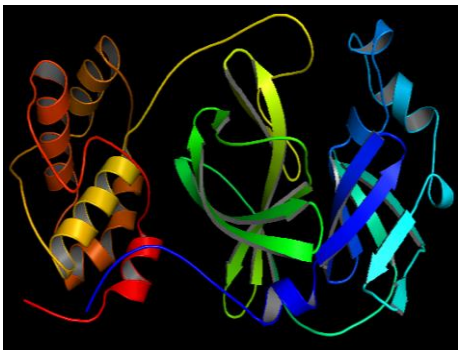
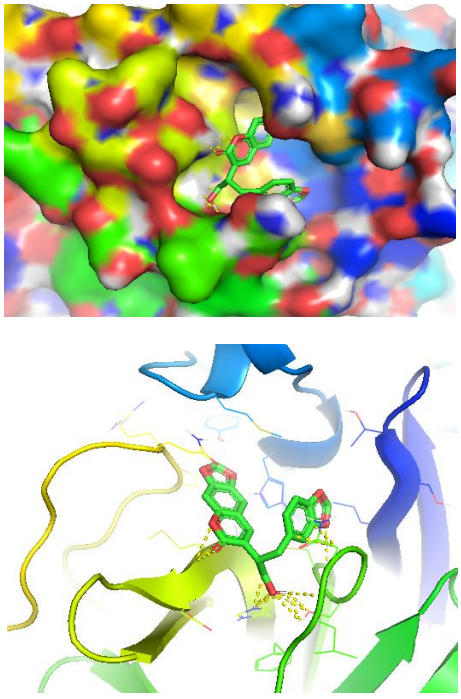


Fig. 2: Crystal structure of the virus main protease in the complex (6LU7) (water molecules and inhibitor N3 are removed for clarity).



Comp9

Fig. 3: Docking simulation of the interaction between isolated compounds, reference drugs, and the 6LU7 protein of SARS-CoV-2.

CONCLUSIONS

This study aims to develop a potential strategy for using plant/herbal extracts in general, and specifically, isolated phytochemicals, to combat the current pandemic SARS-CoV-2. The values of the E_{gap} and reactivity descriptors established that isolated compounds retain good reactivity. The ionization potential revealed that the studied compounds would have a good antioxidant ability, which sounds promising when measured in terms of radical scavenging ability. *In-silico* studies revealed that compounds would be efficient biologically active in nature. The compounds in the studied plant inhibit

Table 1: Docking simulation results with Docking Score Energy (DS), sequence between the referenced and isolated compounds and 6LU7 Protein of SARS-CoV-2.

Compounds	DS	Binding sequence
dexamethasone	-6.69	THR26, ASN142, GLU166
remdesivir	-1.43	TYR237, MET276, ASN277, GLY278
hydroxychloroquine	-5.07	LEU141, SER144, HIS163, GLU166
favipiravir	-3.77	GLN74, LEU75, VAL77, VAL68, LEU67, PHE66
Comp1	-4.99	GLU166, LEU141
Comp2	-4.85	LEU141, GLY143, SER144, HIS163, GLU166,
Comp3	-4.35	LEU141, GLY143, SER144, CYS145, HIS163, GLU166,
Comp4	-6.38	LEU141, SER144, TYR54, GLU166, ASP187, ARG188, GLN189
Comp5	-6.59	THR26, PHE140, LEU141, GLY143, HIS163, GLU166,
Comp6	-6.86	HIS41, PHE140, GLY143, CIS145, HIS163, GLU166, HIS172
Comp7	-5.90	MET165, GLU166, LEU167, THR190, GLN192
Comp8	-6.34	LEU141, GLY143, SER144, CYS145, HIS163
Comp9	-7.39	LEU141, GLY143, SER144, CYS145, HIS163, GLU166,
Comp10	-6.18	GLY143, SER144, CYS145, HIS163,
Comp11	-6.07	HIS41, PHE140, LEU141, GLY143, HIS163, MET165, GLU166,
Comp12	-6.89	LEU141, GLY143, SER144, CYS145, HIS163, GLU166,

the SARS-CoV-2 protein, causing the virus to lose assaulted the 6LU7 protein the prime protease of SARS-CoV-2. It may prevent virus protein development along with infection dissemination. Docking simulation implies the active binding site of better active molecules against 6LU7 protein. By analyzing the docking details, it turns out that isolated phytochemicals are proficient SARS-CoV-2 inhibitors. The phytochemicals Docking Score (DS) energy towards 6LU7 protein of SARS-CoV-2 fluctuates from −4.35 to −7.39 kcal/mol which is even greater than some of the reference drugs. The variation of active phytochemicals resistance towards SARS-CoV-2 is Comp9 > Comp12 > Comp6 > dexamethasone > Comp5 > Comp4 > Comp8 >Comp10 > Comp11 > Comp7 > hydroxychloroquine > Comp1 > Comp2 > Comp3 > favipiravir > remdesivir. The synergistic interactions of 12 substances exhibited good inhibition over virus 6LU7 protein. This research opens the window of opportunity concerning the use of plant/herbal extract or isolated compounds to figure out SARS-CoV-2 handling to stop the current pandemic. Consequently, compounds have potential to develop as drugs, but for this further study is required.

Acknowledgments

Ahmad Irfan would like to acknowledge the financial support of the King Khalid University for this research through a grant RCAMS/KKU/007–20 under the Research Center for Advanced Materials Science at King Khalid University, Kingdom of Saudi Arabia

Received : Sept. 12, 2020 ; Accepted : Oct. 27, 2020

REFERENCES

[1] Chen J., Pathogenicity and Transmissibility of 2019-Ncov—A Quick Overview and Comparison with Other Emerging Viruses, *Microbes and Infection*, **22**(2): 69-71 (2020).

[2] Tipnis S.R., Hooper N.M., Hyde R., Karran E., Christie G., Turner A.J., A Human Homolog of Angiotensin-Converting Enzyme. Cloning and Functional Expression as a Captopril-Insensitive Carboxypeptidase, *J Biol Chem*, **275(43)**: 33238-33243 (2000).

[3] Wu C., Liu Y., Yang Y., Zhang P., Zhong W., Wang Y., Wang Q., Xu Y., Li M., Li X., Analysis of Therapeutic Targets for Sars-Cov-2 and Discovery of Potential Drugs by Computational Methods, *Acta Pharmaceutica Sinica B*: **10(5)**: 766-788 (2020).

[4] Gurung A.B., Ali M.A., Lee J., Farah M.A., Al-Anazi K.M., Unravelling Lead Antiviral Phytochemicals for the Inhibition of Sars-Cov-2 Mpro Enzyme through in Silico Approach, *Life Sciences*, **255**: 117831 (2020).

[5] Mani J.S., Johnson J.B., Steel J.C., Broszczak D.A., Neilsen P.M., Walsh K.B., Naiker M., Natural Product-Derived Phytochemicals as Potential Agents against Coronaviruses: A Review, *Virus Research*, **284**: 197989 (2020).

[6] Joshi T., Joshi T., Sharma P., Mathpal S., Pundir H., Bhatt V., Chandra S., In Silico Screening of Natural Compounds against Covid-19 by Targeting Mpro and Ace2 Using Molecular Docking, *Eur. Rev. Med. Pharmacol. Sci*, **24**: 4529-4536 (2020).

[7] Wan S., Xiang Y., Fang W., Zheng Y., Li B., Hu Y., Lang C., Huang D., Sun Q., Xiong Y., Clinical Features and Treatment of Covid- 19 Patients in Northeast Chongqing, *Journal of medical virology*, **92(7)**: (2020).

[8] Penta S., Advances in Structure and Activity Relationship of Coumarin Derivatives: Academic Press; (2015).

[9] Moshiashvili G., Tabatadze N., Mshvildadze V., The Genus Daphne: A Review of Its Traditional Uses, Phytochemistry and Pharmacology, *Fitoterapia*, **143**: 104540 (2020).

[10] Elsharkawy E.R., Almalki F., Ben Hadda T., Rastija V., Lafridi H., Zgou H., DFT Calculations and Pom Analyses of Cytotoxicity of Some Flavonoids from Aerial Parts of Cupressus Sempervirens: Docking and Identification of Pharmacophore Sites, *Bioorg. Chem.*, **100**: 103850 (2020).

[11] Jin R.-Y., Tang T., Zhou S., Long X., Guo H., Zhou J., Yan H., Li Z., Zuo Z.-Y., Xie H.-L., Tang Y.-P., Design, Synthesis, Antitumor Activity and Theoretical Calculation of Novel PI3Ka Inhibitors, *Bioorg. Chem.*, **98**: 103737 (2020).

[12] Najafi M., Naqvi S.A.R., Theoretical Study of the Substituent Effect on the Hydrogen Atom Transfer Mechanism of the Irigenin Derivatives Antioxidant Action, *J. Theor. Comput. Chem.*, **13(02)**: 1450010 (2014).

[13] Mikulski D., Eder K., Molski M., Quantum-Chemical Study on Relationship between Structure and Antioxidant Properties of Hepatoprotective Compounds Occurring in Cynara Scolymus and Silybum Marianum, *J. Theor. Comput. Chem.*, **13(01)**: 1450004 (2014).

[14] Sadasivam K., Jayaprakasam R., Kumaresan R., A DFT Study on the Role of Different Oh Groups in the Radical Scavenging Process, *J. Theor. Comput. Chem.*, **11(04)**: 871-893 (2012).

[15] Khalil Warad I., Al-Nuri M., Ali O., Abu-Reidah I.M., Barakat A., Ben Hadda T., Zarrouk A., Radi S., Touzani R., Hicham E., Synthesis, Physico-Chemical, Hirschfield Surface and Dft/B3lyp Calculation of Two New Hexahydropyrimidine Heterocyclic Compounds, *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, **38(4)**: 59-68 (2019).

[16] Demirtaş G., Dege N., Ağar E., Şahin S., The Crystallographic, Spectroscopic and Theoretical Studies on (E)-2-[((4-Fluorophenyl)Imino)Methyl]-4-Nitrophenol and (E)-2-[((3-Fluorophenyl)Imino)Methyl]-4-Nitrophenol Compounds, *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, **37(5)**: 55-65 (2018).

[17] Mahmood A., Irfan A., Effect of Fluorination on Exciton Binding Energy and Electronic Coupling in Small Molecule Acceptors for Organic Solar Cells, *Comp. Theor. Chem.*, **1179**: 112797 (2020).

[18] Irfan A., Comparison of Mono- and Di-Substituted Triphenylamine and Carbazole Based Sensitizers @(Tio2)38 Cluster for Dye-Sensitized Solar Cells Applications, *Comp. Theor. Chem.*, **1159**: 1-6 (2019).

[19] Frisch MJ, Trucks GW, Schlegel HB, et al.,. Gaussian-16, Revision A.1, Gaussian, Inc., Wallingford, Ct. (2016).

[20] Morris G.M., Huey R., Lindstrom W., Sanner M.F., Belew R.K., Goodsell D.S., Olson A.J., Autodock4 and Autodocktools4: Automated Docking with Selective Receptor Flexibility, *J. Comput. Chem.*, **16**: 2785-2791 (2009).

[21] Ali M.Y., Seong S.H., Jung H.A., Choi J.S., Angiotensin-I-Converting Enzyme Inhibitory Activity of Coumarins from *Angelica Decursiva*, *Molecules*, **24(21)**: 3937 (2019).

[22] Su W., Zhao J., Yang M., Yan H.-W., Pang T., Chen S.-H., Huang H.-Y., Zhang S.-H., Ma X.-C., Guo D.-A., A Coumarin Lignanoid from the Stems of *Kadsura Heteroclita*, *Bioorganic & Medicinal Chemistry Letters*, **25(7)**: 1506-1508 (2015).

[23] Liu H., Li F., Li C.-J., Yang J.-Z., Li L., Chen N.-H., Zhang D.-M., Bioactive Furanocoumarins from Stems of *Clausena Lansium*, *Phytochemistry*, **107**: 141-147 (2014).

[24] Marumoto S., Miyazawa M., Structure-Activity Relationships for Naturally Occurring Coumarins as B-Secretase Inhibitor, *Bioorganic & Medicinal chemistry*, **20(2)**: 784-788 (2012).

[25] Liu C.-B., Shen Q.-P., Wang Y., Zhang F.-M., He P., Si X.-X., Wang K.-M., Zhu R.-Z., Xiang N.-J., Liu Z.-H., Coumarins from the Leaves of Nicotiana Tabacum and Their Anti-Tobacco Mosaic Virus Activities, *Chemistry of Natural Compounds*, **52(6)**: 992-995 (2016).

[26] Vektariene A., Vektaris G., Svoboda J., A Theoretical Approach to the Nucleophilic Behavior of Benzofused Thieno [3, 2-B] Furans Using Dft and Hf Based Reactivity Descriptors, *Arkivoc*, **7**: 311-329 (2009).

[27] Geerlings P., De Proft F., Langenaeker W., Conceptual Density Functional Theory, *Chemical Reviews*, **103(5)**: 1793-1874 (2003).

[28] Akaike T., Role of Free Radicals in Viral Pathogenesis and Mutation, *Reviews in Medical Virology*, **11(2)**: 87-101 (2001).

[29] Irfan A., Imran M., Khalid M., Sami Ullah M., Khalid N., Assiri M.A., Thomas R., Muthu S., Raza Basra M.A., Hussein M., Al-Sehemi A.G., Shahzad M., Phenolic and Flavonoid Contents in Malva Sylvestris and Exploration of Active Drugs as Antioxidant and Anti-Covid19 by Quantum Chemical and Molecular Docking Studies, *Journal of Saudi Chemical Society*, **25(8)**: 101277 (2021).

[30] *https://www.rcsb.org/structure/6LU7*