Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Saudi Chemical Society (2021) **25**, 101358

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Isolation of phytochemicals from *Malva neglecta* Wallr and their quantum chemical, molecular docking exploration as active drugs against COVID-19

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Received 17 August 2021; revised 12 September 2021; accepted 14 September 2021
Available online 13 October 2021

KEYWORDS

Antiviral;
Molecular docking;
SARS-CoV-2;
Ionization potential

Abstract The Covid-19 pandemics caused by SARS-CoV-19, and the inadequacy of targeted medications, compelled scientists to seek new antiviral drugs. We present our current understanding of plant extracts containing polyphenols that inhibit Covid-19. Natural phytochemicals (polyphenols) derived from plants have the potential to establish research using extracts and/or individual compounds in the treatment and prevention of coronavirus. The polyphenolic drugs (antivirus) capable of inhibiting the coronavirus protein, that are vital for infection and virus replication. The benefit of phytochemicals is that they promote patient well-being while causing minimal side effects. To understand the antiviral behavior of isolated phytochemicals **1**–**6**, various molecular descriptors,

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jscs.2021.101358

molecular electrostatic potential (MEP), and frontier molecular orbitals (FMO) were investigated. A systematic analysis of isolated phytochemicals was accomplished then molecular descriptors, docking score, active sites, and FMOs energies were compared to the commonly used drugs recently to treat COVID19, namely favipiravir, remdesivir dexamethasone and hydroxychloroquine. Using a molecular docking technique, we demonstrate for the first time that these plant phytochemicals can be inhibited by the core protease (6LU7) protein of COVID19.

1. Introduction

The World Health Organization (WHO) declared Covid-19 a global pandemic on March 11, 2020, after the first cases of corona virus were reported from Wuhan, China. It was associated with an acute infection of the respiratory tract caused by the SARS-CoV-2 virus [1]. The bat was assumed to be the natural host of coronavirus based on evolutionary analysis and viral sequence. This virus may be transmitted to humans from bats by binding with the intermediate host ACE-2 Receptor (Angiotensin Converting Enzyme-2 Receptor) [2]. Currently, more than 11 million people are infected around the world, with the true number exceeding 11 million due to asymptomatic cases that cause pandemic. The disease symptoms include sputum production, fatigue, cough, fever, breath shortness, vomiting, sore throat, diarrhea, headache and pneumonia [3,4]. The ongoing situation may result in significant economic deficits all over the world, even though people who are not infected with the virus. There have been numerous advancements in pandemic evolution, but there are still several unknowns [5]. In the future, it may be arising a seasonal virus and, alike flu, as the number of infected people drops significantly during the summer season. As a result, it is critical to understand how this virus works and spreads to develop vaccines/drugs to combat SARS-CoV-2 infection. The numerous therapies were suggested that are mostly SARS-CoV/MERS-CoV antibodies and antiviral drugs, being exercised by clinicians [6,7]. Based on *in-vitro* analysis along with clinical data, the drugs hydroxychloroquine sulphate, remdesivir and chloroquine phosphate were recommended for COVID-19 therapy. The randomized clinical trials on such molecules were submitted, and the drugs listed above, as well as the recently recommended combination therapy of hydroxychloroquine and azithromycin, were approved for use in an emergency. The hydroxychloroquine inhibitory mechanism through viral processes and metabolism during its provision has discovered to inhibit pro-inflammatory cytokines [8]. Its side effects caused retinal toxicity in patients with acute renal impairment. In diabetic patients, high doses of atorvastatin and hydroxychloroquine resulted in the greatest decrease in blood glucose [9]. Numerous natural and synthetic ligands have been proposed for COVID-19 therapy and are currently being evaluated in clinical trials. The adverse effects of hydroxychloroquine and the site of target whereby spike proteins, viral proteasomes, and proteins affected by virus life cycle are unknown. The possibility of natural/synthetic drug compound with slight side effects behave targets are currently being found like SARS-CoV-2, ACE-2 receptors, TMPRSS2, and CD147 to decrease virus life cycle along with disease prognosis. The raltegravir, paritaprevir, dolutegravir, bictegravir in-silico analysis towards 3CLpro and 20-OMTase targets [10] along with provision of theophylline and pyrimidone derivatives RNA bound N terminal domain potential inhibitions was carried out. The natural products flavone, coumarin derivatives along with Remdesivir, Saquinavir, Darunavir inhibit the 3CL protein. Many targets were identified for COVID-19 therapy, including SARS-CoV-2 main protease (Mpro) in infected patients. The virus multiplication within cells was stopped through Mpro with release of polypeptides that cleavage the enzyme along with extensive proteolysis.

Plant/herbs phytochemicals may be considered as most cost-effective, feasible and ideal drug components. The repurposing of the natural Phyto molecules may hasten the drug discovery process. The current study focuses on potential plant compounds to investigate such effective plant/herb molecules that may be capable of viral inhibition [11]. In-silico analysis of extracted phytochemicals against the main protease of SARSCoV-2 crystal structure (PDB ID: 6LU7) was studied [12]. Medicinal plants have traditionally been used for a variety of manifestations and can be used as one of the safest and most secure methods of treatment. The antiviral activity of different plant species has been determined [13]. Plant/herbal lectins have been proposed as anti-SARS-CoV-2 agents [14]. The family Malvaceae species *Malva neglecta* Wallr commonly known as cheese weed, cheese plant, dwarf mallow and button weed traditionally used as wound healing and herbal medicine [15,16]. The *Malva* genus is found in temperate, subtropical, and tropical regions of Asia, Africa and Europe [17,18]. The commonly used traditionally medicinal herb *Malva neglecta*, contained hydroxycinnamic acids, anthocyanins, saponins, tannins, flavonoids, flavonols, alkaloids, organic acids, protein and oils. Plant extract exhibited anti-ulcerogenic, anti-inflammatory, antimicrobial, anti-cholinesterase, antioxidant and enzymatic inhibitory effects [19,20]. There have been no previous reports demonstrating the efficacy of *Malva neglecta* Wallr extracts isolated phytochemicals against COVID-19. As a result, the current research aims to identify isolated phytochemicals from plant extracts that can be used as antiviral agents. In the current study, the inhibition impact of the examined molecules is the first report over COVID-19, which is an important basis for assessing resistance against the 6LU7 protein using docking calculations. Quantum chemical methods can be used to investigate molecule interactions, active sites, and biological potential. We have threw some light on the electronic characteristic, global reactivity parameters, softness(S), chemical potential(μ), electronegativity(χ), electrophilicity index(ω) and chemical hardness(η). The results of the work showed that the calculated compounds can be considered to be a valuable for inhibiting the invasion of the SARS-CoV-2.

2. Material and methods

2.1. Plant collection

The plant of *Malva neglecta* Wallr was collected from khyber pakhtunkhwa, Pakistan and identified by Dr. Muhammad Javid Plant Taxonomist then voucher specimen was placed at University of Education Lahore, DG Khan Campus.

2.2. Extraction and isolation

The plant (whole) material (1 kg) was dried, ground, and extracted three times with CH_3OH. The plant extract was evaporated at pressure, yielding greenish black residue that was separated into *n*-hexane/H_2O, dichloromethane (DCM)/H_2O and finally *n*-butanol/H_2O. Based on its phytochemical screening, the DCM soluble sub-fraction was subjected to column chromatography (CC) over silica gel eluting with *n*-hexane-DCM, DCM, DCM-MeOH, in ascending polarity order. This yielded four sub-portions: $\mathbf{A_A}$ (*n*-hexane- DCM 6:4), $\mathbf{A_B}$ (*n*-hexane- DCM, 3:7) and $\mathbf{A_C}$ (*n*-hexane-DCM 1.5:8.5). The fractions obtained from *n*-hexane-DCM, 5:5 (6.0:4.0) were exposed to CC over silica gel as adsorbent followed by elution with *n*-hexane-DCM with increasing order of polarity to yield compound**1** and two spot major mixtures, which yielded compounds**5** and **6,** respectively, after preparative TLC. The fractions $\mathbf{A_A}$ obtained from *n*-hexane-DCM (3.0: 7.0) upon further extensive column chromatographic separations afforded the isolation of compounds **2** and **3.** Based on their excellent TLC results, the fractions $\mathbf{A_C}$ obtained from *n*-hexane- DCM, (1.5:8.5) were subjected to CC over silica gel eluting with *n*-hexane-DCM mixture in increasing polarity order to get two subfractions A and B. The sub-fraction A was then subjected to preparative TLC, yielding compound **4**.

2.3. Biochemical screening

The alkaloids were identified in the plant crude extract using the Brain and Turner methods [21] and the same procedure was used to detect anthraquinone. Air-dried milled plant material was boiled with distilled water, then acidified with dilute HCl and filtered, with an aliquot of the filtrate being made alkaline. The presence of flavonoids was indicated by the formation of a yellow color [22]. Crushed plant material was extracted with hot water, filtered, extracted with carbon tetrachloride, and washed with ammonia solution. The presence of anthraquinone was revealed by the appearance of pink color. The extract was dissolved in chloroform, evaporated, and the appearance of grayish color revealed terpenoids after the addition of sulphuric acid [23].

2.4. Computational details

In biological sciences the density functional theory (DFT) is fascinating method to analyze numerous important properties [24,25]. DFT analysis is a scientific method used to investigate the electronic properties of molecules [26–30]. It's a persistent methodology in order to do geometries optimization within ground state (S_0) [31,32]. Regarding S_0 geometries computations, B3LYP is a coherent functional for many biological active molecules. Optimizations as well as electronic characteristic are currently being investigated using the B3LYP/6-311 + + G** level within software Gaussian16 [33]. In addition, Autodock version 4.2 was used for molecular docking via MGL tools, by removing H_2O while adding polar hydrogen atoms (details can be found in supporting information).

3. Results and discussion

The methanolic extract of *Malva neglecta* Wallr was separated into soluble *n*-hexane, DCM and *n*-butanol portions. Secondary metabolites such as alkaloids, anthraquinone, cardiac glycosides, flavonoids and terpenoids were discovered using biochemical screening tests on plant fractions. The findings of the study revealed the presence of biologically active secondary metabolites, with CH_2Cl_2 sub portions being the richest. The CH_2Cl_2 fraction was subjected CC chromatography, which resulted in the identification of six new source phytochemicals **1**–**6**. All the compounds were isolated as light-yellow amorphous solids that tested + ive for phenolic moiety using reagent ferric chloride.

The current SARS-CoV-2 situation necessitates the development of an effective antiviral therapy. Initial studies, such as the use of azithromycin and hydroxychloroquine, for the discovery of drugs against SARS-CoV-2 main protease were ineffective. As a result, more research is needed to discover antiviral agents that can be used to treat COVID-19. Scientist from all fields are working day and night for the discovery of antiviral and vaccine against COVID-19 [34]. Recently, some pharmaceutical companies have claimed to develop the vaccine, however genetic mutation in the SARS-CoV-2 have also been reported in some countries [35].

However, the main protease of SARS-CoV-2 is one of the primary drug targets.

All vaccine development efforts are rendered ineffective due to genetic mutation. As a result, this research is being carried out to identify some antiviral agents against COVID-19. Even though multiple drug targets for SARS-CoV-2 have been identified using structural biology and computation approaches. However, the main protease of SARS-CoV-2 is one of the primary drug targets [36]. The discovery of inhibitors against this important protein could be beneficial and serve as a foundation for the discovery of antiviral agents. Phytochemicals (compounds **1**–**6**) were docked in this study to determine their inhibitory potential against the SARS-CoV-2 main protease. All the phytochemicals tested showed intriguing binding interactions with the SARS-CoV-2 main protease. Fig. 1 depicts the structures of compounds **1**–**6**.

3.1. Electronic properties

The highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) of studied compounds are explored at B3LYP/6-311 + + G** level, as shown in Fig. 2. The distribution of HOMO in dexamethasone was noticed at C = O while LUMO at phenanthren. The "intramolecular charge transport (ICT) was noticed from HOMO (C = O) to LUMO (phenanthren). The HOMO in remdesivir was observed at pyrrolotriazin while LUMO at triazin-7-yl aminopyrrolo. The ICT can be perceived from $-NH_2$ (HOMO) to quinolin (LUMO) in hydroxychloroquine. The HOMO in

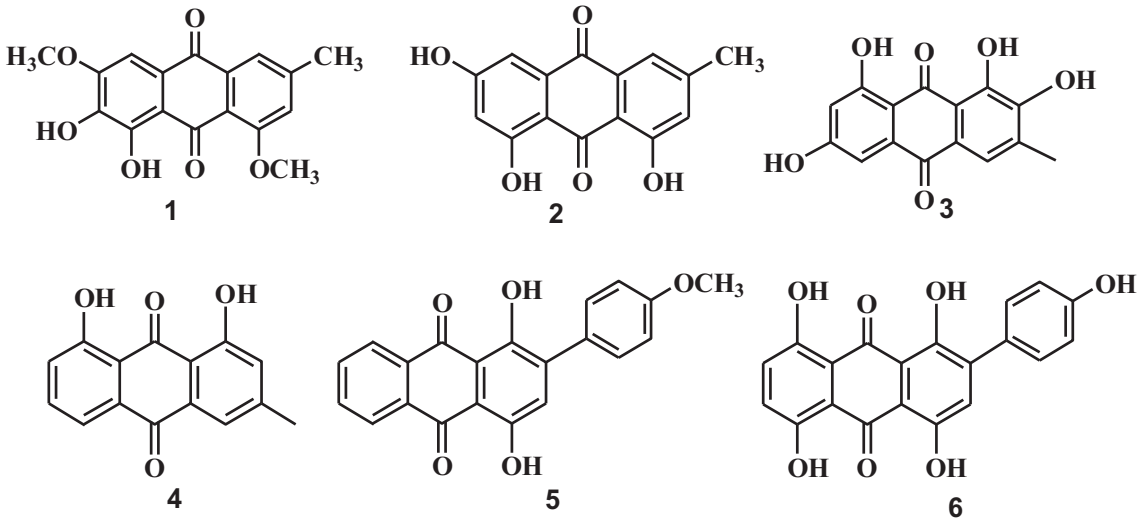

Fig. 1 Structures of isolated compounds **1**–**6**.

favipiravir was detected at 6-fluoro-3-hydroxypyrazine whereas the LUMO at pyrazine-2-carboxamide. Correspondingly, in studied phytochemicals (Compounds1-6) ICT was discerned from HOMO → LUMO. Chemical activity is also strongly associated with the distribution of HOMOs/LUMOs that light up highly reliable sites to be attacked by active agents. The E_{HOMO}, E_{LUMO}, and E_{gap} of the isolated phytochemicals and drug references remdesivir, dexamethasone, favipiravir and hydroxychloroquine are shown in Table 1.

The global chemical reactivity descriptors (GCRD) are important to explore the biological activity behavior of various phytochemicals. We measured different GCRD parameters like electronegativity (χ), electrophilicity index (ω), softness (S), chemical hardness (η) and chemical potential (μ) (SI contains calculation method). The η values are related to aromaticity [37,38]. The ω revealed the stabilizing power created by electrons from outer environment. The μ means the electronic tendency according to its electronic environment. As preceding research showed that the best antioxidant capability of the compound would be appropriate to prevent viral infection [39]. In a single electron transfer pathway, the antioxidant phytochemical brings electron to radical (free), instigating radical cation to be stabilize plentiful to obtain a good antioxidant ability.

The parameter work function (W) of Al/Au are 4.08/5.10 eV [40–42]. The hole and electron injection energy barrier (HIE and EIE) of isolated compounds to Al and Au electrodes were calculated and compared in this study. The EIE for isolated phytochemicals (**1**–**6**) were anticipated like (eV $= -E_{LUMO} - (-W)$) whereas HIE like (eV $= -W - (-E_{HOMO})$). One can see that that hole and electron injection barriers of isolated compounds is smaller than most of the referenced drugs revealing their better charge injection ability, see Table 1.

3.2. Molecular electrostatic potential

The Molecular electrostatic potential (MEP) is a useful parameter for investigating the reactivity of compounds and/or species. The MEP is, in fact, a physically detectable property that can be measured experimentally using diffraction techniques [43,44]. It can also be explored using computational methods. The MEP depicts a wide range of electronic and nuclear charge distributions, which is useful for understanding the reactivity of various species [45]. The Fig. 3 display the color visualizations of the MEP mapped for isolated and reference drugs. The red color denotes higher -ive potential regions that are advantageous for electrophilic attack, whereas the blue color denotes higher +ive potential regions that are advantageous for nucleophilic attack. The decreasing trend of MEP in the following order: blue > green > yellow > orange > red, with red indicating the strongest repulsion and blue indicating sufficient attraction for nucleophiles and vice versa.

The MEP maps are essential for visualizing charged regions within compounds. A MEP map of specific phytochemicals and targeted drugs is shown in color presentations in Fig. 3. The blue and red band means positive and negative potential regions that can favor nucleophilic and electrophilic attacks. In dexamethasone negative potential is on –O atoms where positive potential on -H of –OH. In remdesivir, the negative potential is on -O and positive at the amino hydrogen atoms. In hydroxychloroquine, negative potential is on -O of the quinolin and $–CH_3CH_2OH$ group while positive potential at -H of –OH and –NH. The negative potential is on –O atom while positive at the –H of carboxamide in favipiravir. In isolated phytochemicals, the negative potential was found on -O atoms of C=O and -O (–OH) but positive at –H atoms of –OH and $–OCH_3$ groups. The red region especially oxygen atoms has shown that these could be potential sites for electrophilic attack. While the blue color on -H atoms indicated that these areas would be favorable for nucleophilic attacks.

3.3. Molecular docking

The 6LU7 protein structure of SARS-CoV-2 was found from Worldwide Protein Data Bank. The virus core protease crystal structure in the complex (6LU7) is displayed in Fig. 4. The

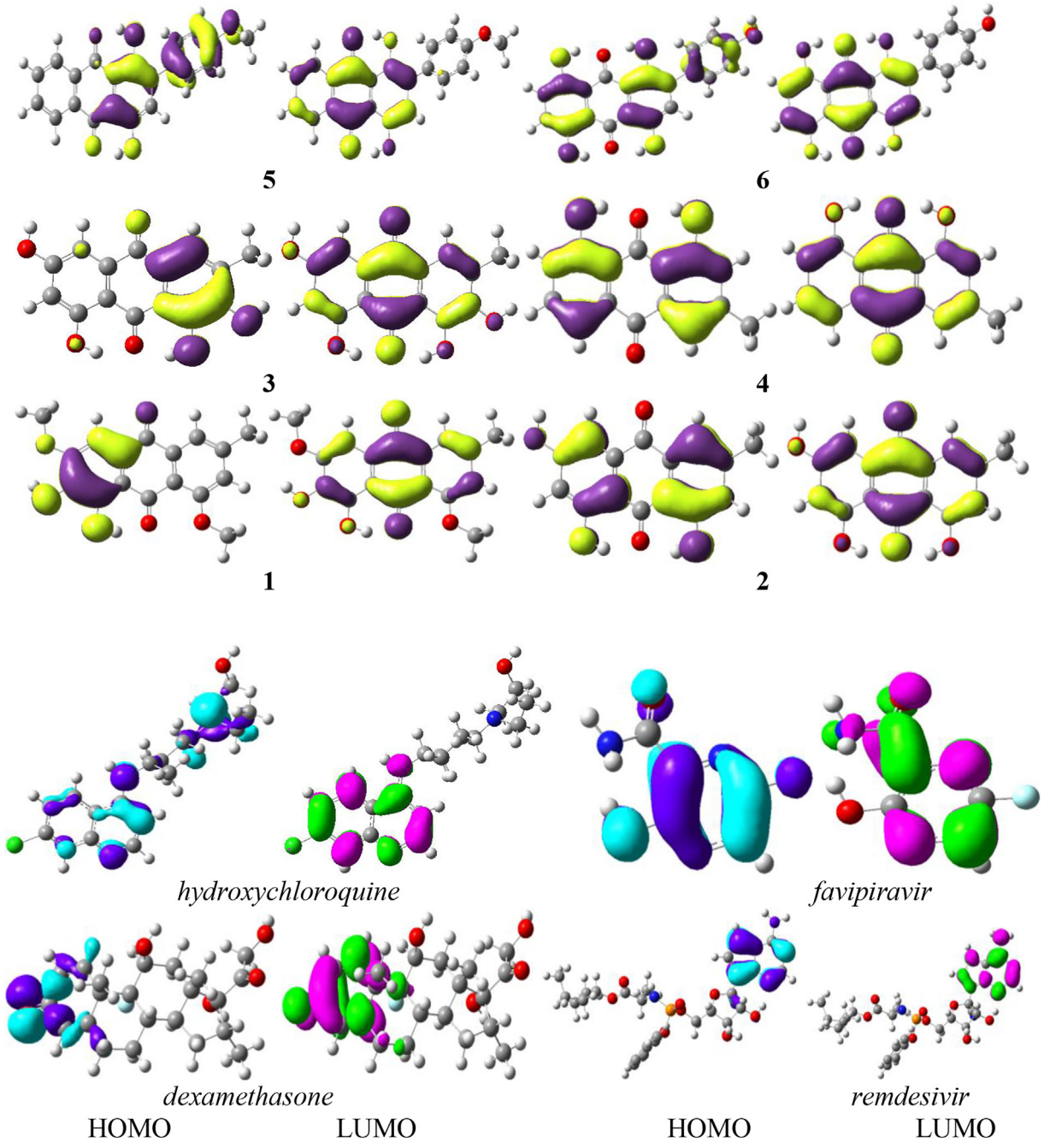

Fig. 2 Spatial distribution of HOMOs and LUMOs of isolated phytochemicals.

6LU7 protein structure was refined using Autodock. The obtained docking results were prosperous in all phytochemicals along with reference compounds. The binding energies (BE) values among ligands and protein (title compounds active sites along with amino acids) are exhibited within Table 2 and Fig. 5. As far as we know, no results already computed accompanying with 6LU7 proteins of SARS-CoV-2 resistance by employing in-silico screening of these isolated phytochemicals. To achieve improved comprehension towards effectiveness of the isolated drugs, we proceeded to explore the interactions of phytochemicals with 6LU7 proteins of SARS-CoV-2 crystal structure. Molecular docking was performed by introducing compounds in 6LU7 proteins. The BE values between title compounds and 6LU7 proteins are exhibited within Table 2 and Fig. 5.

Antioxidant aptitude can be tested using ionization potential (IP), which is a parameter that illuminates the electron transfer distance which is estimated as IP = $-E_{HOMO}$. It is anticipated that the phytochemicals having smaller IP would be better antioxidant compounds which is revealing that Compound **5** will have better antioxidant power. These results are revealing that Compound **5** with smaller IP value might enhance the antiviral aptitude which can leads its suitability as anti-COVID19 candidate. The hydrogen bonding was

Table 1 The E_{HOMO}, E_{LUMO}, E_{gap}, molecular descriptors, hole injection energy (HIE) and electron injection energy (EIE) barriers of phytochemicals computed at B3LYP/6-311 + + G**level.

Parameters	1	2	3	4	5	6	Dexamethasone	Remdesivir	Hydroxyl-chloroquine	Favipiravir
E_{HOMO}	−6.13	−6.75	−6.53	−6.80	−6.09	−6.16	−6.22	−6.20	−5.57	−6.98
E_{LUMO}	−2.95	−3.38	−3.28	−3.40	−3.34	−3.59	−1.39	−1.36	−1.14	−2.24
E_{gap}	3.18	3.37	3.25	3.40	2.75	2.57	4.83	4.84	4.43	4.74
η	1.590	1.685	1.625	1.700	1.375	1.285	2.41	2.42	2.21	2.37
S	1.927	2.003	2.009	2.000	2.214	2.397	1.29	1.28	1.26	1.47
ω	6.481	7.612	7.403	7.650	8.084	9.247	4.428	4.604	4.363	4.609
μ	−4.540	−5.065	−4.905	−5.100	−4.715	−4.875	−3.80	−3.78	−3.35	−4.61
χ	4.540	5.065	4.905	5.100	4.715	4.875	3.80	3.78	3.35	4.61
EA	2.95	3.38	3.28	3.40	3.34	3.59	1.39	1.36	1.14	2.24
IP	6.13	6.75	6.53	6.80	6.09	6.16	6.22	6.20	5.57	6.98
EIE (Al)	1.13	0.70	0.8	0.68	0.74	0.49	2.69	2.72	2.94	1.84
HIE (Al)	2.05	2.67	2.45	2.72	2.01	2.08	2.14	2.12	1.49	2.90
EIE (Au)	2.15	1.72	1.82	1.70	1.76	1.51	3.71	3.74	3.96	2.86
HIE (Au)	1.03	1.65	1.43	1.70	0.99	1.06	1.12	1.10	0.47	1.88

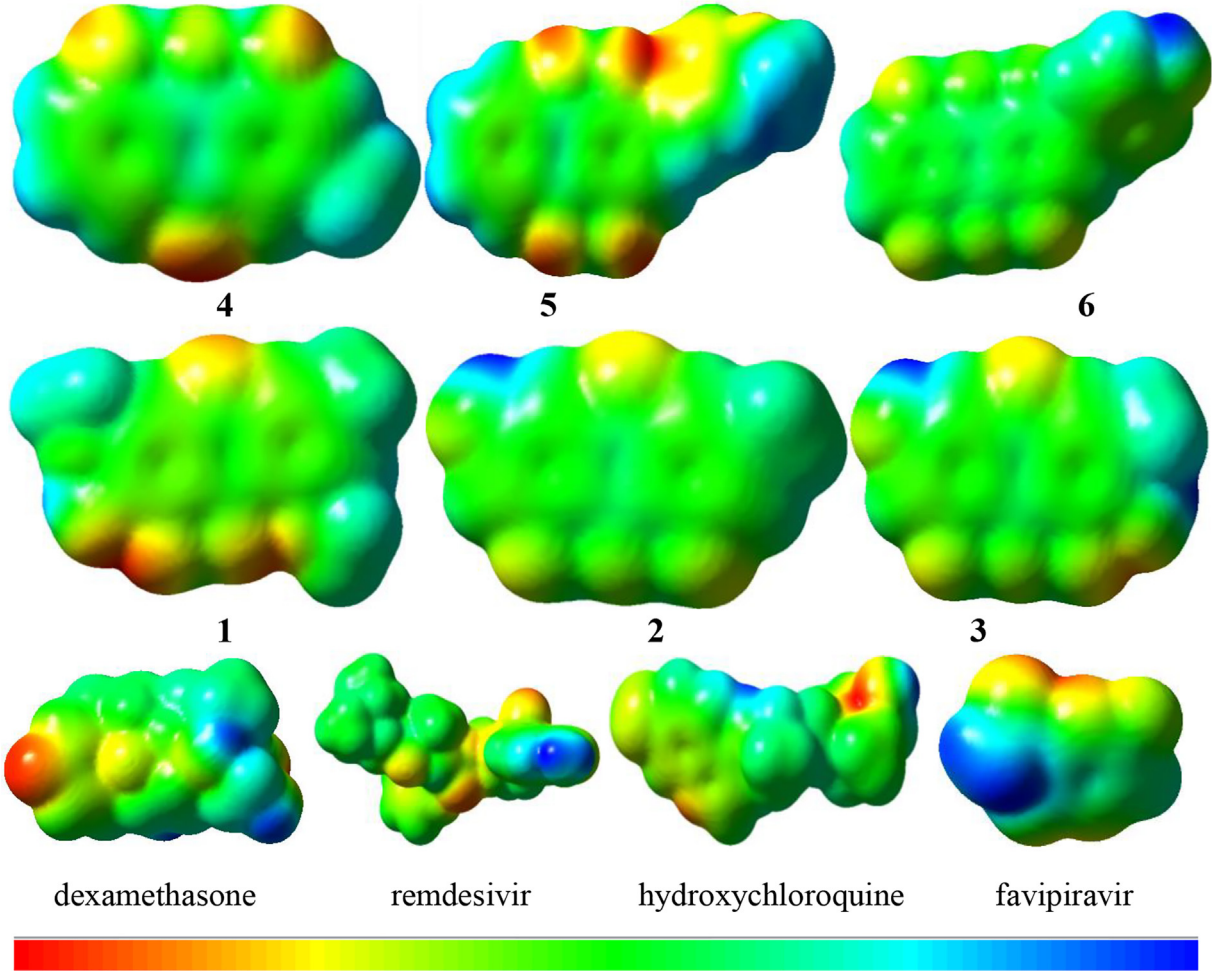

Fig. 3 Molecular electrostatic potential surfaces views of isolated compounds.

observed between hydrogen of phytochemical and oxygen of ARG188 in Compound **1**, *i.e.*, is 2.30 Å while oxygen of TRH190 and hydrogen of phytochemical showed hydrogen bonding 2.30 Å. In Compound **2**, following hydrogen bonding were observed: oxygen of GLU166 to H···O of phytochemical, *i.e.*, 2.50 Å, hydrogen of HIS163 and O···H of phytochemical, *i.e.*, 2.40 Å, hydrogen of CIS145 and keto O of phytochemical, *i.e.*, 2.40 Å, and hydrogen of SER144 and keto O of phytochemical, *i.e.*, 2.20 Å. In Compound**3**, hydrogen bonding was noticed as: oxygen of HIS164 to H···O of the phytochem-

Fig. 4 Main protease of SARS-CoV-2 (6LU7).

ical, *i.e.*, 2.50 Å, oxygen of THR190 and H···O of phytochemical, *i.e.*, 2.20 Å, oxygen of ARG188 and H···O of phytochemical, *i.e.*, 2.30 Å. In Compound **4** and Compound **5** hydrogen bonding was perceived as: hydrogen of GLU166 to O (keto group) of phytochemical, *i.e.*, 2.0 Å and hydrogen of GLY143 to O of phytochemical, *i.e.*, 2.60 Å, respectively. The hydrogen bonding was also observed between oxygen of GLU14 to H···O, oxygen of ALA70 to H···O and oxygen of GLY15 to O···H of phytochemicals, *i.e.*, 1.80 Å, 2.60 Å and 3.0 Å in Compound **6**, respectively. The results obtained from the docking exposed that Compound **5** has well documented to show that this isolated drug may have potent anti-COVID19 and anti-oxidant properties.

Table 2 Docking Score Energy (DS), sequence between phytochemicals/reference compounds and 6LU7 of SARS-CoV-2.

Compounds	BE	Binding sequence
1	−5.28	ARG188, THR190
2	−5.26	LEU141, SER144, CYS145, HIS163, GLU166
3	−5.20	HIS164, ARG188, THR190
4	−5.33	HIS41, GLU166
5	−5.73	GLY143
6	−4.14	GLU14, GLY15, ALA70,
dexamethasone	−6.69	GLU166, ASN142, THR26,
remdesivir	−1.43	GLY278, ASN277, MET276, TYR237
hydroxychloroquine	−5.07	GLU166, HIS163, SER144, LEU141
favipiravir	−3.77	VAL77, LEU75, GLN74, VAL68, LEU67, PHE66

According to the results of the computation, such compounds have a high inhibitory power against 6LU7 of COVID-19. The docking results are fantastic proof of these phytochemicals anti-COVID-19 ability. This reflects the effects of phytochemicals on COVID-19 inhibition. As a result, it is

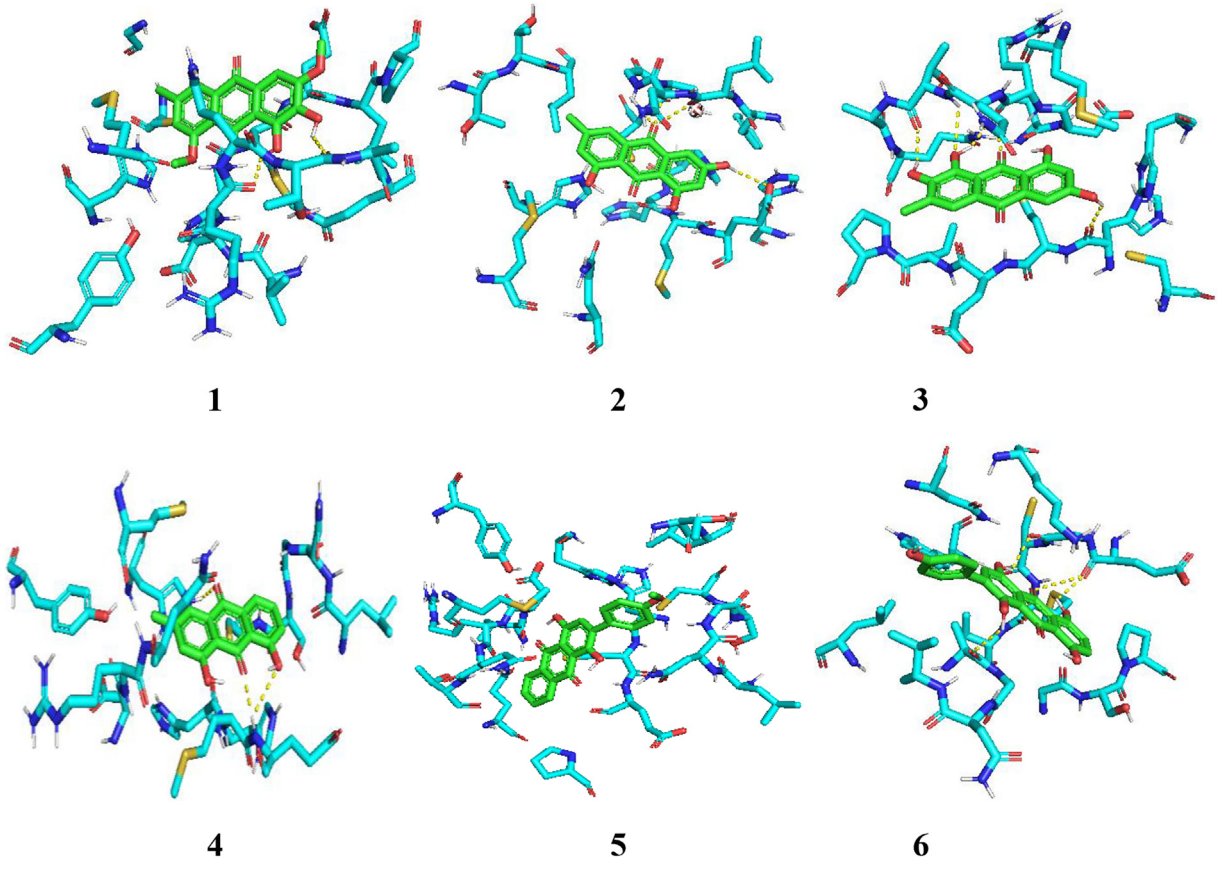

Fig. 5 The interaction between phytochemicals (green color) and 6LU7 protein.

recommended that *Malva neglecta* Wallr extract or active compound(s) be used to inhibit the 6LU7. These outcomes will present further research and possibility in the inhibition and cure of SARSCoV-2.

4. Conclusions

Phytochemicals discovered in traditional medicinal herbs offer an exciting opportunity for the development of newer, safer therapeutics. To identify compounds that have the potential to be used in novel drug development and as inhibitors of therapeutically important enzymes. The antioxidant properties of the *Malva neglecta* plant were investigated, and isolated compounds **1**–**6** were screened for in-silico molecular docking studies. The simulated results have shown that Compound **5** has excellent anti-oxidant ability and that 6LU7 inhibits COVID-19.

The simulation results show that these compounds have anti-COVID-19 ability, which may be a good indication of how these drugs will be used against COVID-19. As a result, it is recommended to use extraction or individual phytochemical that are very effective in simultaneously working on 6LU7 protein. These findings will pave the way for more research into isolated phytochemicals and/or extract that can inhibit SARSCoV-2. The current findings are expected to be useful for future research to develop a drug from *Malva neglecta* Wallr.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through research groups program under grant number R.G. P.1/42/42.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jscs.2021.101358.

References

[1] A.G. Henry, D.R. Piperno, Using plant microfossils from dental calculus to recover human diet: A case study from tell Al-Raqā'i, Syria, J. Archaeol. Sci. 35 (2008) 1943–1950.
[2] F. Conforti, S. Sosa, M. Marrelli, F. Menichini, G.A. Statti, D. Uzunov, A. Tubaro, F. Menichini, R.D. Loggia, Della Loggia, In vivo anti-inflammatory and in vitro antioxidant activities of mediterranean dietary plants, J. Ethnopharmacol. 116 (2008) 144–151.
[3] N. Sleiman, C. Daher, Malva sylvestris water extract: A potential anti-inflammatory and anti-ulcerogenic remedy, Planta Med. 75 (2009) PH10.
[4] L. Barros, A.M. Carvalho, I.C. Ferreira, Leaves, flowers, immature fruits and leafy flowered stems of malva sylvestris: A comparative study of the nutraceutical potential and composition, Food Chem. Toxicol. 48 (2010) 1466–1472.
[5] J.C. Gasparetto, C.A.F. Martins, S.S. Hayashi, M.F. Otuky, R. Pontarolo, Ethnobotanical and scientific aspects of malva sylvestris l.: A millennial herbal medicine, J. Pharm. Pharmacol. 64 (2012) 172–189.
[6] A. Sharma, D.S. Cannoo, A comparative study of effects of extraction solvents/techniques on percentage yield, polyhenolic composition, and antioxidant potential of various extracts obtained from stems of n epeta leucophylla: Rp-hplc-dad assessment of its polyhenolic constituents, J. Food Biochem. 41 (2017) e12337.
[7] E.J. Llorent-Martínez, G. Zengin, M.L. Fernández-de Córdova, O. Bender, A. Atalay, R. Ceylan, A. Mollica, A. Mocan, S. Uysal, G.O. Guler, Traditionally used lathyrus species: Phytochemical composition, antioxidant activity, enzyme inhibitory properties, cytotoxic effects, and in silico studies of l. Czeczottianus and l. Nissolia, Front. Pharmacol. 8 (2017) 83.
[8] E.A. Ainsworth, K.M. Gillespie, Estimation of total phenolic content and other oxidation substrates in plant tissues using Folin–Ciocalteu reagent, Nat. Protoc. 2 (2007) 875–877.
[9] J. Zhishen, T. Mengcheng, W.u. Jianming, The determination of flavonoid contents in mulberry and their scavenging effects on superoxide radicals, Food Chem. 64 (1999) 555–559.
[10] G. Miliauskas, P.R. Venskutonis, T.A. van Beek, Screening of radical scavenging activity of some medicinal and aromatic plant extracts, Food Chem. 85 (2004) 231–237.
[11] M. Imran, A. Irfan, M. Ibrahim, M.A. Assiri, N. Khalid, S. Ullah, A.G. Al-Sehemi, Carbonic anhydrase and cholinesterase inhibitory activities of isolated flavonoids from oxalis corniculata l. And their first-principles investigations, Ind. Crops Prod. 148 (2020) 112285.
[12] M. Ballero, F. Poli, G. Sacchetti, M.C. Loi, Ethnobotanical research in the territory of fluminimaggiore (south-western sardinia), Fitoterapia 72 (2001) 788–801.
[13] S. Redžić, Plant pigments (antioxidants) of medicinal plants malva silvestris l. And malva moschata l.(malvaceae), Bosnian J. Basic Med. Sci. 5 (2005) 53.
[14] L.L. Cogo, C.L.B. Monteiro, M.D. Miguel, O.G. Miguel, M.M. Cunico, M.L. Ribeiro, E.R.d. Camargo, G.M.B. Kussen, K.d.S. Nogueira, L.M.D. Costa, Anti-helicobacter pylori activity of plant extracts traditionally used for the treatment of gastrointestinal disorders, Braz. J. Microbiol. 41 (2010) 304–309.
[15] F. Khatami, F. Ghanati, Effects of UV irradiation on cell viability, anthocyanin, and flavonoid contents of callus-cultured malva neglecta cells, ICLST 3 (2011) 202–204.
[16] B. Özüdoğru, G. Akaydın, S. Erik, E. Yesilada, Inferences from an ethnobotanical field expedition in the selected locations of sivas and yozgat provinces (Turkey), J. Ethnopharmacol. 137 (2011) 85–98.
[17] M. Şenguuml, An ethnobotanical survey of medicinal plants of Yazıkonak and Yurtbaşı districts of Elazığ Province, Turkey, J. Med. Plants Res. 4 (2010) 567–572.
[18] A. Irfan, M. Imran, M. Khalid, M. Sami Ullah, N. Khalid, M. A. Assiri, R. Thomas, S. Muthu, M.A. Raza Basra, M. Hussein, A.G. Al-Sehemi, M. Shahzad, Phenolic and flavonoid contents in Malva sylvestris and exploration of active drugs as antioxidant and anti-covid19 by quantum chemical and molecular docking studies, J. Saudi Chem. Soc. 25 (2021) 101277.
[19] A.E. Al-Snafi, Medical benefit of Malva neglecta-a review, IOSR J. Pharm. 9 (2019) 60–67.
[20] U. Saleem, S. Khalid, S. Zaib, F. Anwar, B. Ahmad, I. Ullah, A. Zeb, M. Ayaz, Phytochemical analysis and wound healing studies on ethnomedicinally important plant malva neglecta wallr, J. Ethnopharmacol. 249 (2020) 112401.

[21] F. Cutillo, B. Dabrosca, M. Dellagreca, A. Fiorentino, A. Zarrelli, Terpenoids and phenol derivatives from malva silvestris, Phytochemistry 67 (5) (2006) 481–485.
[22] M.H. Shahrajabian, W. Sun, H. Shen, Q. Cheng, Chinese herbal medicine for sars and sars-cov-2 treatment and prevention, encouraging using herbal medicine for covid-19 outbreak, Acta Agric. Scand., Sect. B—Soil Plant Sci. 70 (2020) 437–443.
[23] I. Aanouz, A. Belhassan, K. El-Khatabi, T. Lakhlifi, M. El-Ldrissi, M. Bouachrine, Moroccan medicinal plants as inhibitors against sars-cov-2 main protease: computational investigations, J. Biomol. Struct. Dyn. (2020) 1–9.
[24] E.R. Elsharkawy, F. Almalki, T. Ben Hadda, V. Rastija, H. Lafridi, H. Zgou, 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 (2020) 103850.
[25] R.-Y. Jin, T. Tang, S. Zhou, X. Long, H. Guo, J. Zhou, H. Yan, Z. Li, Z.-Y. Zuo, H.-L. Xie, Y.-P. Tang, Design, synthesis, antitumor activity and theoretical calculation of novel pi3ka inhibitors, Bioorg. Chem. 98 (2020) 103737.
[26] M. Najafi, S.A.R. Naqvi, Theoretical study of the substituent effect on the hydrogen atom transfer mechanism of the irigenin derivatives antioxidant action, J. Theor. Comput. Chem. 13 (2014) 1450010.
[27] D. Mikulski, K. Eder, M. Molski, 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 (2014) 1450004.
[28] K. Sadasivam, R. Jayaprakasam, R. Kumaresan, A DFT study on the role of different oh groups in the radical scavenging process, J. Theor. Comput. Chem. 11 (2012) 871–893.
[29] I. Khalil Warad, M. Al-Nuri, O. Ali, I.M. Abu-Reidah, A. Barakat, T. Ben Hadda, A. Zarrouk, S. Radi, R. Touzani, E. Hicham, Synthesis, physico-chemical, hirschfield surface and dft/b3lyp calculation of two new hexahydropyrimidine heterocyclic compounds, Iran. J. Chem. Chem. Eng. (IJCCE) 38 (2019) 59–68.
[30] G. Demirtaş, N. Dege, E. Ağar, S. Şahin, amp, uuml, 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, Iran. J. Chem. Chem. Eng. (IJCCE) 37 (2018) 55–65.
[31] A. Mahmood, A. Irfan, Effect of fluorination on exciton binding energy and electronic coupling in small molecule acceptors for organic solar cells, Comp. Theor. Chem. 1179 (2020) 112797.
[32] A. Irfan, Comparison of mono- and di-substituted triphenylamine and carbazole based sensitizers @(tio2)38 cluster for dye-sensitized solar cells applications, Comp. Theor. Chem. 1159 (2019) 1–6.
[33] M.J. Frisch, G.W. Trucks, H.B. Schlegel et al., Gaussian-16, revision a.1, Gaussian, Inc., Wallingford, CT, in, 2016.
[34] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y.J.J. Xiong, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, 323 (2020) 1061-1069.
[35] I. Saha, N. Ghosh, D. Maity, N. Sharma, J.P. Sarkar, K.J.I. Mitra, Genetics, Evolution, Genome-wide analysis of Indian Sars-Cov-2 genomes for the identification of genetic mutation and SNP, 85 (2020) 104457.
[36] M. Prajapat, P. Sarma, N. Shekhar, P. Avti, S. Sinha, H. Kaur, S. Kumar, A. Bhattacharyya, H. Kumar, S.J.I.j.o.p. Bansal, Drug targets for corona virus: A systematic review, 52 (2020) 56.
[37] A. Vektariene, G. Vektaris, J. Svoboda, A theoretical approach to the nucleophilic behavior of benzofused thieno [3, 2-b] furans using dft and hf based reactivity descriptors, Arkivoc 7 (2009) 311–329.
[38] P. Geerlings, F. De Proft, W. Langenaeker, Conceptual density functional theory, Chem. Rev. 103 (2003) 1793–1874.
[39] T. Akaike, Role of free radicals in viral pathogenesis and mutation, Rev. Med. Virol. 11 (2001) 87–101.
[40] A. Irfan, M. Imran, R. Thomas, M.W. Mumtaz, M.A.R. Basra, S. Ullah, A.G. Al-Sehemi, M.A. Assiri, Hole transport nature exploration of 4,4-difluoro-8-(c4h3x)-4-bora-3a,4a-diaza-s-indacene (x = o, s, se) (bodipy) systems, Mol. Simul. 46 (2020) 1334–1339.
[41] A. Irfan, M. Imran, R. Thomas, M.W. Mumtaz, M.A. Qayyum, S. Ullah, M.A. Assiri, A.G. Al-Sehemi, Exploration of electronic nature and intrinsic mobility of 10-(1,3-dithiol-2-ylidene)anthracene based organic semiconductor materials, Optik 224 (2020) 165530.
[42] A. Irfan, A. Rasool Chaudhry, A.G. Al-Sehemi, Electron donating effect of amine groups on charge transfer and photophysical properties of 1,3-diphenyl-1h-pyrazolo[3,4-b] quinolone at molecular and solid state bulk levels, Optik 208 (2020) 164009.
[43] P. Politzer, D.G. Truhlar (Eds.), Chemical Applications of Atomic and Molecular Electrostatic Potentials, Plenum Press, New York, 1981.
[44] R.F. Stewart, On the mapping of electrostatic properties from bragg diffraction data, Chem. Phys. Lett. 65 (1979) 335–342.
[45] J.S. Murray, P. Politzer, The electrostatic potential: An overview, WIREs Comput. Mol. Sci. 1 (2011) 153–163.