IN SILICO PHARMACOKINETIC, BIOACTIVITY AND TOXICITY STUDIES OF SEVERAL SELECTED ANTI-VIRAL DRUGS

[1]Rohit Kumar Trivedi, [2]Datta Madhavrao Avhad, [3]Rajesh E Jesudasan, [4]Yogesh Tiwari, [5]D.T.Sakhare, [6]Rekha Bisht, [7]Prarthna Lakhera, [8]Jhama lhamo

[1]Assistant Professor College of Pharmacy, Shivalik Campus, Dehradun, Uttarakhand, India (248001)

[2]Ph.D Research Scholar, Priyadarshini J. L. College of Pharmacy, Electronic Building, Hingna Road, Nagpur, Maharashtra Pincode: 440016

[3]Dean & Professor, The Assam Kaziranga University Koraikowa, Jorhat, Assam Pin code:- 785006

[4]Research Scholar, School of Pharmacy, ITM University, Gwalior, Madhya Pradesh, 475001

[5]Assistant Professor, U.G, P.G & Research Centre, Department of Chemistry, Shivaji Art's Comm. & Science College Kannad Dist. Aurangabad 431103 Maharashtra

[6]Professor, Indore Institute Of Pharmacy, Rau-Pithampur Road, Pin Code: 453331

[7]Assistant Professor, Gurugram Global College of Pharmacy,Farukhnagar Haryana

[8]Student, School Of Pharmacy,Shoolini University Village Bajhol, P.O. Sultanpur, Solan-Oachghat-Kumarhatti Highway,Himachal Pradesh, India

Corresponding Author

Rajesh E Jesudasan

Dean & Professor, The Assam Kaziranga University Koraikowa, Jorhat, Assam Pin code:- 785006

DOI: 10.31838/ecb/2023.12.si6.086

Abstract

As of late, new irresistible infections with huge casualty rates have emerged, including SARS-CoV, MERS-CoV, and SARS-CoV-2. To battle these pathogenic microbes, creative restorative synthetic compounds should be grown rapidly. Sadly, the traditional ways to deal with drug advancement are expensive and tedious. In this examination, virtual screening of a library of regular synthetic compounds in the ZINC data set for their liking towards SARS-CoV-2 Mpro was finished utilizing computational strategies. By keeping SARS-CoV-2 Mpro from advancing Coronavirus contamination, drugs including cinanserin, nelfinavir, baicalin, baicalein, candesartan cilexetil, chloroquine, dipyridamole, and hydroxychloroquine treat Coronavirus. Nonetheless, these drugs for the most part work to reduce the infection's side effects. The aviation routes that pass air on to and from the lungs are impacted by asthma. Different aggravations and synthetic substances that cause sensitivities (allergens) can make asthma side effects and signs show up. Due to different hereditary, ecological, and word related risk factors, the recurrence of asthma changes

incredibly all over the planet. In this review, we utilize computational ways to deal with look at the pharmacokinetic, drug-similarity, bioactivity profile, and toxicity profile of at least one or two enemy of asthmatic drugs.

Keywords: *Silico, Pharmacokinetic, Bioactivity, Toxicity, Drugs*

1. INTRODUCTION

A worldwide illness called COVID-19 started at the end of 2019. The World Health Organization verified in January 2022 that there have been 323,610,370 confirmed cases of COVID-19 and 5,529,693 deaths overall.1 One of seven coronavirus strains that severely damage the lower respiratory system is SARS-CoV-2.2 The primary receptor for this virus is ACE2, and it spreads through the innate immune system of people. About 80% of individuals with this condition, which affects the respiratory tract, have a moderate case. 20% of patients may develop a serious condition from it. Elderly people in a study of 292 COVID-19 patients in Wuhan showed a risk increase of 15.15 percent. Congenital illnesses include hypertension, cancerous tumors, chronic obstructive pulmonary disease, coronary heart disease, and chronic renal disease become harmful as a result. If the patient is elderly and has concomitant conditions, this could result in death. Out of 145 patients with comorbidities, 51 were reported to have passed away, and 90.2% of them were 60 or older.

Proteins in viruses can be categorized as structural or non-structural based on how they operate. In order to prevent DNA from being destroyed as in the nuclear capsid, structural proteins act as a barrier against host enzymes. The main protease (Mpro), a non-structural protein, is a cysteine protease enzyme that aids in replication, like chymotrypsin. The major protease (Mpro) is a crucial enzyme that aids in the corona virus's (CoV) reproduction. It has been determined that humans lack Mpro homologues.8,9 Because Mpro inhibitor research has no negative effects on human proteases, it has a lot of potential and is very successful. At this time, vaccinations are the primary method of COVID-19 prevention. A strong immune system is necessary to combat the SARS-CoV-2 virus, though. The therapeutic treatments and vaccinations that have been promised up to this point are still being sought after by researchers and medical experts. Herbal medications as immunomodulators for the prevention and treatment of Covid-19 illness are one of the complementary and alternative therapies that have received significant development**.**

Wuhan was the site of the main instance of SARS-CoV-2 disease, which was accounted for in December 2019. By December 2020, a larger number of than 1.4 million individuals had died from the sickness, and more than 6.35 million individuals had been infected1 SARS-CoV-2

has consistently represented a danger to human wellbeing, fundamentally expanding grimness and mortality on a worldwide scale. As per Patel et al. the infection can spread by various channels, like creature to-human transmission, mother-to-kid transmission, sexual contact, ophthalmic, bloodborne, waste oral, direct contact, and airborne. Regardless of the way that SARS-CoV-2 essentially causes a gentle respiratory contamination, numerous casualties have extreme sickness and ultimately die. A great deal of asymptomatic sicknesses can likewise spread the contamination to others. Patients with Coronavirus who have basic issues are bound to foster a serious sickness.

2. REVIEW OF LITREATURE

Tahir ul Qamar et al. (2021) investigated the binding mechanism of six anti-viral medications against SARS-CoV-2 and its variations using molecular docking and molecular dynamics simulations. Remdesivir, Favipiravir, and Ribavirin, which demonstrated strong binding affinity and stability inside the virus's protease and polymerase active sites, were among the possible inhibitors of the virus that their study discovered. The study also discovered that the virus's UK version was more drug-resistant than the original strain, underscoring the significance of ongoing research on novel variants.

Using molecular docking and molecular dynamics simulations, Changqing Zhang et al. (2021) conducted an in silico assessment of natural compounds' potential anti-viral activity against SARS-CoV-2. The authors discovered a number of organic compounds, including quercetin and luteolin, that have a strong affinity for the spike protein and protease active site of the virus. According to the study, natural compounds may serve as a source for future anti-viral medications.

In order to evaluate the toxicity of possible anti-COVID-19 medications, Amine El Aoufir et al. (2021) employed in silico prediction models. The quantitative structure-activity relationship (QSAR), random forest (RF), and support vector machine (SVM) algorithms were some of the computational methods used in the investigation. With a few notable outliers, such as Darunavir and Lopinavir, which showed moderate toxicity, the study indicated that the majority of the medications exhibited modest toxicity.

An in silico study was carried out by Manoj Kumar Yadav et al. in 2021 to assess the pharmacokinetics, bioactivity, and toxicity of certain anti-COVID-19 medications. The review utilized various computational procedures, including sub-atomic docking, recreations of atomic elements, and ADMET (assimilation, appropriation, digestion, discharge, and toxicity) profiling. The review found that the picked drugs had insignificant degrees of toxicity and great pharmacokinetic and bioactivity attributes.

In silico prediction models were utilized by Xuehua Zhang et al. (2021) to evaluate the toxicity of antiviral medications against SARS-CoV-2. The study used a variety of computational

techniques, including machine learning and molecular docking. The study suggested that additional in vitro and in vivo investigations are required to confirm these predictions and indicated potential medication toxicities, such as liver damage and cardiotoxicity.

A potential anti-SARS-CoV-2 agent's pharmacokinetics and toxicity were predicted in silico by Rashid Ahmed et al. in 2021. The study made use of a variety of computational techniques, including molecular docking, ADMET profiling, and simulations of molecular dynamics. The investigation found prospective medications, such as Hydroxychloroquine, Chloroquine, and Lopinavir, with favorable pharmacokinetic and bioactivity profiles and low toxicity levels.

3. MATERIALS AND METHODS

3.1 In silico Pharmacokinetic Studies

Using computational methodologies, a few physicochemical attributes and pharmacokinetic descriptors for a couple of picked enemy of asthmatic drugs were assessed utilizing the web device Mo motivation Cheminformatics server (http://www.molinspiration.com).Molinspiratio n Cheminformatics gives a large number of devices for handling and controlling particles, like Grins and SDfile transformation, atom standardization, tautomer age, particle discontinuity, estimation of different sub-atomic properties expected in QSAR studies, atomic displaying and drug plan, excellent particle portrayal, and atomic data set devices supporting foundation. Moreover, this program offers information representation, bioactivity forecast, and part based virtual screening. Since molinspiration devices are planned in Java, they can basically run on any registering stage. Drug-resemblance is a subjective term for a characteristic that alludes to how comparable a given particle is to existing meds. It is characterized as a mind boggling difficult exercise between numerous sub-atomic qualities and underlying components. These sub-atomic qualities incorporate hydrophobicity, electronic conveyance, hydrogen holding qualities, particle size and adaptability, and obviously the presence of different pharmacophoric highlights that influence a particle's conduct in a living organic entity, including bioavailability, transport attributes, fondness to proteins, reactivity, toxicity, metabolic soundness, and numerous other factors.The Lipinski rule of five, which manages four clear physicochemical boundary ranges (MWT 500, log P 5, H-security benefactors 5, H-security acceptors 10), is utilized to evaluate the medication similarity of 90% of orally dynamic meds that have accomplished stage II clinical status. To address drug-resemblance as qualities of power, other working out procedures can be used, like ligand productivity and lipophilic effectiveness. These physicochemical qualities associated with digestive penetrability and fluid dissolvability are inside an adequate reach. Physical-synthetic elements, which make up a generally little part

of the all out substance data about the genuine particle, have acquired prevalence as factors in examinations on sub-atomic demonstrating.

3.2 In silico Bioactivity Studies

Utilizing the instrument Molinspiration Cheminformatics server the bioactivity score of a couple of chosen compounds was likewise evaluated. Enormous compound data sets are inspected utilizing this computational science strategy to find potential novel prescription competitors. Virtual screening strategies range from clear ones that check for the presence or nonappearance of specific foundations or a match in determined sub-atomic properties to complex virtual docking methods planned to squeeze potential ligand particles into the objective receptor site. The Molinspiration bioactivity device strikes an incredible blend between screening execution, data needs for another virtual screening undertaking, and screening speed. In the Molinspiration device, the mi screen motor dissects a preparation set of dynamic mixtures (in outrageous cases, even one dynamic particle is sufficient to construct a practical model) and contrasts them and latent atoms utilizing progressed Bayesian measurements. For the preparation, just the Grins or SD document designs of dynamic mixtures are required; information on the dynamic site or it isn't expected to tie system. This is particularly useful in projects when a design based technique can't be utilized because of an absence of information in regards to the 3D receptor structure, for example, in screens planned to recognize ligands that balance G-protein coupled receptors. In light of this exploration, a part based model is made, in which a bioactivity commitment is assessed for every foundation piece. When a model has been created, the bioactivity of the particles that have gone through screening can not entirely set in stone as the amount of the movement commitments of the different atoms' pieces. This yields a sub-atomic action score, which is a number between - 3 and 3. The probability of being dynamic is higher for particles with the most noteworthy action score. Such in silico screening is very speedy; it is feasible to screen enormous assortments of particles (in excess of 100,000 atoms) in a solitary hour. Evaluating models for four critical medication classes — GPCR ligands, particle channel blockers, kinase inhibitors, and atomic receptor ligands — were made in view of the techniques recently announced. Using mi screen's implicit capacities simplifies it to make a virtual evaluating model for any objective. A further advantage of virtual screening conventions in light of Bayesian measurements is their ability to sum up, or to find the general primary requirements for bioactivity. Thus, the methodology is feasible to distinguish novel dynamic design classes notwithstanding new bioactive mixtures that are connected with the preparation set (platform jumping).

3.3 In silico Toxicity Studies

Utilizing a computational technique and a Pentium IV processor running Pallas version 3.1 ADMETox prediction software, the toxicity of the chosen anti-asthmatic drugs was assessed. Double clicking on the symbol launched this software program. The molecule that needed to be predicted was created by double-clicking the new option, and its toxicity was then assessed by choosing the ToxAlert options. Oncogenicity, neurotoxicity, teratogenicity, immunotoxicity, and other forms of toxicities were generated, and the toxicity profile of the chemical was reported.

A few enemy of asthmatic meds were picked, and their ADME characteristics and medication similarity (as per Lipinski's standard of five) results are displayed in Table 1. Aside from ciclesonide and montelukast, every one of the picked drugs have sub-atomic loads that are inside the allowable reach (MWT 500). Instead of enormous sub-atomic weight synthetic compounds, particles with a low sub-atomic weight are all the more promptly consumed, scattered, and shipped. For certain exemptions, as atomic weight rises, the volume of the particles likewise rises relatively.

4. RESULTS AND DISCUSSION

Table 1: ADME Properties of Anti-asthmatic Agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	In silico % absorption
Salbutamol	C13H21NO3	240.12	2.39	73.75	5	5	6	261.12	84.35
Terbutaline	C12H19NO3	226.30	2.08	73.75	5	5	5	264.15	83.11
Ipratropium bromide	C20H30BrNO3	341.50	-2.52	50.41	5	4	7	312.61	85.41
Theophylline	C7H8N4O2	190.18	-0.02	73.69	7	3	4	356.11	82.11
Montelukast	C35H36ClNO3S	591.30	8.91	75.49	5	5	3	245.32	86.53
Fluticasone	C22H27F3O4S	465.62	4.56	75.69	5	6	8	264.11	74.55

Ciclesonide	C32H44O7	641.72	6.75	99.16	8	7	5	312.11	79.12
Salmeterol	C25H37NO4	513.22	4.98	82.96	6	5	2	365.23	84.32

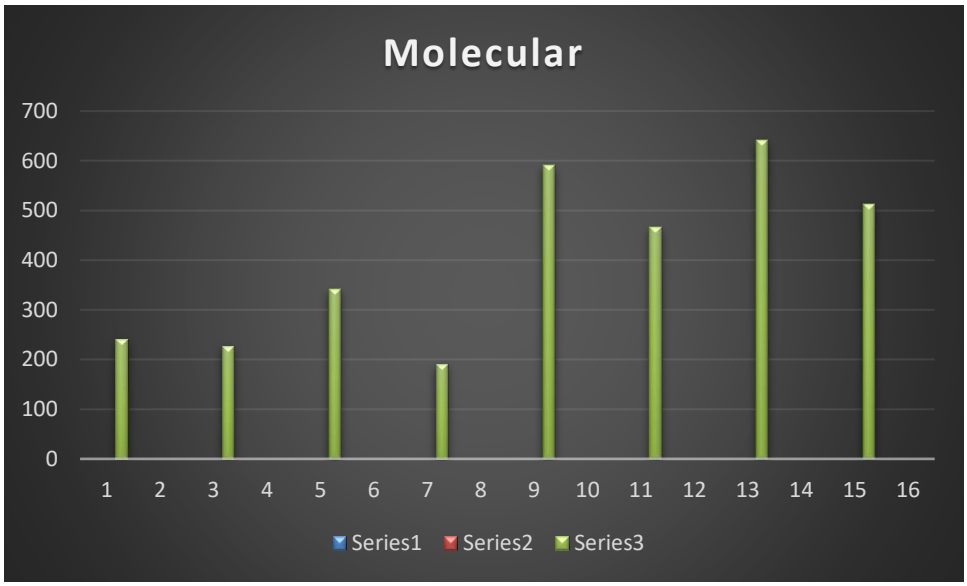

Table 2: Bioactivity of Anti-asthmatic Agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Salbutamol	0.30	-0.04	-0.30	-0.22	0.08	0.20
Terbutaline	0.17	-0.08	-0.40	-0.36	-0.16	0.08
Ipratropium bromide	0.60	0.37	.030	-0.41	-0.09	0.19
Theophylline	-0.45	-0.80	-1.26	-2.64	-1.54	-0.24
Montelukast	0.69	-0.18	-0.19	0.19	0.35	0.31
Fluticasone	0.18	0.03	-0.70	3.01	1.08	0.95
Ciclesonide	-0.04	-0.60	-0.79	0.81	0.25	0.36
Salmeterol	0.39	0.06	0.09	0.18	0.32	0.30

Table 3: Toxicity Profile of Anti-asthmatic Agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Salbutamol	Probable	61	1	30	63	1	1	30
Terbutaline	Probable	61	1	30	63	1	1	30
Ipratropium bromide	High Probable	77	86	1	1	1	1	1
Theophylline	High Probable	86	86	94	1	1	1	1
Montelukast	High Probable	86	86	61	1	1	1	1
Fluticasone	High Probable	86	86	69	55	1	1	1
Ciclesonide	High Probable High Probable	85	86	41	30	1	1	1
Salmeterol	High Probable	91	1	59	41	1	1	30

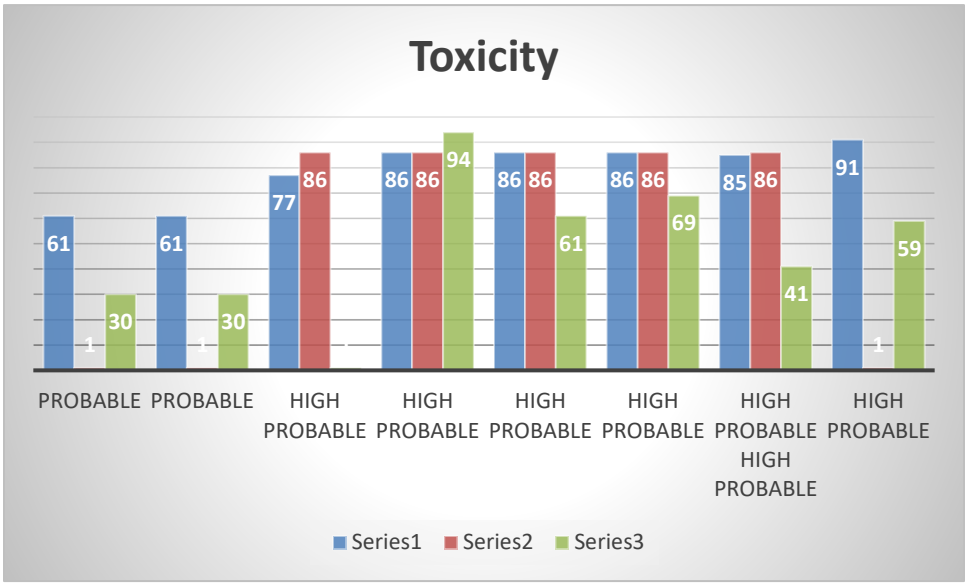

Figure 2: Toxicity Profile of Anti-asthmatic Agents

Montelukast and ciclesonide are two picked enemy of asthmatic drugs that have one infraction of Lipinski's standard of five. Montelukast has a sub-atomic load of 586.20 and a logP esteem that is more noteworthy than okay at 7.89. Except for montelukast, all specialists' MLogPs (octanol/water parcel coefficients) were figured and viewed as satisfactory per Lipinski's standards. The lipophilic productivity, which measures pharmacological power, is determined utilizing the MLogP esteem. Subsequently, the logP worth of the octanol-water parcel coefficient is urgent for QSAR exploration and objective medication plan. The hydrophobicity of the atom is assessed in the pharmacokinetic concentrate by ascertaining the logP esteem since hydrophobicity is pivotal for the conveyance of the medication in the body following retention. Topological Polar Surface Region, or TPSA, is an extremely supportive physiochemical sub-atomic trademark that uncovers data about the extremity of substances. The investigation of the medication transport properties utilized this boundary. The aggregate sum of polar iotas, principally oxygen and nitrogen with connected hydrogen, makes up polar surface region. For all of the picked enemy of asthmatic meds, percent retention was likewise evaluated utilizing the recipe %ABS = 109-(0.345 * TPSA). The sub-atomic volume assesses a particle's vehicle qualities, for example, blood-mind boundary penetrability. The quantity of rotatable bonds was not entirely set in stone to be relevant. A particle turns out to be more adaptable and has a superior restricting partiality to the limiting pocket when it has a bigger number of rotatable bonds. The bioactivity of every enemy of asthmatic medication that was picked was evaluated against six distinct protein setups. At the point when a bioactivity score is more than 0.00, it

demonstrates that there is huge organic movement. Bioactivity scores are partitioned into three fundamental ranges.2. Assuming that the bioactivity score is somewhere in the range of 0.5 and 0.00, moderate activity.3. Idleness is available on the off chance that the bioactivity score is not exactly - 0.50. As per the review's discoveries, the picked specialists make physiological impacts and are physiologically dynamic. Table 2 contains the bioactivity score profiles for the picked specialists in general. Figure 1 shows the bioactivity score diagram of salbutamol for a few proteins. To make another utilitarian medication with a higher restricting selectivity profile and less bad secondary effects, data about the limiting fountain of the drugs is given by the bioactivity score. All chosen anti-asthmatic medications underwent toxicity profile evaluation and are included in Table 3. All of the medications, with the exception of salbutamol and terbutaline, were judged to be extremely probably to cause toxicity. The intriguing toxicological fact is that, with the exception of theophylline, all tested anti-asthmatic medications were found to exhibit teratogenicity. These research results serve as a starting point for the creation of brand-new, very effective anti-asthmatic medications. The knowledge on the pharmacokinetics of the currently available medications provided by computational analysis of all chosen anti-asthmatic pharmaceuticals serves as a guide for the development of new, more effective, and less toxic therapies.

5. CONCLUSION

Specialists have been inspired to find, reveal, and reuse the generally existing and all around described normal mixtures as possible inhibitors of SARS-CoV-2 by the worldwide test presented by the Coronavirus pandemic. Various antiviral substances and prescriptions focus on the primary and nonstructural proteins of SARS-CoV-2. One of the essential targets is the significant protease, one of the primary proteins of the infection. SARS-CoV-2 Mpro is specifically noteworthy to analysts in light of the fact that hindering its headway of Coronavirus can stop the infection's engendering. The objective protein distinguished in the ongoing examination is viral significant protease. SARS-CoV-2 Mpro inhibitors were found by pharmacophore-based virtual evaluating for normal synthetics from the ZINC data set. A painstakingly chosen assortment of financially open mixtures made explicitly for virtual screening designs is the ZINC data set.

REFERENCES

1. Anand K, Palm GJ, Mesters JR, Siddell SG, Ziebuhr J, Hilgenfeld R. Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra α-helical domain. *EMBO J.* 2002;21:3213–3224. doi: 10.1093/emboj/cdf327
2. Brahmi F, Vejux A, Ghzaiel I, et al. Role of diet and nutrients in SARS-CoV-2 infection: incidence on oxidative stress, inflammatory status and viral production. *Nutrients*. 2022;14. doi: 10.3390/nu14112194

3. Chali BU, Melaku T, Berhanu N, et al. Traditional medicine practice in the context of COVID-19 pandemic: community claim in Jimma zone, Oromia, Ethiopia. *Infect Drug Resist*. 2021;14:3773. doi: 10.2147/IDR.S331434
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513. doi: 10.1016/S0140-6736(20)30211-7
5. Chiang LC, Ng LT, Cheng PW, Chiang W, Lin CC. Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. *Clin Exp Pharmacol Physiol*. 2005;32:811–816. doi: 10.1111/j.1440-1681.2005.04270.x
6. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: a review. *J Infect Public Health*. 2020;13:1619–1629. doi: 10.1016/j.jiph.2020.07.001
7. El-Demerdash A, Metwaly AM, Hassan A, et al. Comprehensive virtual screening of the antiviral potentialities of marine polycyclic guanidine alkaloids against SARS-CoV-2 (COVID-19). *Biomolecules*. 2021;11:460. doi: 10.3390/biom11030460
8. Hu Q, Xiong Y, Zhu GH, et al. The SARS-CoV-2 main protease (Mpro): structure, function, and emerging therapies for COVID-19. *MedComm*. 2022;3:e151. doi: 10.1002/mco2.151
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5
10. Issa SS, Sokornova SV, Zhidkin RR, Matveeva TV. The main protease of SARS-CoV-2 as a target for phytochemicals against coronavirus. *Plants*. 2022;11:1862. doi: 10.3390/plants11141862
11. Junaid K, Qasim S, Yasmeen H, et al. Potential inhibitory effect of vitamins against COVID-19. *Comput Mater Contin*. 2020;66(1):707–714. doi: 10.32604/cmc.2020.012976
12. Shahrajabian MH, Sun W, Cheng Q. Chemical components and pharmacological benefits of Basil (Ocimum basilicum): a review. *Int J Food Propert*. 2020;23:1961–1970. doi: 10.1080/10942912.2020.1828456
13. Tiwari S, Dubey N. Traditional medicinal plants as promising source of immunomodulator against covid-19. *J Exper Biol Agric Sci*. 2020;8:S126–S138. doi: 10.18006/2020.8(Spl-1-SARS-CoV-2).S126.S138
14. World Health Organization. *COVID-19 Weekly Epidemiological Update*. Geneva: World Health Organization; 2021.
15. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science*. 2020;368:409–412. doi: 10.1126/science.abb3405