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ORIGINAL RESEARCH

# Inhibitory effects of selected isoquinoline alkaloids against main protease ($M^{pro}$) of SARS-CoV-2, in silico study

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**Abstract**
The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global threat. Despite the production of various vaccines and different treatments, finding natural compounds to control COVID-19 is still a challenging task. Isoquinoline alkaloids are naturally occurring compounds known to have some potential antiviral activity. In this study, ten abundant isoquinoline alkaloids with antiviral activity were selected to analyze the preventive effect on COVID-19. A scrutinized evaluation based on Lipinski's rule showed that one out of ten compounds was toxic. Based on molecular docking analysis using Autodock software one of the best molecules with maximum negative binding energy was selected for further analysis. The Gromacs simulation analysis revealed that Coptisine has more action against active site $M^{pro}$ of COVID-19. Overall, to make a rational design of various preventive analogues that inhibit the COVID-19, associated in vitro and in vivo analyses are needed to confirm this claim.

**Keywords** $M^{pro}$ · Isoquinoline alkaloids · Molecular docking · Inhibitor · Molecular dynamics simulation

## Introduction

COVID-19 has become a global pandemic to the health care system of almost every country in the world. In late December 2019, a new coronavirus was identified, originally named the 2019 new Corona Virus (nCoV 2019), which developed during the spread of the disease in Wuhan, Hubei Province, China (Wu et al. 2020; Narkhede et al. 2020; Kumar et al. 2020). In China, an abrupt prevalence was declared by The Emergency Committee of the World Health Organization (WHO) in late 2020 which was then recognized internationally as a public health emergency (Rodríguez-Morales et al. 2019; Chen et al. 2020). Afterward, the World Health Organization (WHO) has converted the appellation to coronavirus illness (COVID-19), in February 2020 (Khaerunnisa et al. 2020; Velavan and Meyer 2020; Cao 2020). According to the WHO, millions of people have been infected with the coronavirus, and this number is increasing. Lately, the complete number of the patient about around the world was reported to be 235,190,113 confirmed cases with more than 4,808,189 deaths (https://www.worldometers.info/coronavirus/).

One of the identified drug targets among the coronaviruses is main protease ($M^{pro}$), also known as 3CLpro. Amino acid sequences showed that there are many similarities between the main protease of COVID 19 with other SARS-CoV families and the majority of the sequences are conserved. This enzyme plays an important role in the processing of polyproteins translated from viral RNA and it is essential for the efficiency of the virus (Garg and Roy 2020; Alamri et al. 2020; Cao et al. 2020). Inhibition of this enzyme activity would prevent the proliferation of the virus. Despite the production of various vaccines and different treatments, finding natural compounds to control COVID-19 is still a challenging task. (Uddin et al. 2020; Cortegiani et al. 2020). Numerous inhibitors such as dipyridamole, candesartan cilexitil, hydroxychloroquine, chloroquine, disulfiram, atazanavir, indinavir, sulfacetamide, cimetidine, maribavir, and candesartan have been introduced to control SARS-CoV-2 $M^{pro}$ (Li et al. 2020).

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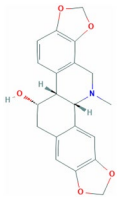
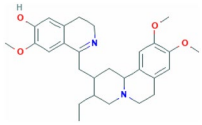
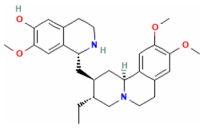
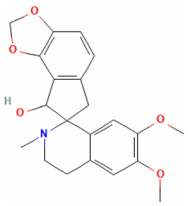
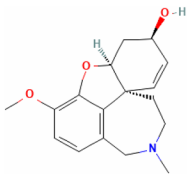
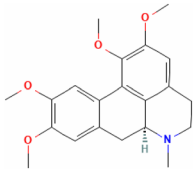
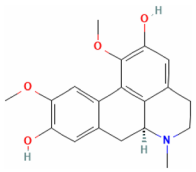
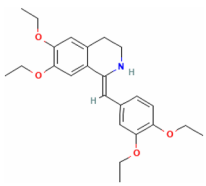
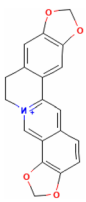
Isoquinoline alkaloids are important metabolites that contain a variety of biological and medicinal activities (Diamond and Desgagné-Penix 2016). Isoquinoline alkaloids are found in the plants (families of Papaveraceae, Fumariaceae, Menispermaceae, Annonaceae, and Rutaceae). These compounds are generally composed of the amino acids of PHE and TYR. Isoquinoline ring is an important feature in all of them (Bentley 2001). Different therapeutic approaches such as antiviral activity, antibacterial, anti-convulsant, anti-tussive, etc., are of special importance (Kukula-Koch and Widelski 2017). Previous studies have tested the effect of selected alkaloids against $M^{pro}$ of COVID-19. The compounds such as Thalimonine, Lycorine, Hemanthamine, Berberine, Hippeastrine, Hirsutine, Fangchinolone, Tetrandrine, Cepharanthine, Skimmianine, and Emetine had the potential to inhibit the $M^{pro}$ (Garg and Roy 2020). Therefore, in this study, ten isoquinoline alkaloid compounds were selected based on their antiviral activity reported in the literature. Chelidonine is found in *Chelidonium majus* and possesses diverse biological activities. Its antiviral activity was reported against immunodeficiency virus type 1 (HIV-1) (Da et al. 2015). Pscychotrine and Cephaeline both can be isolated from the roots of *Psychotria nervosa* and are being tested for potential activity against HIV-1 reverse transcriptase (Chinsembu 2019). Fumaricine is derived from *Fumaria officinalis* and act as an anti-virus (Dey et al. 2020). Galanthamine is an isoquinoline alkaloid that is extracted from *Leucojum aestivum*. It is a potent inhibitor of Herpes simplex type 1 viruses (Georgiev et al. 2012). Glaucine is found in the members of *Papaveraceae* family and shows various medical importance. Various studies reported its potential antivirus (anti-HIV) (Modarresi et al. 2020). Boldine was collected from *Peumus boldus* and has been investigated for the anti-influenza A virus (Zhao et al. 2006). Hydrastine and Coptisine from Ranunculaceae have been found as potential alkaloids against Hepatitis B virus (HBV) is the causative agent of B-type hepatitis in humans (Orhan et al. 2007). This study aimed to investigate the inhibitory nature of isoquinoline alkaloids on Mpro of COVID-19. Therefore, in silico parameters such as toxicity, Lipinski's rule, molecular docking, and molecular dynamics simulation were performed.

**Table 1** Compound structure and PubChem CID of Isoquinoline alkaloids

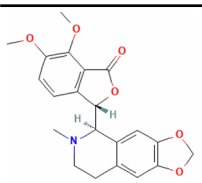
| S. no | Ligands | Compound structure | PubChem CID |
|---|---|---|---|
| 1 | Chelidonine |  | 197,810 |
| 2 | Psychotrin |  | 3,496,498 |
| 3 | Cephaeline |  | 442,195 |
| 4 | Fumaricin |  | 609,998 |
| 5 | Galanthamine |  | 9651 |
| 6 | Glaucine |  | 16,754 |
| 7 | Boldine |  | 10,154 |
| 8 | Drotaverine |  | 1,712,095 |
| 9 | Coptisine |  | 72,322 |

## Methodology

### Protease and ligands download

At first, the isoquinoline alkaloid molecules were fetched from the literature. The 3-dimensional (3D) structure of

**Table 1** (continued)

| S. no | Ligands | Compound structure | PubChem CID |
|---|---|---|---|
| 10 | Hydrastine |  | 197,835 |

the compounds was download from the PubChem chemical database (http://pubchem.ncbi.nlm.nih.gov) (Kim et al. 2016) (Table 1). A crystallographic structure of COVID-19 main protease (PDB ID 6LU7) (Jin et al. 2020) with the resolution of 2.16 Å was obtained from a protein data bank (http://www.rcsb.org).

### The toxicity of ligands

The study of the toxicity of compounds is an important feature in the selection of a drug molecule. In this study, the toxicity of isoquinoline alkaloids (Hepatotoxicity, Mutagenicity, Carcinogenicity, Cytotoxicity, and Immunotoxicity) and their toxicity class were predicted by the ProTox-II server (tox.charite.de/protox_II/) (Banerjee et al. 2018) and Toxtree 2.5.4 tool (Mombelli et al. 2016), respectively.

### Evaluation of Lipinski's parameters

The potential effective of isoquinoline alkaloids compounds was evaluated using the Lipinski parameter to inhibit the activity of COVID-19 main protease. Items such as Molecular weight (Mw), high lipophilicity, hydrogen bonds donor, hydrogen bonds acceptor, and Molar refractivity were considered for the compounds (Walters 2012; Daina et al. 2017a). The SwissADME tools (http://www.swissadme.ch/index.php) (Sadeghi and Zarei 2020; Behbahani et al. 2021) and PubChem (http://pubchem.ncbi.nlm.nih.gov) were used to find Lipinski's rule (Daina et al. 2017b; Sadeghi et al. 2021a).

### Molecular docking

Autodock (version 4.2) (Sadeghi et al. 2022, 2021b) was used to perform molecular binding of each compound with 6LU7. Before molecular docking, the receptor and all compounds were optimized by Chimera software v1.7 (Sadeghi et al. 2021a; Kiffer-Moreira et al. 2014). Water molecules were removed, polar hydrogens were added and charged by Kollman charges. Then the grid box parameters were set to the appropriate scale (70 × 70 × 70 & spacing; 0.383). The 10 conformations were considered for each compound, and the best conformation (lower binding energy) was selected. Finally, Discovery Studio Visualizer (v16.2.0.16349) (Sadeghi and Zarei 2020; Heh et al. 2013) was used to show the two-dimensional image of the ligand-receptor complex.

### Molecular Dynamics simulation (MDs)

Simulation of $M^{pro}$-ligand was studied using MDs for a time of 10 ns using GROMACS program v4.5.5. (Joshi et al. 2020). Gromacs 9643a1 was performed as the force field for the simulation of the $M^{pro}$-ligand complex. The $M^{pro}$-ligand complex was solvated in SPC/E Water Models (Mark and Nilsson 2001). After adding the water, the complex was neutralized by adding three ions $Na^+$. The covalent contacts between the atoms were limited by short energy minimization. Then the system was equilibrated in two stages. The first stage contained a fixed number of particles, volume, and temperature (NVT). The second stage included a constant number of particles, pressure, and temperature (NPT). The simulation was performed at 300 K and 1 bar pressure for 10 ns. Covalent bonds and electrostatic interactions were adjusted by Linear Constraint Solver (LINCS) and Mesh Ewald (PME) methods, respectively. Molecular dynamics simulation protocol between receptor-ligand complex was considered by previous reports (Thirumal et al. 2017). Finally, the stability of the system was calculated by analysis the root mean square deviations (RMSD), an accessible radius of gyration (Rg), and root mean square fluctuations (RMSF).

## Results and discussion

### Toxicity analysis

All selected ligands were tested for toxicity (Table 2). One of the important medicinal properties of a compound is its non-toxicity. Therefore, the comparison of toxicity helps to remove toxic ligands. The toxicity of the compounds is divided into six different classes. The I class is highly toxic, the II and III classes are toxic, the IV class is low toxic and the V and VI classes are safe (Zhu et al. 2017). The results of analysis showed that among ten selected compounds, one compound had hepatotoxicity and immunotoxicity. So, this compound was removed and the remaining nine compounds were examined for Lipinski parameters.

### Lipinski's analysis

The ten selected compounds were compared according to Lipinski parameters (Table 3). These parameters remove ligands that may not be drug candidates. In addition to all of Lipinski's parameters of 5, the Veber filter was considered as

**Table 2** Evaluation of toxicity, toxicity class, and toxicity status of ligands

| Ligands | Hepatotoxicity | Carcinogenicity | Immunotoxicity | Mutagenicity | Toxicity Class | Status |
|---|---|---|---|---|---|---|
| Chelidonine | − | − | − | − | V | N.T |
| Psychotrin | + | − | + | − | III | T |
| Cephaeline | − | − | − | − | VI | N.T |
| Fumaricin | − | − | − | − | V | N.T |
| Galanthamine | − | − | − | − | V | N.T |
| Glaucine | − | − | − | − | V | N.T |
| Boldine | − | − | − | − | V | N.T |
| Drotaverine | − | − | − | − | VI | N.T |
| Coptisine | − | − | − | − | VI | N.T |
| Hydrastine | − | − | − | − | V | N.T |

A positive sign (+) indicates toxicity and a negative sign (−) indicates no toxicity

N.T; no toxic, T; toxic

**Table 3** Lipinski and Veber filter analysis of ligands

| Compounds | Hydrogen bond donors (≤5) | Hydrogen bond acceptors (≤10) | Molecular mass (<500) | Log*p* (<5) | Molar Refractivity (35–150) | Veber filter (30–80) |
|---|---|---|---|---|---|---|
| Chelidonine | 1 | 6 | 353.4 | 2.2 | 96.12 | 60.39 |
| Coptisine | 0 | 4 | 320.3 | 3.5 | 87.95 | 40.80 |
| Cephaeline | 2 | 6 | 466.6 | 4.41 | 142.58 | 63.19 |
| Fumaricin | 1 | 6 | 369.4 | 2.28 | 102.92 | 60.39 |
| Galanthamine | 1 | 4 | 287.35 | 1.8 | 84.05 | 41.93 |
| Glaucine | 0 | 5 | 355.4 | 3.4 | 104.94 | 40.16 |
| Boldine | 2 | 5 | 327.4 | 2.7 | 96.00 | 62.16 |
| Drotaverine | 1 | 5 | 397.5 | 4.5 | 121.38 | 48.95 |
| Hydrastine | 0 | 7 | 383.4 | 2.7 | 103.38 | 66.46 |

another parameter for comparing of isoquinoline alkaloids. The eligibility of most parameters does not guarantee a specific substance as a drug. It only gives information about the drug-likeliness of the drug and only helps to eliminate weak ligands in the preclinical stage. The results of Lipinski parameter showed that all selected isoquinoline alkaloids follow this rule, and therefore 9 selected ligands were considered as drug candidates. The interaction was performed between $M^{pro}$ ligand complexes.

## Molecular docking

Molecular docking is one of the important factors in drug design. In this method, the interaction between the receptor-ligand complexes is predicted, and the docking energy is investigated. The lowest docking energy creates the strongest binding (Sadeghi et al. 2021b). Natural products like coumarins, flavonoids, terpenoids, and diarylheptanoids are potent inhibitors of the $M^{pro}$ (Paraiso et al. 2020). In silico and in vitro studies have found that catechin, quercetin, and gallocatechin are potent inhibitors of the $M^{pro}$ (Mahmud et al. 2021). $M^{pro}$ duplication was inhibited by isoquinoline alkaloids such as cepharanthine, berberine, fangchinoline, berbamine, tetrandrine, coptisine, palmatine, and jatrorrhizine (Chakravarti et al. 2021). Another in silico study

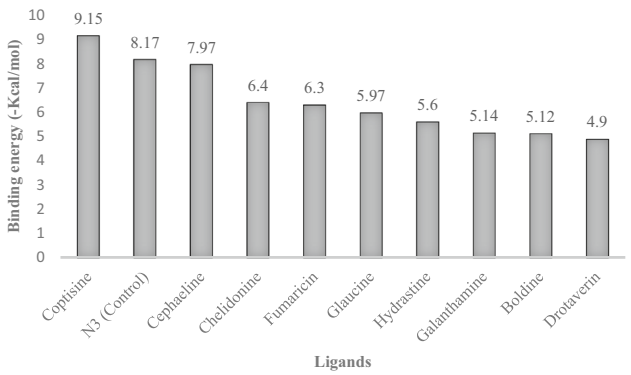



**Fig. 1** The chart related of binding energy (-kcal/mol) of Isoquinoline alkaloids and N3 (Standard inhibitor) with $M^{pro}$

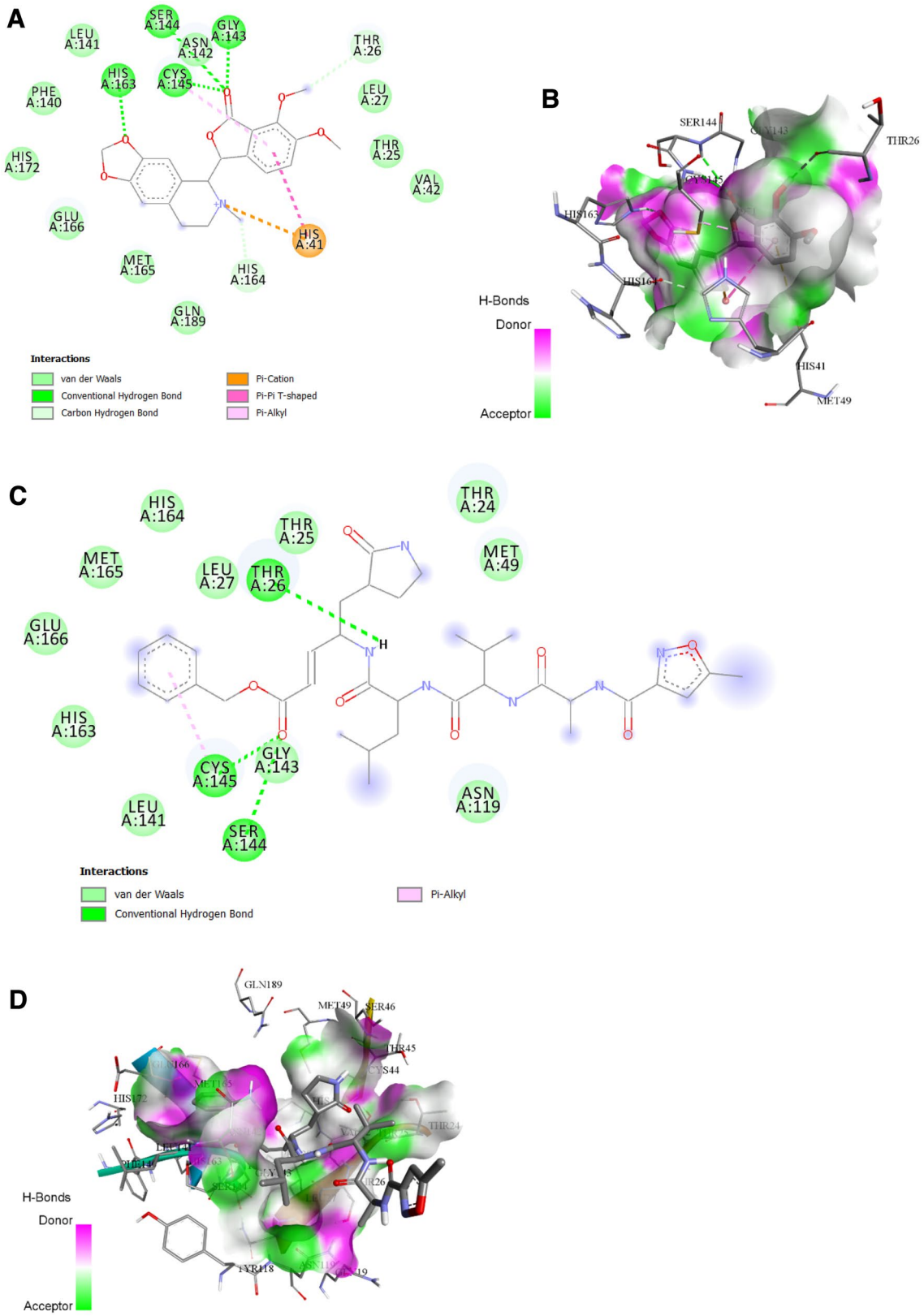



**Fig. 2** 2D and 3D interactions of $M^{pro}$ and two inhibitors: **A** 2D interaction of Coptisine-$M^{pro}$ complex. **B** 3D interaction of Coptisine-$M^{pro}$ complex. **C** 2D interaction of N3-$M^{pro}$ complex. **D** 3D interaction of N3-$M^{pro}$ complex

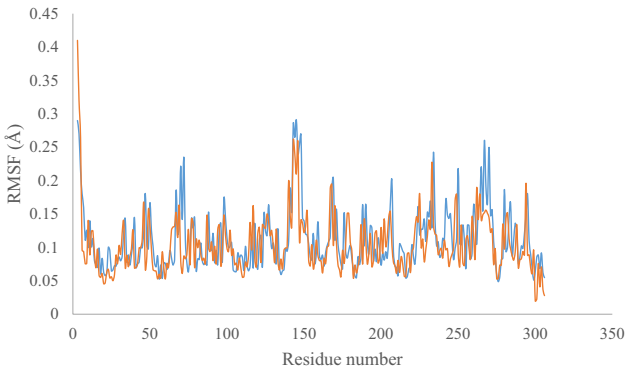



**Fig. 3** Root mean square fluctuation (RMSF). Orange color indicates Coptisine-M$^{pro}$ complex; Blue color indicates N3-M$^{pro}$ complex

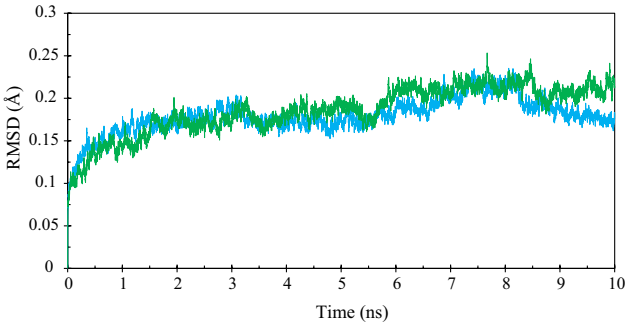



**Fig. 4** Root mean square deviations (RMSD) levels for Coptisine-M$^{pro}$ complex and N3-M$^{pro}$ complex during 10 ns molecular dynamics simulation. Blue color indicates Coptisine-M$^{pro}$ complex; Green color indicates N3-M$^{pro}$ complex

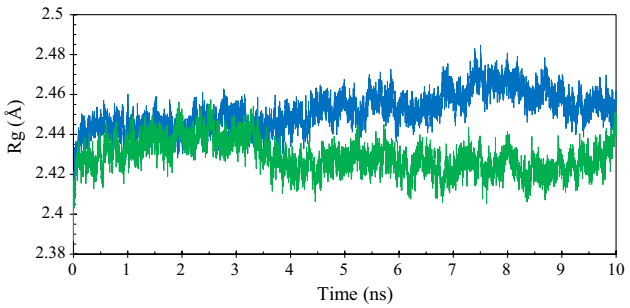



**Fig. 5** radius of gyration (Rg). Green color indicates Coptisine-M$^{pro}$ complex; Blue color indicates N3-M$^{pro}$ complex

showed that berberine, an isoquinoline alkaloid found in the leaves of *Strychnos usambarensis* (Gyebi et al. 2021), cryptoquindoline, and cryptospirolepine, two alkaloids found in *Cryptolepis sanguinolenta* (Borquaye et al. 2020), had high binding affinity for M$^{pro}$. The same study displayed that Hydroxyusambarensine revealed the strongest interactions with M$^{pro}$ of SARS-CoV-2, and Amarogentin exhibited the highest binding affinity and selectivity for M$^{pro}$ of SARS-CoV (Kar et al. 2020).

All the nine selected ligands were placed in M$^{pro}$ active site. According to previous reports, the active site of the M$^{pro}$ includes the amino acids of GLY143, SER144, CYS145, THR26, HIS163, THR27, and HIS172 (Garg and Roy 2020; Mpiana et al. 2020; Enmozhi et al. 2020). Docking scores were calculated for all compounds and compared with the standard inhibitor (N3). The binding energy of the N3-M$^{pro}$ complex was − 8.17 kcal/mol. The binding energy of the ligands was ranged from − 4.9 to − 9.15 kcal/mol (Fig. 1). The results showed that all the compounds had a high potential for binding to M$^{pro}$. But Coptisine-M$^{pro}$ complex had lower binding energy and stronger bond than N3-M$^{pro}$ complex.

In the binding method, N3-M$^{pro}$ complex via three conventional hydrogen bonds (THR26, CYS145, and SER144) as well as eleven van der Waals interactions. However, the Coptisine-M$^{pro}$ complex had better binding energy via four conventional hydrogen bonds (GLY143, SER144, CYS145, and HIS163) and twelve van der Waals interactions (Fig. 2A, B, C, D).

## Molecular dynamics simulation analysis

Molecular dynamics is used to study ligand-receptor complexes overtime at the atomic level. various factors such as RMSF, RMSD, and Rg help in understanding the binding template (Sneha and Doss 2016). Figure 3 depicts the RMSF factor of the N3-M$^{pro}$ complex and Coptisine-M$^{pro}$ complex. RMSF studies the flexibility among the residues in the presence of Coptisine and N3. From the RMSF plot, it was perceived that the Coptisine-M$^{pro}$ complex (fluctuation total = 31.7103) showed a lower fluctuation level than the N3-M$^{pro}$ complex (fluctuation total = 33.8953) indicates the restricted movements during the simulation.

Examining RMSD factors provides accurate structural information in understanding the structural stability of any complex. Therefore the RMSD analysis for M$^{pro}$ was performed in the presence of Coptisine ligand as well as N3 inhibitor. According to the results, the equilibrium of both complexes is established up to 5 ns, but after 5 ns the Coptisine-M$^{pro}$ complex shows less deviation. N3-M$^{pro}$ complex achieves equilibrium at 0.19 nm at 10 ns whereas the Coptisine-M$^{pro}$ complex achieves equilibrium at 0.16 nm at 10 ns (Fig. 4). The lower RMSD factor of the Coptisine-M$^{pro}$ complex indicates higher stability of the Coptisine-M$^{pro}$ complex structure than that of the N3-M$^{pro}$ complex.

To observation the total compactness of resistance M$^{pro}$ in the presence of Coptisine and N3, we performed the Rg level of Coptisine-M$^{pro}$ complex and N3-M$^{pro}$ complex (Fig. 5).

From the plot, it is obvious that the Coptisine-$M^{pro}$ complex showed a lesser Rg level than the N3-$M^{pro}$ complex, demonstrated the low conformational changes during the simulation. This lesser the Rg clarify the complex had more compactness and contrariwise.

## Conclusion

In this study, the aim was to find effective inhibitors among isoquinoline alkaloids against the main protease of COVID 19. Four filtering steps were considered for this purpose. The toxicity of ten ligands was evaluated and nine compounds entered the Lipinski stage. Molecular docking was performed for nine compounds. Among the isoquinoline alkaloids compounds, the Coptisine had the best binding energy compared to the standard inhibitor with a binding energy of − 9.15 kcal/mol. Therefore, molecular dynamics simulations were considered for the Coptisine-$M^{pro}$ complex and N3-$M^{pro}$ complex. RMSD, RMSF, and Rg values were compared for both complexes. It can be concluded that the Coptisine as a natural inhibitor can have a potential effect on the $M^{pro}$ of COVID-19 in silico. The tests in vitro and in vivo are essential to ensure the inhibitory effect of the desired compound.

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**Author contribution** MS: Investigation, Methodology, Project administration, Data curation, Formal analysis, Writing–original draft, Writing–review and editing. MM: Supervision, Resources, Conceptualization, Validation, Writing–review and editing.

**Data availability statement** The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interests.

**Consent to participate** All authors have seen the manuscript and approved to submit the manuscript.

**Consent to publish** All authors consent to the publication of the manuscript.

## References

Alamri MA, Tahir Ul Qamar M, Mirza MU, Bhadane R, Alqahtani SM, Muneer I et al (2020) Pharmacoinformatics and molecular dynamics simulation studies reveal potential covalent and FDA-approved inhibitors of SARS-CoV-2 main protease 3CLpro. J Biomol Struct Dyn 39:4936–4948

Banerjee P, Eckert AO, Schrey AK, Preissner R (2018) ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res 46:W257–W263

Behbahani M, Moradi M, Mohabatkar H (2021) In silico design of a multi-epitope peptide construct as a potential vaccine candidate for Influenza A based on neuraminidase protein. In Silico Pharmacol 9:1–13

Bentley KW (2001) β-Phenylethylamines and the isoquinoline alkaloids. Nat Prod Rep 18:148–170

Borquaye LS, Gasu EN, Ampomah GB, Kyei LK, Amarh MA, Mensah CN et al (2020) Alkaloids from *Cryptolepis sanguinolenta* as potential inhibitors of SARS-CoV-2 viral proteins: an in silico study. BioMed Res Int. https://doi.org/10.1155/2020/5324560

Cao X (2020) COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 20:269–270

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G et al (2020) A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New Engl J Med 382:1787–1799

Chakravarti R, Singh R, Ghosh A, Dey D, Sharma P, Velayutham R et al (2021) A review on potential of natural products in the management of COVID-19. RSC Adv 11:16711–16735

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513

Chinsembu KC (2019) Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants. Rev Bras 29:504–528

Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S (2020) A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 57:279–283

Da C, Gu X, Pei G (2015) 5-Phytochemical and biological research of Chelidonieae pharmaceutical resources. Medicinal plants chemistry, biology and omics. Woodhead Publishing, Cambridge, pp 171–216

Daina A, Michielin O, Zoete V (2017a) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:1–13

Daina A, Michielin O, Zoete V (2017b) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717

Dey P, Kundu A, Kumar A, Gupta M, Lee BM, Bhakta T et al (2020) Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). Recent advances in natural products analysis. Elsevier, Amsterdam, pp 505–567

Diamond A, Desgagné-Penix I (2016) Metabolic engineering for the production of plant isoquinoline alkaloids. Plant Biotechnol J 14:1319–1328

Enmozhi SK, Raja K, Sebastine I, Joseph J (2020) Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. J Biomol Struct Dyn. https://doi.org/10.1080/07391102.2020.1760136

Garg S, Roy A (2020) In silico analysis of selected alkaloids against main protease (Mpro) of SARS-CoV-2. Chemico-Biol Interact 332:1009309

Georgiev V, Ivanov I, Berkov S, Ilieva M, Georgiev M, Gocheva T et al (2012) Galanthamine production by *L. eucojum L. aestivum* shoot culture in a modified bubble column bioreactor with internal sections. Eng Life Sci 12:534–543

Gyebi GA, Ogunro OB, Adegunloye AP, Ogunyemi OM, Afolabi SO (2021) Potential inhibitors of coronavirus 3-chymotrypsin-like protease (3CLpro): an in silico screening of alkaloids and

terpenoids from African medicinal plants. J Biomol Struct Dyn 39:3396–3408
Heh CH, Othman R, Buckle MJ, Sharifuddin Y, Yusof R, Rahman NA (2013) Rational discovery of dengue type 2 non-competitive inhibitors. Chem Biol Drug Des 82:1–11
Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y et al (2020) Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature 582:289–293
Joshi T, Sharma P, Joshi T, Pundir H, Mathpal S, Chandra S (2020) Structure-based screening of novel lichen compounds against SARS Coronavirus main protease (Mpro) as potentials inhibitors of COVID-19. Mol Divers. https://doi.org/10.1007/s11030-020-10118-x
Kar P, Kumar V, Vellingiri B, Sen A, Jaishee N, Anandraj A et al (2020) Anisotine and amarogentin as promising inhibitory candidates against SARS-CoV-2 proteins: a computational investigation. J Biomol Struct Dyn. https://doi.org/10.1080/07391102.2020.1860133
Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S (2020) Potential inhibitor of COVID-19 main Protease (M pro) from several medicinal plant compounds by molecular docking study. Preprints. https://doi.org/10.20944/preprints202003.0226.v1
Kiffer-Moreira T, Sheen CR, da Silva Gasque KC, Bolean M, Ciancaglini P, van Elsas A et al (2014) Catalytic signature of a heat-stable, chimeric human alkaline phosphatase with therapeutic potential. PLoS ONE 9:e89374
Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A et al (2016) PubChem substance and compound databases. Nucleic Acids Res 44:D1202–D1213
Kukula-Koch W, Widelski J (2017) Alkaloids. Pharmacognosy. Elsevier, Amsterdam, pp 163–198
Kumar N, Awasthi A, Kumari A, Sood D, Jain P, Singh T et al (2020) Antitussive noscapine and antiviral drug conjugates as arsenal against COVID-19: a comprehensive chemoinformatics analysis. J Biomol Struct Dyn 40:101–116
Li Z, Li X, Huang Y-Y, Wu Y, Liu R, Zhou L et al (2020) Identify potent SARS-CoV-2 main protease inhibitors via accelerated free energy perturbation-based virtual screening of existing drugs. Proc Natl Acad Sci 117:27381–27387
Mahmud S, Biswas S, Paul GK, Mita MA, Promi MM, Afrose S et al (2021) Plant-based phytochemical screening by targeting main protease of SARS-CoV-2 to design effective potent inhibitors. Biology 10:589
Mark P, Nilsson L (2001) Structure and dynamics of the TIP3P, SPC, and SPC/E water models at 298 K. J Phys Chem A 105:9954–9960
Modarresi M, Chahardoli A, Karimi N, Chahardoli S (2020) Variations of glaucine, quercetin and kaempferol contents in Nigella arvensis against Al2O3, NiO, and TiO2 nanoparticles. Heliyon 6:e04265
Mombelli E, Raitano G, Benfenati E (2016) In silico prediction of chemically induced mutagenicity: how to use QSAR models and interpret their results. In silico methods for predicting drug toxicity. Springer, Berlin, pp 87–105
Mpiana PT, Tshibangu DS, Kilembe JT, Gbolo BZ, Mwanangombo DT, Inkoto CL et al (2020) Identification of potential inhibitors of SARS-CoV-2 main protease from Aloe vera compounds: a molecular docking study. Chem Phys Lett 754:751
Narkhede RR, Pise AV, Cheke RS, Shinde SD (2020) Recognition of natural products as potential inhibitors of COVID-19 main protease (Mpro): In-silico evidences. Natl Prod Bioprospecting 10:297–306
Orhan I, Özçelik B, Karaoğlu T, Şener B (2007) Antiviral and antimicrobial profiles of selected isoquinoline alkaloids from *Fumaria* and *Corydalis* species. Z Für Naturforschung C 62:19–26
Paraiso IL, Revel JS, Stevens JF (2020) Potential use of polyphenols in the battle against COVID-19. Curr Opin Food Sci. https://doi.org/10.1016/j.cofs.2020.08.004
Rodríguez-Morales AJ, MacGregor K, Kanagarajah S, Patel D, Schlagenhauf P (2020) Going global–travel and the 2019 novel coronavirus. Travel Med Infect Dis 33:1078
Sadeghi M, Zarei MA (2020) Molecular docking studies of some flavone analogues as α-Glucosidase inhibitors. J Med Plants 19:55–64
Sadeghi M, Miroliaei M, Shorakai Z (2021a) In silico investigation of flavanone compounds' inhibitory effects on alpha-amylase enzyme and predicting their inhibitory role in diabetes progression. J Fasa Univ Med Sci 10:2786–2795
Sadeghi M, Moradi M, Madanchi H, Johari B (2021b) In silico study of garlic (*Allium sativum* L.)-derived compounds molecular interactions with α-glucosidase. In Silico Pharmacol 9:11
Sadeghi M, Miroliaei M, Fateminasab F, Moradi M (2022) Screening cyclooxygenase-2 inhibitors from *Allium sativum* L. compounds: in silico approach. J Mol Model 28:1–12
Sneha P, Doss CGP (2016) Molecular dynamics: new frontier in personalized medicine. Advances in protein chemistry and structural biology, 102nd edn. Elsevier, Amsterdam, pp 181–224
Thirumal KD, Lavanya P, George PDC, Tayubi IA, Naveen KD, Francis YI et al (2017) A molecular docking and dynamics approach to screen potent inhibitors against fosfomycin resistant enzyme in clinical klebsiella pneumoniae. J Cell Biochem 118:4088–4094
Uddin M, Mustafa F, Rizvi TA, Loney T, Suwaidi HA, Al-Marzouqi AHH et al (2020) SARS-CoV-2/COVID-19: Viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses 12:526
Velavan TP, Meyer CG (2020) The COVID-19 epidemic. Trop Med Int Health 25:278
Walters WP (2012) Going further than Lipinski's rule in drug design. Expert Opin Drug Discov 7:99–107
Wu JT, Leung K, Leung GM (2020) Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 395:689–697
Zhao Q, Zhao Y, Wang K (2006) Antinociceptive and free radical scavenging activities of alkaloids isolated from *Lindera angustifolia* Chen. J Ethnopharmacol 106:408–413
Zhu YC, Yao J, Adamczyk J, Luttrell R (2017) Feeding toxicity and impact of imidacloprid formulation and mixtures with six representative pesticides at residue concentrations on honey bee physiology (*Apis mellifera*). PLoS ONE 12:e0178421