Discovery of Potential Plant-derived Iradoides with COVID-19 M^{pro} *in silico*

Mohd Rehan (✉ rehancy3@gmail.com)

AMU Aligarh

Research Article

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Abstract

Iradoides are a small class of plant derived natural products, which used in traditional system of medicine such as Unani, Tibetan, Ayurveda, Siddha, and Chinese medicine. The several diverse types of iradoides have been isolated from many parts of the plant such as root, leaves, flowers, stem, rhizomes, bark, and seed. Here, we used bioactive iradoides to know the potency against COVID-19 M^{pro}. The COVID-19 M^{pro} is a potential target of the drug, which identified by Chinese scientist (published manuscript in Nature on June 2020). From several studies, we found that many natural products such as flavonoids, saponins, steroids, terpenoids, and synthesized compounds have been used on this target (COVID-19 M^{pro}). We screened a series of iradoides against COVID-19 M^{pro} (PDB ID: 6LU7) by using many docking software as BIOVIA Discovery Studio 2017 R2, Chimera 1.13.1, Auto Dock Tools-1.5.6, AutoDock Vina to known best inhibitor against COVID-19 M^{pro}. According to obtained results, 6'-O-trans-feruloylnegundoside, p-hydroxybenzoyl-6'-O-trans-caffeoylgardoside, 2'-O-p-hydroxybenzoyl gardoside, 6-deoxyharpagide, reptoside show binding energies -8.1, -8.3, -8.2, -7.0, and -7.1 Kcal/mol, respectively. From this study, we found that all iradoides show more potency on COVID-19 M^{pro} when compared with Chloroquine and hydroxychloroquine. The Chloroquine and hydroxychloroquine used as standards for comparison. From the results of this study, we found that iradoides may be useful in the treatment of COVID-19 patients.

1. Introduction

The new strain of of coronavirus [named COVID-19 (coronavirus disease 2019)] was first time reported at the end of 2019 in Wuhan, China and spreading globally. The COVID-19 now known severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which belongs to the genus betacoronavirus and causing severe acute respiratory syndrome (SARS) in human [1]. The coronaviruses are positive sense, single stranded RNA viruses, genome range from 26 to 32 kilobases in length [2]. The coronaviruses family divided into four categories such as (a) α -coronaviruses includes the human coronaviruses (HCoV)-NL-63 and HCoV-229E (b) β -coronaviruses contains HCoV-OC43, HCoV-HKU1, MARS-CoV (Middle Eastern Respiratory Syndrome coronaviruses), and SARS-HCoV (Severe Acute Respiratory Syndrome human coronaviruses); (c) γ -coronaviruses contains birds and whales viruses; (d) δ -coronaviruses, which isolated from birds and pigs [3]. The genome of SARS-CoV-2 is closely related (with about 88 % similarity) to two bats-derived SARS-like coronaviruses (bat-SL-CoVZXC21 and bat-SL-CoVZC45) [4]. The infection of this virus (SARS-CoV-2) is seen in major organs as the lungs, liver, kidney, hearts and genitals [5-7]. Early symptoms of this virus are chest and muscle pain, cough and chills, persistent fever, breathlessness, etc. Severe conditions include sudden confusions, trouble breathing, chest pain, and bluish lips or face [8]. The human infection is spreading from novel SARS-2 β -coronavirus by human to human transmission in the World [9]. Approximately, 15,18,12,556 cumulative cases and 31,86,817 cumulative deaths have been confirmed till 04 may 2021, according to the WHO report [10]. There are not available approved vaccines and drugs for treatment of this infection. Few anti-viral drugs are being used for treatment of this infection, but human infection is being increased day by day [11].

Main protease (M^{pro}) of SARS-2 is the best target of several drugs. In current, many potential bioactive natural products as saponins, flavonoids, steroids, terpenes, are used on COVID-19 M^{pro} *in silico* [12-14]. In this study, we used diverse types of iradoides on this target using molecular docking. The iradoides are a small class of bioactive natural products, which have been reported from several parts of medicinal plants as bark, stem, root, leaves, rhizomes, flowers. The several diverse types of iradoides have been used in pharmacology as bacterial infection, malaria, inflammation, neuroprotection, perkinson disease, diabetes, cancer disease etc [15]. The many iradoides glycoside from *Fructus gardenia* shown antiviral activity against influenza A virus by PACT-dependent suppression of viral RNA replication [16]. These exhibited an antiasthmatic effect by suppression of elevated IgE, IL-4, and IL-13 level and eosinoplilia in the plasma, so are useful in antiallergic activity [17]. These iradoides increased activities of SOD, NO, GSH-Px, and NOS production, so are more effective anti-oxidant [18]. The iradoides glycoside restricts HIV-1 replication on the early stage of HIV infection, so shows anti-HIV activity [19]. These increased social interaction time and demonstrated to exert an anxiolytic effect [20]. These iradoides have potent in vitro activity against respiratory syncytial virus [21]. The above activities confirmed that bioactive iradoides are most useful in infection.

The chloroquine is an anti-viral medicine, which have high potential to treat and prevent viral infection [22]. This drug has been used to treat COVID-19 patients, but there is not a specific treatment for SARS-CoV-2 infection. There is an immediate need of specific drugs or vaccines to treat of this infection. The computational screening studies can play a pivotal in COVID-19 drug discovery and save money, time resources. In this article, we screened diverse types of plant derived iradoides against COVID-19 M^{pro} using molecular docking. From these studies, we identified the potential of iradoides against COVID-19 M^{pro}.

2. Materials And Methods

2.1. Preparation of Protein

We obtained protein of COVID-19 M^{pro} from protein data bank (<https://www.rcsb.org>) (PDB ID: 6LU7) [23]. Protein Data Bank (PDB) is a database of large biological molecules such as nucleic acids and protein. BIOVIA Discovery Studio 2017 R2 software (San Diego, CA, USA) was used to remove H₂O and ligand from protein. After removing H₂O and ligand, this protein was saved in PDB format. PDB file of this protein was opened in Auto Dock Tools-1.5.6 software (Scripps Research Institute, San Diego, Florida, US (<http://vina.scripps.edu/>)). In this software, the hydrogen atom and gasteiger charges were added and grid box generated by grid dimension and grid center by proximity to ligand. This protein was saved in a pdbqt format by this software.

2.2. Preparation of Ligands

3D-structures of all diverse types of iradoides was performed by using software Chem 3D Pro 12.0.2.1076 (Perkin Elmer, Waltham, US) and saved in PDB format. This PDB file was opened in Auto

Dock Tools-1.5.6 software, compute gasteiger charges, non polar hydrogen added. All diverse types ligand (iradoides) was saved in a pdbqt format by this software.

2.3. Molecular Docking

The pdbqt file from all diverse types of iradoides and pdbqt file of protein (COVID-19 M^{Pro}) were performed by using Auto Dock Tools-1.5.6 software. The docking calculation of ligand (diverse types of iradoides) with protein was performed on AutoDockVina software (Scripps Research Institute, San Diego, Florida, US). AutoDock Vina is much faster and give more accurate results of ligand-binding affinity. This is free open-source packages and is very easy to use [24]. Vina shows best performance in calculating the ligand-binding affinity for many targets such as amyloid beta 1-40 peptide system [25], cytochrome P450 [26], and influenza virus [27].

Finally, visualization of all iradoides with protein was performed in BIOVIA Discovery Studio 2017 R2 software (San Diego, CA, USA). Two drugs as chloroquine and hydroxychloroquine were docked for known binding energy with COVID-19 M^{Pro} (*in silico*). These drugs have high potency and used against COVID-19, experimentally [28]. These effective drugs are utilized as a positive control.

3. Results And Discussion

The all diverse types of iradoides were screened with 6LU7 M^{Pro} (COVID-19 M^{Pro}) for known high potency against COVID-19. The iradoide glucosides as 6'-O-trans-feruloylnegundoside (**1**) from *Vitex altissima* [29] shows binding energy -8.1 Kcal/mole at the active site of COVID-19. It forms one conventional hydrogen bond with residue Ile-152 at 2.35 distances and one alkyl hydrophobic bond with residue Lys-12 at 4.17 distance (Fig. 1, structure 1, Fig. 2, entry 1, and Fig. 7, entry 1). The 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoylgardoside (**2**) [29] shows binding energy -8.3 Kcal/mole. It forms one conventional hydrogen bond with Thr-280 at 2.00 distances, two carbon hydrogen bond with Gly-215, Asp-216 at 3.49, 3.09, 3.75 distances, and one alkyl hydrophobic bond with Leu-282 at 5.46 distances (Fig. 1, structure 2, Fig. 2, entry 2, and Fig. 7, entry 2). The 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoyl-8-epiloganic acid (**3**) [29] shows binding energy -8.4 Kcal/mole. It forms binding interaction with amino acid Ser-1, Asp-153 at 1.95, 2.53 distance (Fig. 1, structure 3, Fig. 2, entry 3, and Fig. 7, entry 3). The 2'-O-p-hydroxybenzoyl gardoside (**4**) [29] shows binding energy -8.2 Kcal/mole. It forms three conventional hydrogen bonds with amino acid Trp-218, Asn-274, Arg-279 at 3.10, 2.68, 2.65, one carbon hydrogen bond at Asn-274 at 3.40 distances, and one pi cation bond with Arg-279 at 4.23 distances (Fig. 1, structure 4, Fig. 2, entry 4, and Fig. 7, entry 4). The natural iradoide (**5**) [30] shows binding energy -9.7 Kcal/mole at the active site of COVID-19. It forms binding interaction with amino acid Leu-272, Leu-286 at 4.76, 5.33 distance (Fig. 1, structure 5, Fig. 2, entry 5, and Fig. 7, entry 5). The bioactive iradoide (**6**) [30] shows binding energy -8.4 Kcal/mole. This compound forms carbon hydrogen interaction with residue Ser-139, alkyl hydrophobic interaction with Lys-137 (Fig. 1, structure 6, Fig. 2, entry 6, and Fig. 7, entry 6). The potential iradoide (**7**) [31] isolated from *Gentiana triflora*, forms binding interaction with amino acid Asp-153, Pro-9, Ile-152, Arg-298 at 3.77, 3.91, 4.31, 5.06 distances (binding energy -7.9 Kcal/mole) (Fig. 1, structure 7, Fig. 2, entry 7, and Fig. 7, entry 7).

The high potential iradoide (**8**) from *Valeriana* [32] forms carbon hydrogen bond interaction with amino acid Tyr-237 and pi alkyl hydrophobic interaction with Tyr-237 (binding energy -8.1 Kcal/mole) (Fig. 3, structure 8, Fig. 4, entry 8, and Fig. 7, entry 8). The patented iradoide (**9**) from *Valeriana officinalis* [33] forms three conventional hydrogen bonds with amino acid Ser-1, Asn-214, Thr-280, one carbon hydrogen bond with Leu-282, one pi-pi stacked bond with phe-305, and two alkyl/pi-alkyl bond with Trp-218, Arg-279 (Fig. 3, structure 9, Fig. 4, entry 9, and Fig. 7 entry 9). The cytotoxic iradoide (**10**) [33] shows binding energy -7.9 Kcal/mole and forms conventional hydrogen bond with amino acid Asn-238, three carbon hydrogen bond with Leu-287, Tyr-237, Thr-199, and three alkyl hydrogen bond Leu-287, Leu-271, Met-276 (Fig. 3, structure 10, Fig. 4, entry 10, and Fig. 7, entry 10). The inhibitory iradoide (**11**) was reported from *Eucommia ulmoides* [34], which forms four conventional hydrogen bonds with residues Leu-287, Asp-289, Lys-137, Arg-131, and one alkyl hydrophobic bond with Leu-272 (binding energy -6.9 Kcal/mole) (Fig. 3, structure 11, Fig. 4 entry 11, and Fig. 7, entry 11). The anticancerous active iradoide (**12**) from *Swertia mussoitii* [35], shows binding energy -7.6 Kcal/mole. It forms carbon hydrogen binding interaction with amino acid Thr-199, and alkyl hydrophobic interaction with Lys-137, and Leu-286, Leu-287, Met-276 (Fig. 3, structure 12, Fig. 4, entry 12, and Fig. 7, entry 12). The valtrate J iradoide (**13**) [36] shows binding energy -6.8 Kcal/mole and forms one conventional hydrogen bond interaction with amino acid Thr-199, three carbon hydrogen bond Leu-287, Thr-199, Tyr-239, and alkyl/pi-alkyl hydrophobic interaction with Tyr-237, Leu-286, Leu-287 (Fig. 3, structure 13, Fig. 4, entry 13, and Fig. 7, entry 13). The bioactive iradoide (**14**) [33] shows binding energy -6.3 Kcal/mole and forms conventional hydrogen bond interaction with amino acid Arg-4, and alkyl/pi-alkyl hydrophobic interaction with Trp-207, Leu-282, Phe-291 (Fig. 3, structure 14, Fig. 4, entry 14, and Fig. 7, entry 14). The active iradoide (**15**) from *Swertia mussoitii* [37], shows binding energy -6.5 Kcal/mole and forms two conventional hydrogen bonds with residues Ser-158, Gln-110, and one pi-alkyl hydrophobic bond with Phe-294 (Fig. 3, structure 15, Fig. 4, entry 15, and Fig. 7, entry 15).

Ajuga bracteosa has high potential in medicine, which used is diseases as pneumonia, hepatitis. Two iradoides as 6-deoxyharpagide (**16**) and reptoside (**17**) have been isolated from this species [38-40]. The 6-deoxyharpagide (**16**) forms four hydrogen bonds with Ser-267, Phe-219, Gly-275, Asn-277, one pi-alkyl bond with Trp-218, and one violation bond with Arg-279 (Fig. 5, structure 16, Fig. 6, entry 16, and Fig. 7, entry 16). The reptoside (**17**) shows binding energy -7.1 Kcal/mole and forms one conventional hydrogen bond with Phe-219, and one carbon hydrogen bond with Phe-219 (Fig. 5, structure 17, Fig. 6, entry 17, and Fig. 7, entry 17). *Vitex peduncularis* has high medicinal importance, which used for malarial type fever, especially in black water fever. The new iradoides as pedunculariside (**18**) and agnuside (**19**) have been reported from stem bark of this plant [41]. The pedunculariside (**18**) screened *in silico*, which forms two conventional hydrogen bond interaction with Gln-127, Lys-5, one carbon hydrogen bond interaction with Val-125, and one pi-alkyl hydrophobic bond with Tyr-126 (Fig. 5, structure 18, Fig. 6, entry 18, and Fig. 7, entry 18). The agnuside (**19**) has high potential, which shows binding energy -8.0 Kcal/mole. It forms binding interaction with amino acid Asp-153, Gln-110, Ile-249 (Fig. 5, structure 19, Fig. 6, entry 19, and Fig. 7, entry 19). The *Scrophularia deserti* found in Saudi Arabia, which use in hypoglycaemic, as a diuretic in typhoid fever, kidney infection, lung, etc. The harpagoside (**20**), scropolioside-D2 (**21**) and koelzioside (**22**)

were isolated from the aerial parts of *Scrophularia deserti* [42-43]. The harpagoside (**20**) forms three conventional hydrogen bond interaction with Thr-199, Leu-271, Thr-199, two carbon hydrogen bond with Leu-272, Leu-287, and pi-alkyl hydrophobic bond with Tyr-239 (Fig. 5, structure 20, Fig. 6, entry 20, and Fig. 7, entry 20). The scropolioside-D2 (**21**) is more inhibitory iradoide, which shows binding energy -9.4 Kcal/mole. It forms four conventional hydrogen bonds, two alkyl/pi-alkyl hydrophobic bond, and one violation bond with COVID-19 protein (Fig. 5, structure 21, Fig. 6, entry 21, and Fig. 7, entry 21). The koelzioside (**22**) has high potency with COVID-19 M^{Pro}, because shows binding energy -9.0 Kcal/mole. It forms two conventional hydrogen bonds with Lys-5, Leu-282, two carbon hydrogen bond with Lys-137, Ser-284, and alkyl hydrophobic bond with Leu-286, Lys-137 (Fig. 5, structure 22, Fig. 6, entry 22, and Fig. 7, entry 22). The chloroquine (**23**) and hydroxychloroquine (**24**) are more effective drugs, which have been used for treatment of COVID-19 patients. The chloroquine (**23**) and hydrochloroquine (**24**) shows binding energies -5.6 and -4.6 Kcal/mole with COVID-19 M^{Pro} (PDB ID: 6LU7). The chloroquine and hydroxychloroquine drugs are used as a positive control.

Currently, coronaviruses have a major problem for health, which infecting liver, respiratory, digestive, and central nervous systems humans. There are no specific clinical treatment SARS-CoV-2 medicated infection [44]. Thus, we urgent, necessary to identify novel drug for treatment of this infection. In the present study, we use medicinal plant derived diverse types of iradoides against COVID-19 M^{Pro} in silico. Approximately, 22 diverse types of iradoides are showing more binding energy with COVID-19 M^{Pro} than chloroquine and hydroxychloroquine. The harpagoside (**20**), scropolioside-D2 (**21**) and koelzioside (**22**) showing excellent binding energy with COVID-19 M^{Pro}. The aerial parts of *Scrophularia deserti* plant are the main source of these iradoides. The 6'-O-trans-feruloylnegundoside (**1**), 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoylgardoside (**2**), 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoyl-8-epiloganic acid (**3**), and 2'-O-p-hydroxybenzoyl gardoside (**4**) showing moderate binding energy (range = -8.1 to -8.4 Kcal/mol) with COVID-19 M^{Pro}. The *Vitex altissima* species of medicinal plant is a source of these potential iradoides. The 6-deoxyharpagide (**16**) and reptoside (**17**) showing strong binding energy (range = -7.0 to -7.1 Kcal/mol) with COVID-19 M^{Pro}. The *Ajuga bracteosa* plant has high potential in medicine, which is the main source of these iradoides. These effective iradoides play highly potential role in drug discovery.

4. Conclusion

In summary, COVID-19 is the major problem of whole world, which being increased day by day. Currently, no specific drug is available for treatment of this disease. But several drugs are available, which act on M^{Pro} for treatment of this disease. Several drugs are being used in trial form for treatment of COVID-19 patients day by day. In the present study, we screened 35 medicinal plants based iradoides with COVID-19 M^{Pro}, in which, approximately, 22 iradoides show more binding energy than chloroquine and hydroxychloroquine. From this study, we observed that several diverse types of iradoides target of COVID-19 M^{Pro}. So, we need further research on plant based iradoides for treatment of COVID-19.

Declarations

Conflict of interest

The author declares no conflict of interest.

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Figures

Figure 1

Binding energy of diverse type of iradoides (entry, 1-7) with COVID-19 Mpro (PDB ID: 6LU7)

Figure 2

Binding interaction with bond distance of ligand (iradoides entry 1-7, ball and stick, brown color) with 6LU7 amino acid (stick, green color)

Figure 3

Iradoides (entry 8-15) binding energy with 6LU7 protein

Figure 4

Ligand interaction of iradoides (entry 8-15, structure brown color) with amino acid of COVID-19 Mpro.

Figure 5

Ligand (iradoides, entry 16-22) binding energy with 6LU7 of COVID-19 Mpro.

Figure 6

Iradoides (entry 16-22, ball and stick, brown color) binding interaction with amino acid (stick form, green color) of 6LU7 protein.

Figure 7

Docking studies of natural products iradoides (entry 1-22, ball and stick, brown color), chloroquine (entry 23, ball and stick, pink color), hydroxychloroquine (entry 24, ball and stick, pink color) with COVID-19 Mpro protein (ribbon form)