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Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors

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ABSTRACT

The SARS-CoV-2 causes severe pulmonary infectious disease with an exponential spread-ability. In the present research, we have tried to look into the molecular cause of disease, dealing with the development and spread of the coronavirus disease 2019 (COVID-19). Therefore, different approaches have investigated against disease development and infection in this research; First, We identified hsa-miR-1307-3p out of 1872 pooled microRNAs, as the best miRNA, with the highest affinity to SARS-CoV-2 genome and its related cell signaling pathways. Second, the findings presented that this miRNA had a considerable role in PI3K/Act, endocytosis, and type 2 diabetes, moreover, it may play a critical role in the prevention of GRP78 production and the virus entering, proliferation and development. Third, nearly 1033 medicinal herbal compounds were collected and docked with ACE2, TMPRSS2, GRP78, and AT1R receptors, which were the most noticeable receptors in causing the COVID-19. Among them, there were three common compounds including berbamine, hypericin, and hesperidin, which were more effective and appropriate to prevent the COVID-19 infection. Also, it was revealed some of these chemical compounds which had a greater affinity for AT1R receptor inhibitors can be suitable therapeutic targets for inhibiting AT1R and preventing the adverse side effects of this receptor. According to the result, clinical assessment of these three herbal compounds and hsa-miR-1307-3p may have significant outcomes for the prevention, control, and treatment of COVID-19 infection.

1. Introduction

The SARS-CoV-2 induces severe respiratory syndrome in humans [1]. The viral major proteins include spike (S) protein, matrix protein (M), small envelope protein (E) protein, and nucleocapsid protein (N) [2]. The location of viral attachment to the host cell resides within the S protein [3]. SARS-CoV-2 is able to bind to angiotensin-converting enzyme 2 (ACE2) [4], transmembrane protease serine 2 (TMPRSS2) [5], glucose regulating protein 78 (GRP78) [6]. There are several strategies to tackle the SARS-CoV-2, including inhibiting virus multiplication, inhibiting virus entry through receptors (blocking receptors), and blocking viral proteins. The first approach is using miRNAs’ to attach to the 3’UTR of the SARS-CoV-2 genome, so that viral translation will be inhibited [7,8]. Blocking the aforementioned three receptors is the second approach to prevent SARS-CoV-2. It has suggested that decreasing the levels of ACE2 on the cell surface or inhibiting its function, helps in preventing SARS-CoV-2 infection [9]. By binding the spike protein to the ACE2, the angiotensin 2 is produced in large quantities by the ACE and then binds to the AT1R receptor. This process leads to fibrosis and damage lung tissues. A possible way of combating the infection could be the injection of soluble ACE2 into the bloodstream which will have the two-fold effect; preventing the attachment of the virus to non-infected cells and replenishing ACE2 in infected cells [3]. Secondly, it is assumed that SARS-CoV-2 uses the serine protease TMPRSS2 for S protein priming [10,11]. So, the inhibition of TMPRSS2 protease is required for a robust blockade of viral entry. Thirdly, given the fact that diabetic individuals are more likely to get infected by the SARS-CoV-2 virus as its receptor is highly expressed on the lung and intestine and liver cells of individuals with type 2 diabetes. To our knowledge the role of GRP78 is facilitating the entrance of virus to the

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host cells [12]. Finally, the AT1R receptor is one of the important receptors in modulating blood pressure. High blood pressure is directly linked to the SARS-CoV-2 virus, by inhibition of this receptor, presumably we would be able to prohibit lung injury. Researches have shown that some of the AT1R-blockers such as Azilsartan and Olmesartan can overexpress the ACE2 and it could be a risky situation for SARA-CoV-2 entry [13]. The third approach could be to target the respective enzyme to prevent the virus from progressing and surviving in the host cell. In this study, we have surveyed these approaches to address alternative therapeutic methods against viral infection. For this purpose, thirty medicinal herbs that have the most impact on the pathways associated with each receptor were selected to analyze their affinity to bind the ACE2, TMPRSS2, GRP78, and AT1R receptors. Besides, to control the virus genome, a comprehensive investigation was performed on the SARS-CoV-2 genome inhibitors.

2. Material and methods

Information about the virus (structure, reproduction, and genome) was obtained from the Viral Zone database (www.viralzone.expasy.org) [14].

2.1. Calculation of 3' UTR and miRNAs affinity

The nucleotide sequences of all 1872 miRNAs were downloaded from the miRBase database (http://mirbase.org) [15] and their expression levels were determined in normal lung squamous cells and lung tissue through TCGA-Assembler 2 package by R software, version 4.0.0 [16]; non-expressed microRNAs were deleted. Then, the 3' UTR sequence of the SARS-CoV-2 RNA was obtained from NCBI database entry MTO49951.1 (www.ncbi.nlm.nih.gov) [17]. The affinity between each miRNA and 3' UTR of the viral genome was computed by the RNAhybrid database (https://bio.tools/rnahybrid) [18].

2.2. Identification of the efficient miRNAs, and transcriptional factors

By using the miRWalk database (http://mirwalk.umm.uni-heidelberg.de/) [19] and the TransmiR database (http://www.cuilab.cn) [20] the targetome and transcription factors of the best miRNA were achieved. Then, those which had expression in lung tissue were checked and selected by the TCGA-Assembler 2 package of R software. Finally, the signaling pathways of the selected miRNAs, targetome, and transcription factors were separately obtained from the KEGG database (www.kegg.jp) [21]. The schematic figure of the signaling pathways related to both targetome and transcription factors of the best miRNAs were drown by the Biorender software. The targetome schematic figure was produced by Cytoscape software, version 3.8.0 [22].

2.3. Modeling analysis for each receptor

First, the sequence of ACE2, GRP78, TMPRSS2, and AT1R receptors were acquired from the NCBI database and modeled using SWISSMODEL modeling tools (https://swissmodel.expasy.org/) [23]. The SARS-CoV-2 structure was downloaded from the RCSB PDB database (https://www.rcsb.org/) [24] and the binding site of each receptor related to SARS-CoV-2 obtained from articles.

2.4. Collecting the herbal phytochemicals

After determining thirty medicinal herbs (Table 1), their phytochemical compounds were obtained by reviewing different articles that have used gas chromatography-mass spectrometry (GC-MS) technique. The 3-D structure of 1033 compounds from thirty herbs and that of each receptor blockers were downloaded from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/) [25].

2.5. Preparation and molecular docking analysis

The 3-D structure of receptor blockers (Table 2) and herbal compounds were prepared for docking by removing all water and H-bond optimization, then, Gasteiger charges were added. After that, molecular docking analysis was performed for each herbal compound and receptor blockers using AutoDock vina. Figures were made by Chimera software version 1.14 [26].

2.6. Determination of beneficial compounds characteristics

The activity, daily dose carcinogenicity, blood-brain barrier penetration, and antiviral features caught from way 2 drug [27] (www.pharmaexpert.ru/passonline/predict.php), lazar (lazar.in-silico.ch/predict) [28] and AVCPred (http://crdd.osdd.net/servers/avcpred) [29], respectively.

3. Results

3.1. Selecting the most efficient miRNAs

According to affinity examination between 3' UTR of SARS-CoV-2 and all 1872 miRNAs, 42 miRNAs with the highest score were identified (Table 3). Among them, hsa-miR-1307-3p had the highest score among miRNAs with −37.6 kCal/mol, and high expression level in lung and squamous tissues (Fig. 1).

3.2. The hsa-miR-1307-3p targetome enrichment study

Approximately 377 predicted and valid targets of hsa-miR-1307-3p which were predicted (Supplementary figure 1). The results revealed hsa-miR-1307-3p had an important role in the “PI3K/Act signaling pathway”, “endocytosis signaling pathway”, and “type 2 diabetes signaling pathway” (Fig. 2). SP1, CREB1, MYC, ELF1, CTCF, MAX, GABPA, MAI1, and TAF1, are the most notable of transcription factors.

| Name of receptor blockers for TMPRSS2, AT1R, and GRP78. |
|---------------------------------------------------------|
| Meclizine                                               |
| Probufol                                                |
| Amhralin                                                |
| 2,3-dihydroxy-6,7- dichloroquinoxaline                   |
| 50k                                                    |
| Azilsartan (Edarbi)                                     |
| Candesartan (Atacand)                                   |
| Eprosartan                                              |
| Irbesartan (Avapro)                                     |
| Losartan (Cozaar)                                       |
| Olmesartan (Benicar)                                    |
| Telmisartan (Micardis)                                  |
| Valsartan                                               |
| OSU-03012                                               |
| EGCG                                                   |

| Name of herbal compound | Name of medicinal herb |
|-------------------------|------------------------|
| Meclizine               | 3.02                   |
| Probufol                | 3.02                   |
| Amhralin                | 3.02                   |
| 2,3-dihydroxy-6,7- dichloroquinoxaline | 3.02 |
| 50k                     | 3.02                   |
| Azilsartan (Edarbi)     | 3.02                   |
| Candesartan (Atacand)   | 3.02                   |
| Eprosartan              | 3.02                   |
| Irbesartan (Avapro)     | 3.02                   |
| Losartan (Cozaar)       | 3.02                   |
| Olmesartan (Benicar)    | 3.02                   |
| Telmisartan (Micardis)  | 3.02                   |
| Valsartan               | 3.02                   |
| OSU-03012               | 3.02                   |
| EGCG                    | 3.02                   |

Table 1

| Name of herbal compound | Name of medicinal herb |
|-------------------------|------------------------|
| Meclizine               | 3.02                   |
| Probufol                | 3.02                   |
| Amhralin                | 3.02                   |
| 2,3-dihydroxy-6,7- dichloroquinoxaline | 3.02 |
| 50k                     | 3.02                   |
| Azilsartan (Edarbi)     | 3.02                   |
| Candesartan (Atacand)   | 3.02                   |
| Eprosartan              | 3.02                   |
| Irbesartan (Avapro)     | 3.02                   |
| Losartan (Cozaar)       | 3.02                   |
| Olmesartan (Benicar)    | 3.02                   |
| Telmisartan (Micardis)  | 3.02                   |
| Valsartan               | 3.02                   |
| OSU-03012               | 3.02                   |
| EGCG                    | 3.02                   |

Table 2

| Name of medicinal herbs |
|-------------------------|
| Salvia officinalis      |
| Anethum graveolens      |
| Coriandrum sativum      |
| Trigonella foemugraecum |
| Thymes                  |
| Allium sativum          |
| Camellia sinensis       |
| Sillybum marianum       |
| Taxus baccata           |
| Matricaria chamomilla   |
| Apium graveolens        |
| Olea europea            |
| Hibiscus sabdariffa     |
| Lavandula angustifolia  |
| Berberis vulgaris       |
| Zizipora                |
| Achillea millefolium    |
| Rhus                    |
| Taraxacum              |
| Glycine max             |

Table 3

| Name of medicinal herbs |
|-------------------------|
| Salvia officinalis      |
| Anethum graveolens      |
| Coriandrum sativum      |
| Trigonella foemugraecum |
| Thymes                  |
| Allium sativum          |
| Camellia sinensis       |
| Sillybum marianum       |
| Taxus baccata           |
| Matricaria chamomilla   |
| Apium graveolens        |
| Olea europea            |
| Hibiscus sabdariffa     |
| Lavandula angustifolia  |
| Berberis vulgaris       |
| Zizipora                |
| Achillea millefolium    |
| Rhus                    |
| Taraxacum              |
| Glycine max             |

Table 4

| Name of medicinal herbs |
|-------------------------|
| Salvia officinalis      |
| Anethum graveolens      |
| Coriandrum sativum      |
| Trigonella foemugraecum |
| Thymes                  |
| Allium sativum          |
| Camellia sinensis       |
| Sillybum marianum       |
| Taxus baccata           |
| Matricaria chamomilla   |
| Apium graveolens        |
| Olea europea            |
| Hibiscus sabdariffa     |
| Lavandula angustifolia  |
| Berberis vulgaris       |
| Zizipora                |
| Achillea millefolium    |
| Rhus                    |
| Taraxacum              |
| Glycine max             |
compounds to receptors. The molecular docking results of the ACE2, GRP78, and AT1R are presented in Supplementary Figure 3.  

Table 3  
The most important microRNAs which were expressed in lung tissue according to their affinity to the 3’UTR of SARS-COV-2 genome.

| Importance miRNAs in COVID-19 with high affinity to SARA-COV-2 genome 3’UTR | Affinity (kCal/mol) |
|---|---|
| hsa-miR-6762-3p | -27.1 |
| hsa-miR-6746-5p | -27.1 |
| hsa-miR-636 | -27.2 |
| hsa-miR-6842-3p | -27.4 |
| hsa-miR-449a | -27.4 |
| hsa-miR-6885-5p | -27.6 |
| hsa-miR-4640-5p | -27.6 |
| hsa-miR-5p | -27.6 |
| hsa-miR-6783-3p | -27.7 |
| hsa-miR-939-5p | -27.8 |
| hsa-miR-4649-5p | -27.8 |
| hsa-miR-181d-5p | -27.8 |
| hsa-miR-615-3p | -27.9 |
| hsa-miR-4674 | -27.9 |
| hsa-miR-6830-3p | -28.0 |
| hsa-miR-5090 | -28.0 |
| hsa-miR-6812-5p | -28.1 |
| hsa-miR-572 | -28.1 |
| hsa-miR-4756-5p | -28.2 |
| hsa-miR-34a-5p | -28.2 |
| hsa-miR-6729-5p | -28.3 |
| hsa-miR-1296-5p | -28.3 |
| hsa-miR-6789-5p | -28.4 |
| hsa-miR-4523 | -28.4 |
| hsa-miR-4469 | -28.6 |
| hsa-miR-484 | -29.0 |
| hsa-miR-449b-5p | -29.0 |
| hsa-miR-1268b | -29.1 |
| hsa-miR-4745-5p | -29.3 |
| hsa-miR-92b-3p | -29.4 |
| hsa-miR-4734 | -29.4 |
| hsa-miR-7974 | -29.6 |
| hsa-miR-6727-5p | -29.6 |
| hsa-miR-2467-5p | -29.9 |
| hsa-miR-1909-3p | -30.2 |
| hsa-miR-7108-5p | -30.3 |
| hsa-miR-381-3p | -30.3 |
| hsa-miR-5087 | -30.6 |
| hsa-miR-6821-3p | -30.7 |
| hsa-miR-4741 | -31.6 |
| hsa-miR-449c-5p | -33.4 |
| hsa-miR-1307-3p | -37.6 kcal/mol |

(TFs) upstream of hsa-miR-1307 (Fig. 3A), which the upstream respective signaling pathways responsible for activating these TFs are shown in Fig. 3B.

3.3. Docking analysis

The best herbal compounds for ACE2, TMPRSS2, GRP78, and AT1R receptors were identified based on their binding energy.

3.4. The common medicinal herbs and blocker drugs

Thirty-five common medicinal herbal compounds and blocker drugs were investigated between ACE2, TMPRSS2, GRP78, and AT1R; with a score of -7 kCal/mol or higher. Among them, Berbamine had the highest binding energy for all four receptors (Supplementary Table 1).

3.5. Selecting top common compounds

Berbamine, Hesperidin, and Hypericin were the best common compounds for interaction with ACE2 (Supplementary Figure 2), TMPRSS2 (Supplementary Figure 3), GRP78 (Supplementary Figure 4), and AT1R (Supplementary Figure 5).  

The results of molecular docking also showed a high tendency of compounds to receptors. The molecular docking results of the ACE2, TMPRSS2, GP78, and AT1R receptors with medicinal herbal compounds are presented in Supplementary Table 2.

3.6. Comparison of the binding energy for receptors

The results of molecular docking to compare the binding energy between the available blocking drugs and the herbal compounds investigated from the present study presented that the affinity of herbal compounds to bind to the ACE2, TMPRSS2, GRP78, and ACE2 receptors were higher (Table 4).

3.7. Attaining the specifications of top common compounds

The lazar database had no result for Hestridine, but characteristics of other top three common compounds include antitussive, respiratory analeptic, hepatoprotection, antivirus, RNA synthesis inhibitor. Furthermore, features such as blood-brain barrier penetration, carcinogenicity, maximum recommended daily dose, and antiviral ability of each three common herbal compounds were surveyed and presented in Table 5.

4. Discussion

The high mortality rate around the world due to COVID-19 has led to the recognition and treatment of the SARS-CoV-2. There has been a lot of research on this disease over the past few months, but there is still a need for a comprehensive study that considers all aspects of the disease [30]. In this bioinformatics study, it was tried to attend different approaches related to the SARS-CoV-2 before and after the infection.

The most important receptors for SARS-CoV-2 are ACE2 [31], TMPRSS2 [32], and GRP78 [6], which by blocking these receptors can protect the body against the virus. In the process of infecting by SARS-CoV-2, binding the virus to ACE2 prevents the attachment of angiotensin I and 2 to ACE2. In the lack of ACE2 enzyme, angiotensin I
convert to angiotensin II by ACE enzyme. Subsequently, angiotensin II binds to the AT1R, which causes more damage to the lungs. Therefore, targeting the AT1R [33] could be an alternative treatment goal.

Some studies have shown that AT1R blockers result in more ACE2 production. ACE2, in turn, is not harmful to normal lung cells, but it can play a leading role in SARS-CoV-2 infection, as the spike virus uses this receptor to enter the cell. Therefore, in this study, the effect of blocking the active compounds of medicinal plants on AT1R was investigated, and compounds with the high binding affinity to AT1R were identified. Some compounds have a much higher affinity than AT1R common blockers such as Losartan, Olmesartan, Telmisartan. Berbamine, which is Berberis vulgaris phytochemical compound, has the highest affinity to AT1R, with an affinity higher than of losartan. Moreover, recent studies stated that some blockers of AT1R lead to enhance ACE2 expression. The 3-D structure of Berbamin differs from the common blockers, which may not lead to an increase in the expression of ACE2; hence, fewer ACE2 could be available to the SARS-CoV-2 virus. As mentioned earlier, blocking ACE2, GRP78, and TMPRSS2 could be a suggestive therapeutic option. In the present study, phytochemical compounds of each medicinal herbs were surveyed in terms of their blocking ability for each receptor. The binding energy of Berbamine is about 12.3 kCal/mol, 11 kCal/mol, and 11.8 kCal/mol for ACE2, GRP78, and TMPRSS2 respectively. This indicates the efficiency of this compound in a competitive circumstance with the virus. Thirty-five effective compounds with proper scores for ACE2, GRP78, AT1R, and TMPRSS2 receptors were obtained through screening the 1033 medicinal herbal compounds and it was found that the Berbamine, Losartan, Hypericin,
and Hesperidin with the highest rate of affinity are common to all four receptors. Moreover, recent studies have shown that Hypericin [34] and Hesperidin [35, 36] are important in the ACE2 receptor and Berbamine [37] is related to increasing secretion of ACE2 and DPP receptors and decreasing the amount of these receptors on the plasma membrane. Therefore, blocking receptors can prevent the progression of infection at the lung or it can decrease even the risk of infection for people exposing the virus. As previously stated, Losartan may increase the expression of ACE2, thus, it was not examined in the subsequent investigation in this study. But, Berbamine, Hypericin, and Hesperidin compounds were included in this study to investigate their pharmacological properties. It has been found that Berbamine and Hypericin have a completely

![Fig. 3B. SP1, Smad2/3, PKA, CREB1, MYC, MAX, ELF1 are the most significant of TFs related to hsa-mir-1307, which present in field shapes. The most important receptors to activate the TFs of hsa-mir-1307 are shown in the cell surface.](image)

| AT1R blockers | Score (kCal/mol) | TMPRSS2 blockers | Score (kCal/mol) | GRP78 blockers | Score (kCal/mol) | ACE2 blockers | Score (kCal/mol) |
|---------------|------------------|------------------|------------------|----------------|------------------|--------------|------------------|
| Losartan (Cozaar) | –13.3 | epigallocatechin-3-gallate | –8.9 | OSU-03012 | –6.8 | Losartan (Cozaar) | –9.3 |
| Telmisartan (MiraLung) | –11 | 50K | –8.9 | epigallocatechin-3-gallate | –6.2 | Scutellarin | –8.6 |
| Azilsartan (Edarbi) | –10.5 | meclizine | –7.8 | – | – | baicalin | –8.3 |
| Irbesartan (Avapro) | –9.9 | anthralin | –7.4 | – | – | Hesperetin | –7 |
| Candesartan (Atacand) | –9.8 | 2,3-dihydroxy-6,7-dichloroquinoxaline | –7.1 | – | – | N-[4-(4-methylpiperazin-1-yl)phenyl][methyl]-L2-oxazole-5-carboxamide | –6.8 |
| Olmesartan (Benicar) | –9.5 | – | – | – | – | Chloroquine phosphate (ResochinTM) | –5.8 |
| valsartan | –8.9 | – | – | – | – | Nicotaminan | –5.5 |
| Eprosartan | –8.1 | – | – | – | – | N-(2-aminoethyl)-1aziridine-ethanamine | –3.7 |

| Herbal compounds for AT1R | Score (kCal/mol) | Herbal compounds for TMPRSS2 | Score (kCal/mol) | Herbal compounds for GRP78 | Score (kCal/mol) | Herbal compounds for ACE2 | Score (kCal/mol) |
|---------------------------|------------------|------------------|------------------|------------------|--------------|------------------|------------------|
| Berbamine | –15.7 | Berbamine | –11.8 | Berbamine | –11 | Berbamine | –12.3 |
| Hop-17(21)-en-3β-ol | –11.4 | Hesperidin | –9.9 | Lupedol | –7.7 | Naringin | –8.6 |
| 18β-glycyrrhetinic acid | –11.4 | Berberine | –9.8 | Shinflavanone | –7.7 | Officinatrione | –8.4 |
| Glycyrrhetinic acid | –11.4 | Isolysili B | –9.8 | Glabrolide | –7.7 | α-Carotene | –8.4 |
| Hipsaglabridin B | –11.3 | Plantamajoside | –9.8 | – | – | – | – |
| – | – | Apigenin-7-O-rutinoside | –9.7 | – | – | – | – |
| – | – | Isomartrinolide | –9.7 | – | – | – | – |
| – | – | Rutin | –9.6 | – | – | – | – |
| – | – | Silindrin | –9.6 | – | – | – | – |
| – | – | Silylfermin | –9.5 | – | – | – | – |
Different characteristics of common medicinal herbs with high affinity to ACE2, AT1R, TMPRSS2, and GRP78 receptors.

| Name of Compound | activity ● | Blood-Brain Barrier Penetration (Human)* | Carcinogenicity (Mouse)* | Maximum Recommended Daily Dose (Human)* | ANTIVIRAL (Predicted percentage)* |
|------------------|-----------|------------------------------------------|-------------------------|----------------------------------------|----------------------------------|
| Berbamine        | Antitussive, Apoptosis agonist, Leukopoiesis stimulant, Antinociceptive, Respiratory analeptic, Spasmolytic, Membrane permeability inhibitor | Penetrating | non-carcinogenic | 0.0064 (mmol/kg-bw/day) | 54.176 |
|                  |           |                                          |                         | 3.9 (mg/kg-bw/day)                   |                                  |
|                  |           |                                          |                         | 0.022 (mmol/kg-bw/day)               |                                  |
|                  |           |                                          |                         | 13.5 (mg/kg-bw/day)                  |                                  |
| Hesperidin       | Free radical scavenger, Anticarcinogenic, Hepatoprotectant, Membrane permeability inhibitor, Chemopreventive, Vasoprotector, Hemostatic, Membrane integrity agonist, Caspase 3 stimulant, Proliferative diseases treatment, Cardioprotectant, Antihypercholesterolemic, Antiprotrozoal (Leishmania), Skin whitener, Antioxidant, Antineoplastic, Laxative, Antifungal, Expectorant, TP53 expression enhancer, Caspase 8 stimulant, Vasodilator, Antihemorrhagic, Antitussive, Antiulcerative, Antinflammatory, Apoptosis agonist, Antibacterial, Hepatic disorders treatment, Antiinfective, Respiratory analeptic, RNA synthesis inhibitor, Antiviral (Herpes), | non-penetrating | non-carcinogenic |                                  |                                  |
| Hypericin        | Membrane integrity agonist, TP53 expression enhancer, Antineoplastic, Membrane permeability inhibitor, Apoptosis agonist, Caspase 3 stimulant, Antineborethic, Antisptic, Kidney function stimulant, Antimutagenic, Vasoprotector | – | – | – | 58.805 |

● The activity of each active substance gained from the pass online database (http://www.pharmaexpert.ru/passonline/index.php). § The Blood-Brain Barrier, Carcinogenicity, and Maximum Recommended Daily Dose prediction was obtained from the lazard database (https://lazar.in-silico.ch). The antiviral activity of each active substances predicted by AVCpred database (http://crdd.osdd.net/servers/avcpred).

different 3-D structure from those of conventional AT1R blockers, which it seems that probably not lead to enhancing ACE2. Patients with higher blood pressure are more likely at risk of COVID-19, so there is a doubt about prescribing anti-blood pressure drugs. Accordingly, the mentioned herbal compounds may downregulate the blood pressure and lung injury by blocking the AT1R receptor without activating ACE2. Among the aforementioned components, Berbamine, Hypericin, and Hesperidin are not carcinogenic. Berbamine has other properties such as antitussive, respiratory protection, non-toxic, antibacterial, which makes the use of this substance as a very safe respiratory tract. By examining the essential oils and extracts of various medicinal plants, it was found that the extracts of Berberis vulgaris (Berbamine), Ziziphora (Hesperidin), and Hibiscus sabdariffa (Hypericin) can play the best role in the prevention and treatment of COVID-19. Finally, Silybum marianum, Glycyrrhiza glabra, and Achillea millefolium had the highest effects on all four receptors.

If the lung cell is infected with the SARS-CoV-2, preventing the virus from replicating is another treatment option [38]. Many studies have shown that miRNAs play an important role in inhibiting viruses’ replication by preventing the translation of the viral genome [7]. In this study, among 1872 miRNAs, has-miR-1307-3p was selected as the best miRNA because of its high affinity to SARS-CoV-2 genome 3′UTR and high expression in lung tissue [39]. Increased expression of hsa-miR-1307-3p may lead to a reduction in SARS-CoV-2 replication through binding to the 3′UTR site of the virus genome. miRNAs can be synthesized for therapeutic purposes and inserted into the target area, but their delivery is a complicated and meticulous process. Therefore, the use of TFs to induce the expression of the desired miRNA by lung cells may be a better choice. After obtaining all the signaling pathways related to the hsa-miR-1307-3p transcription factors, the receptors responsible for activating the TFs were also examined. As a result, using the ligand of each of these receptors can lead to the expression of the TFs genes; eventually triggers the induction of the hsa-miR-1307-3p production.

Of important, hsa-miR-1307-3p can affect receptors that are responsible for survival and proliferation. The hsa-miR-1307-3p also affects anti-apoptotic proteins like BCL2 and inhibits them to induce apoptosis, leading to the prohibition of the proliferation. Investigations have proven that the PI3K signaling pathway is so critical for virus survival and spread [40]. The hsa-miR-1307-3p inhibits the PI3K pathway by suppressing the activators of PI3K, and eventually, the cell cycle proliferation is prevented. On the other hand, hsa-miR-1307-3p can ban clathrin-dependent endocytosis by inhibiting AP-2, PI-5PK, and might suppress exocytosis by inhibiting of actin. It has been confirmed that endocytosis and exocytosis are associated with virus entry and spread, therefore, controlling these pathways by hsa-miR-1307-3p could be an effective strategy for SARS-CoV-2 infection.

The WHO has stated that obesity and diabetes mellitus are other risk factor for developing COVID-19. In obesity that leads to type 2 diabetes, hyperglycemia leads to inhibition of the immune system [41] as well as the activation of PKC, as a result of its activity, inhibits IRS2, and leads to indirect inhibition of ACT, which in turn leads to glycolysis and glucose uptake. On the other hand, hyperglycemia increases the expression of GRP78 on the cell surface, which can activate the ACT pathway to reduce blood sugar [42]. Activating the tyrosine kinase receptor activates the ERK protein, and this protein inhibits IRS1 that also indirectly prevents the ACT and its downstream pathway. Studies have implicated that GRP78, which is increased in response to hyperglycemia in diabetes, is a receptor for COVID-19. The hsa-miR-1307-3p can induce glycolysis and glucose uptake by inhibiting PKC and ERK, which are inhibitors of RS1 and RS2. Thus, this miRNA indirectly reduces GRP78 production by lowering blood sugar. On the other hand, hsa-miR-1307-3p inhibits insulin expression by inhibiting PDX1 and VDCC, which activates insulin, increasing insulin-dependent proliferative pathways in type 2 diabetes. MicroRNA 1307 also inhibits insulin expression by inhibiting insulin-activated PDX1 and VDCC, resulting in insulin-dependent proliferative pathways in type 2 diabetes, thus controlling insulin-dependent proliferative pathways in type 2 diabetes. Studies have shown [40] that in COVID-19, with increased cytokine storms, lung tissue damage increases. For example, one of the treatment strategies for receptor inhibition is cytokines such as interleukin 6 receptor. Therefore, hsa-miR-1307-3p can be a therapeutic solution to inhibit tissue damage by inhibiting cytokine receptors.

5. Conclusion

The results of this study have indicated the inhibiting effect of Berbamine, Hypericin, and Hesperidin on ACE2, TMPRSS2, GRP78, and AT1R receptors. Also, enrichment analysis of hsa-miR-1307-3p revealed the suppressing role of this miRNA on proliferative, endocytosis, exocytosis, and diabetes signaling pathways. Additionally, hsa-miR-
1307-3p targets genes in type 2 diabetes indirectly by repressing the GRP78 receptor expression. Overall, further clinical assessment of these herbal compounds and hsa-miR-1307-3p is required to validate the treating ability of these compounds over COVID-19 infection.

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Negar Balmeh, Samira Mahmoudi, Niloufar Mohammadi, Anasik Karabedianhajabadi have a similar contribution to the first authors. All authors equally contributed to this work, outlined the manuscript, critically updated, and approved the last version before submission. All authors have studied and acknowledged the published version of the manuscript.

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.

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Abbreviation

| Term          | Abbreviation |
|---------------|--------------|
| ACE2         | angiotensin-converting enzyme 2 |
| AT1R         | Angiotensin 1 receptor |
| AP-2         | complex subunit alpha |
| BCL2         | B-cell lymphoma 2 |
| CDK          | Cyclin-dependent kinase |
| CREB1        | CAMP responsive element binding protein 1 |
| CTCF         | CCCTC-binding factor |
| ELF1         | E74-like factor 1 |
| GRP78        | Binding immunoglobulin protein |
| GABPA        | GA binding protein transcription factor |
| GC-MS        | Gas chromatography-mass spectrometry |
| ITGA         | Integrin Subunit Alpha |
| ITGB         | Integrin Subunit Beta |
| MERS-CoV     | Middle East respiratory syndrome coronavirus |
| MYC          | proto-oncogene protein |
| MAX          | myc-associated factor X |
| MXII         | MAX Interactor 1 |
| PDX1         | pancreatic and duodenal homeobox 1 |
| PIP5k        | Phosphatidylinositol-4-phosphate 5-kinase |
| PKC          | Protein kinase C |
| PKA          | Protein kinase A |
| P13K         | phosphoinositide 3-kinase |
| RTK          | Receptor tyrosine kinase |
| Rab10        | Ras-related protein Rab-10 |
| RAB35        | Ras-related protein Rab-35, SARS-CoV, severe acute respiratory syndrome coronavirus |
| SP1          | specificity protein 1 |
| SMAD2        | Mothers against decapentaplegic homolog 2, SMAD3, |
| SMAD3        | Mothers against decapentaplegic homolog 3 |
| TMPRSS2      | Transmembrane protease serine 2 |
| TAFI         | TATA-Box Binding Protein Associated Factor 1 |
| VDCC         | Voltage-dependent calcium channels |
| WHO          | World Health Organization |

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2020.100407.

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