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(54) **Title:** METHOD AND COMPOSITIONS FOR TREATING, PREVENTING OR LIMITING THE OCCURRENCE OF VIRAL INFECTION

(57) **Abstract:** Method and pharmaceutical compositions for treating or limiting the occurrence of viral infections by administering a therapeutically effective amount of a pharmaceutical composition that targets the ACE2 active site. The pharmaceutical compositions include those of Formula (I), Formula (II), Formula (III), including Formulas (IIIa) and (IIIb), and the viral infections including but not limited to respiratory viruses and disease conditions and syndromes that are associated with the viral infections.

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METHOD AND COMPOSITIONS FOR TREATING, PREVENTING OR LIMITING THE OCCURRENCE OF VIRAL INFECTION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/990,168, filed March 16, 2020, herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method and composition for treating viral infection including a method and composition that targets an Angiotensin Converting Enzyme (ACE2) active site in a host or patient to thereby treat, prevent or limit the occurrence of the viral infection.

BACKGROUND OF THE INVENTION

[0003] Many human diseases result from infection by microscopic organisms called viruses. Infection by viruses can give rise to symptoms that vary from mild to severe. Viral infections can result in large numbers of deaths. Examples of such pandemics include the Spanish flu of 1918-1919 that killed approximately 40 million people and the HIV/AIDS epidemic that has killed almost 2 million people.

[0004] Viruses require host organisms in order to replicate and viruses are transmitted from an infected host to an uninfected host through a number of mechanisms. A virus will first attach itself to a host cell. It will then enter the cell and release its genetic code (i.e., RNA or DNA). The virus makes use of the host cell's functional proteins and enzymes in order to replicate. Eventually, the host cell may die because the mechanisms it needs to survive are controlled by the virus. After death of the cell, the replicated viruses are released, allowing them to attack new host cells and continuing the replication process. Some viruses cause modification of the host cells leading to cancer, while other viruses can remain dormant in the host for an extended period prior to the infection becoming symptomatic in the host.

[0005] The symptoms that result from viral infections can vary from virus-to-virus as any one virus typically will infect only certain types of cells. This

observation also means that a specific virus will typically infect only certain species, although mutation of a virus can allow it to extend the number of species that any one virus is able to infect.

[0006] Host species have developed a number of defense mechanisms to protect themselves from viral infections. The first lines of defense are mechanisms that prevent viral entry into the host. The skin provides an impermeable barrier to entry. Viruses typically enter the body through body cavities and can pass through the mucosal surfaces that line these cavities. Once a virus is in the body and detected by the body's immune system, lymphocytes and monocytes in the blood learn how to attack the invader. Invaded cells release cytokines such as the interferons (for example IL 1, IL 6, IL 12, IL 16), tumor necrosis factor (TNF-α), and interferons (typically interferons a and g). The role of these cytokines is to increase the resistance of other host cells to the invading virus. Many of the symptoms of viral infection experienced by the host results from the extensive release of cytokines, commonly referred to as the cytokine storm.

[0007] The white blood cells are able to remember how to combat viruses that have previously invaded the body. So if the host survives the initial attack of the virus, the immune system is able to respond much more quickly to subsequent infections of the same virus. The body has developed an immunity to the virus. Such immunity can also be induced by presenting the immune system with a surrogate (vaccine) for the virus in a process known as immunization.

[0008] Antiviral drugs are known in the art to assist the immune system in overcoming a viral infection in a patient. Most antiviral drugs work by slowing the replication of the virus in the infected patient's body thus allowing the body's immune system to launch an effective response when the disease symptoms are less severe. Antiviral drugs may work specifically on one or two viruses or may be effective across a broad spectrum of viruses. There are many known mechanisms by which antiviral agents can slow viral replication. One antiviral strategy is to slow or prevent the virus infiltrating a target cell, for example by binding to a receptor on the target cell which is required by the virus to enter the cell or by coating the virus so preventing its ability to bind to the target receptor(s). Other antiviral agents can slow viral replication once the virus particle has entered the target cell. Such mechanisms are well known in the art.

SUMMARY OF THE INVENTION

[0009] The present invention relates to methods and compositions for treating or limiting the occurrence of viral infection using compositions including pharmaceutical compositions that target the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting the occurrence of infection. Advantageously, the infection and disease conditions and syndromes are caused by viruses and the present treatment addresses the disease conditions and syndromes produced by the viral infection. Possible viral infections (and their related disease conditions/syndromes) for which targeting the ACE2 active site treat include but are not limited to respiratory viruses and their related disease conditions or syndromes, such as those caused by coronaviruses including but not limited to COVID-19.

[0010] Further, the present invention relates to methods and compositions for treating viral diseases using various formulations which include but are not limited to those of granted U.S. Patents Nos. 8,034,838; 10,123,991; and 10,383,842 and pending applications U.S. Serial Nos. 16/302,292 and 16/544,308; all herein incorporated by reference.

[0011] The present invention relates to the use of compositions, pharmaceutical agents and the like which are effective antiviral agents to treat, prevent, or limit the occurrence of various infection diseases including viruses such as but not limited to influenza, rhinovirus and coronaviruses.

[0012] Although the treatment may include the various compositions and compounds of the aforementioned granted U.S. patents and pending applications (see paragraph [0010] above), therapeutic treatment of individuals suffering from an infection by one or more coronavirus including the COVID-19 coronavirus includes those pharmaceutical agents (compounds and compositions) which the target ACE2 active site. The present method and treatment using the aforementioned compounds and compositions disclosed in the above-cited patents/applications are especially suitable to making an individual less susceptible to a corona infection via ACE2 based on the currently understood way in which the coronavirus is pathogenic.

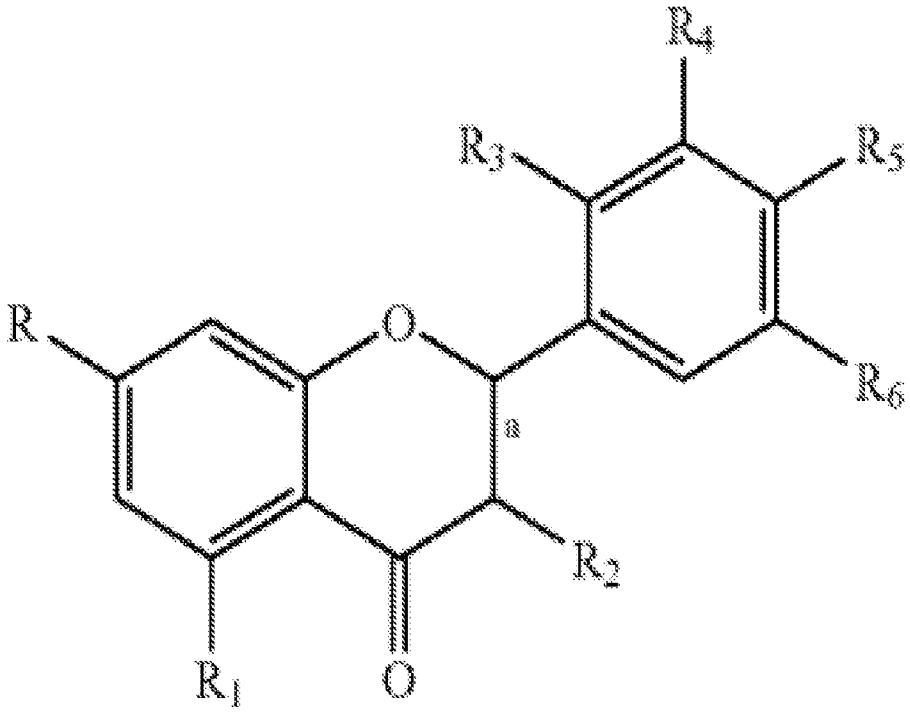
[0013] Referring to the currently perceived pathology of infection of an individual coronavirus, the coronavirus presents a unique challenge in that it appears to exploit a 'hand shake' docking site to human cellular membranes that is atypical of influenza and rhinovirus. Influenza attaches to the cell membranes of a host (e.g., human) through the use of ICAM or intercellular adhesion molecules to download (insert) its genetic material. It is now becoming clear that the present strain of coronavirus (i.e., COVID-19) is hijacking the ACE2 or Angiotensin Converting Enzyme pathway to accomplish the same goal. The issue or challenge is that ACE2 is essential for maintaining the health of the pulmonary system and may not be a straightforward target for inhibition.

[0014] The compounds and compositions in the aforementioned granted patents and pending applications of paragraph [0010] above including the compounds in the claims of the aforementioned respective patents/applications can be used as therapeutics in the form of molecular probes which make an individual ACE2 less susceptible to the corona infection by modulating.

[0015] Compounds of the aforementioned patents and pending applications were shown in advanced computational models to inhibit ACE2 and cause conformational changes of ACE2 on the spike protein, helicase, and protease sites. That renders it less susceptible to interact with coronavirus.

[0016] In various advantageous forms, the pharmaceutical composition comprises compounds of Formula I, Formula II, and Formula III including Formula IIIa and Formula IIIb having the chemical structure as follows:

Formula I:

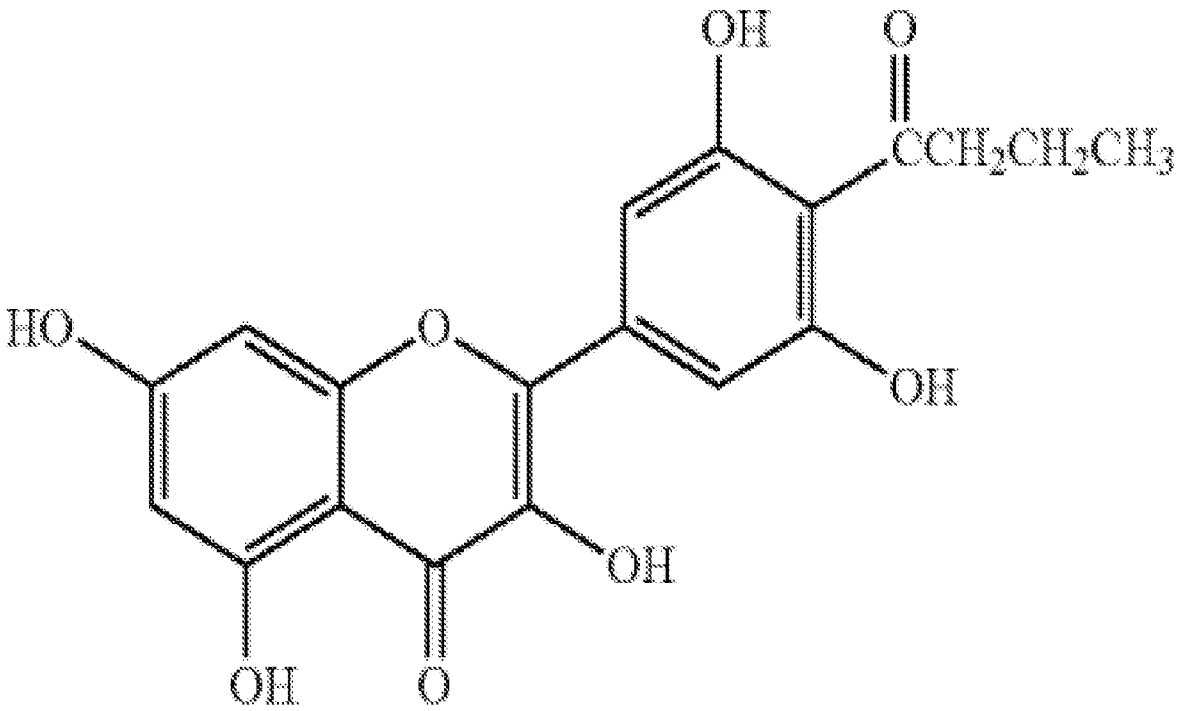


formula (I)

wherein R and R_5 are each independently hydrogen, a hydroxy group, an alkoxy group, a rutinosyl group, and a rhamnosyl group; R_1=OH, R_2=OH, R_3=H, R_4=OH and R_6=OH; and

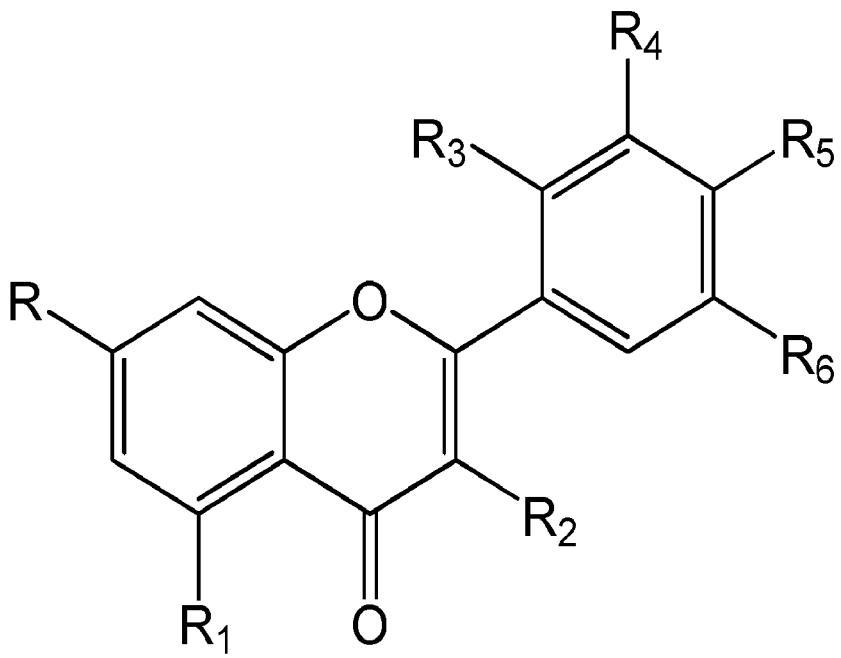
a is a single bond or a double bond; provided that at least one of R and R5 comprises an electrophilic group chosen from aldehyde, haloalkane, alkene, butyryl, fluorophenol, sulfonamide and fluorophenyl sulfoxide,

Formula (II):



formula (II).

Formula (III)

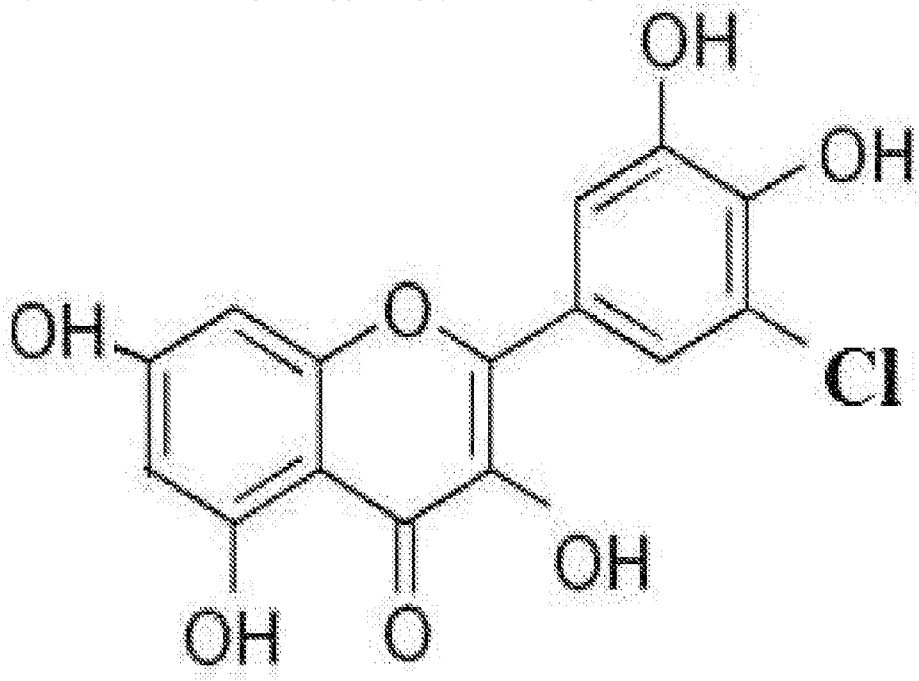


formula (III)

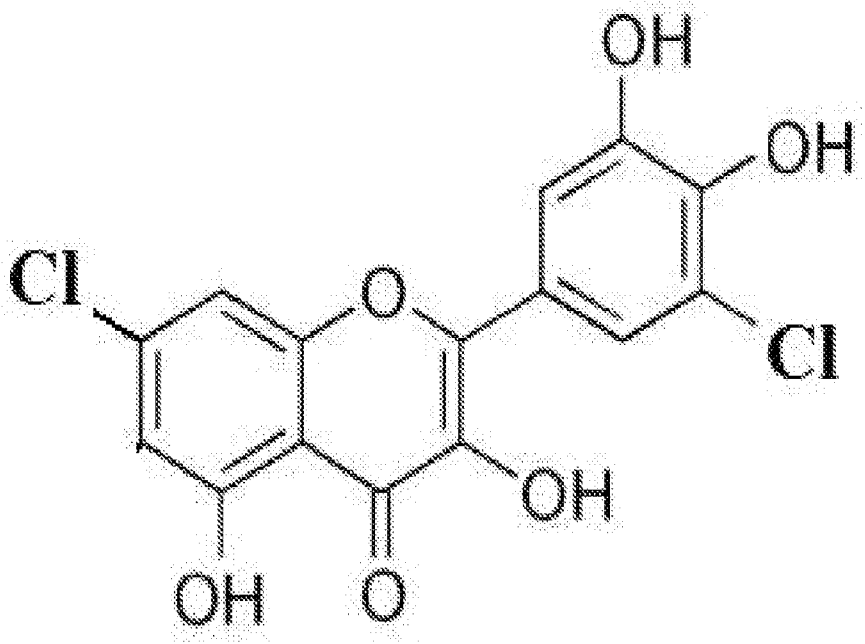
wherein R, R_1, R_2, R_4, R_5, and R_6 are a hydroxyl group or chlorine,

R_3 is hydrogen; and wherein, at least one of R, R_1, R_2, R_4, R_5, and R_6 is chlorine,

Formula (IIIa)
2-(3-chloro-4,5-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one



Formula (IIIb)



[0017] The present invention, in one advantageous form is directed to a method for treating or limiting the occurrence of viral infection and includes administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I.

[0018] The method in one advantageous form includes the composition having an effective amount for treating a virus by targeting the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of infection. In one further advantageous form, the viral infection is caused by COVID-19.

[0019] The present invention in another advantageous form is directed to a method for treating or limiting the occurrence of viral infection by administering a therapeutically effective amount of a pharmaceutical composition comprising Formula II.

[0020] The present invention in yet another advantageous form is directed to a method for treating or limiting the occurrence of a viral infection by administering a therapeutically effective amount of a pharmaceutical composition comprising Formula III.

[0021] The present invention in one advantageous form comprises Formula III having a chemical structure selected from Formula IIIa and Formula IIIb.

[0022] The present invention in still yet another form is directed to a method of treating viral infection with a therapeutically effective composition selected from the group consisting of Formula I, Formula II, Formula III, Formula IIIa, and Formula IIIb further comprising hesperidin and piperine.

BRIEF DESCRIPTION OF THE FIGURE

[0023] The sole Figure is Table 1 for Δ G (kcal/mol) values for binding of select compounds to the ACE2 active site.

DETAILED DESCRIPTION

[0024] The present invention will now be described with reference to specific examples of treatment using the pharmaceutical compositions of the present invention including administering a therapeutically effective amount of the selected compound.

[0025] As used herein, the following terms and phrases shall have the meaning set forth below.

[0026] The phrase "naturally occurring" when referring to a compound means a compound that is in a form in which it can be found naturally. A compound is not in a form that is naturally occurring if, for example, the compound has been purified and separated from at least some of the other molecules that are found with the compound in nature. A "naturally occurring compound" refers to a compound that can be found in nature, i.e., a compound that has not been created or modified by man.

[0027] "Treating" a condition or disease refers to curing as well as ameliorating at least one symptom of the condition or disease.

[0028] The term "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The phrase "therapeutically effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the patient and disease or condition being treated, the weight and age of the patient, the severity of the disease or condition, the manner of administration and the like, which can readily be determined by one or ordinary skill in the art. For example, certain compositions described herein may be administered in a sufficient amount to produce a desired effect at a reasonable benefit/risk ratio applicable to such treatment.

[0029] For example, in the context of the therapeutic methods provided in this disclosure, a therapeutically effective amount is an amount that will target the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of infection including but not limited to viral infects caused by coronavirus including COVID-19.

[0030] The term "pharmaceutically acceptable carrier" means a carrier or diluent that does not give a stimulus to an organism and destroy the natures and bioactivities of an administered compound.

[0031] The present method and compositions were identified through research and experimentation to determine compounds which target, i.e., bind or act as an inhibitor bound to human Angiotensin Converting Enzyme-related carboxypeptidas (ACE2). Predictive and empirical Δ G values for binding compounds to the ACE2

active site demonstrated efficacy of the present compounds to treat and limit viral infections. The Δ G values were measured in terms of kcal/mol noting that the more negative the Δ G value, the higher predictive binding affinity. Table 1 (Figure) summarizes Δ G values for select compounds effective for treating viral infections in accordance with the disclosed treatment of viral infections.

[0032] The data summarized in Table 1 demonstrates that hesperidin, chlorinated myricetin (compound formula 3(a)), and myricetin are effective in treating viral diseases as targeting the ACE2 binding site. Additional inhibitors of ACE2, i.e., targeting the ACE2 binding site can be identified by conducting similar studies and determining the Δ G value as summarized in Table 1 above and in Table 2 below.

[0033] Table 2

α-Pinene	Hesperetin	Linalool	Formula IIIa*	Myricetin
Blind Docking				
-6.2	-6.2	-5.9	-7.9	-7.3
-5.9	-5.9	-5.8	-7.9	-7.3
-5.7	-5.7	-5.7	-7.8	-7.3
-5.7	-5.7	-5.6	-7.7	-7.3
-5.7	-5.7	-5.5	-7.7	-7.2
-5.6	-5.6	-5.4	-7.7	-7.2
-5.6	-5.6	-5.3	-7.7	-7.2
-5.5	-5.5	-5.2	-7.5	-7.2
-5.5	-5.5	-5.2	-7.5	-7.2
MERS Pocket Docking				
-5.9	-6.8	-5.3	-6.6	-6.5
-5.6	-6.4	-5.2	-6.3	-6.2
-5.6	-5.6	-5.1	-5.9	-6.1
-5.5	-5.3	-5.1	-5.8	-5.7

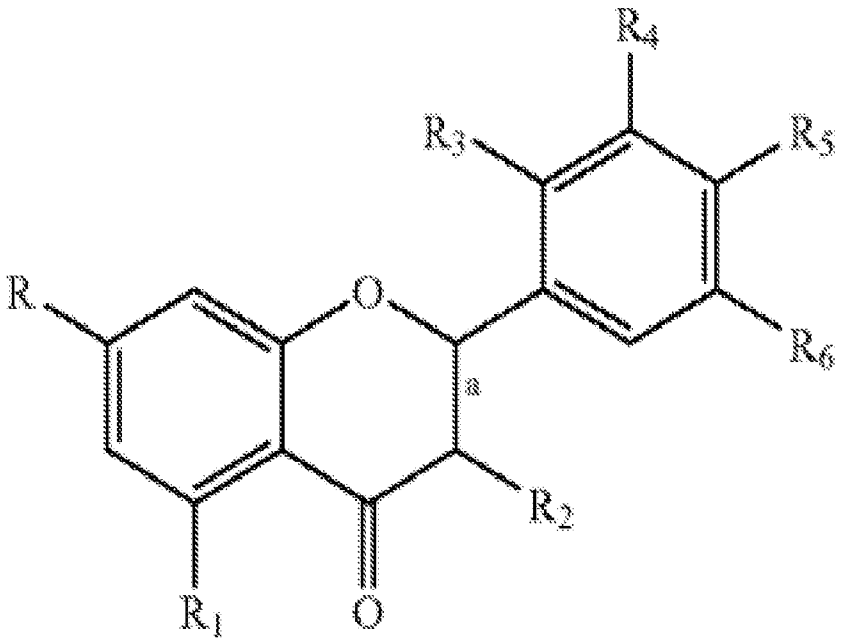
[0034] It will now be clear to a person of ordinary skill in the art that the present compounds are effective for treating various viral infections by acting as ACE2 inhibitors binding to the ACE2 active site. Additional compounds relating to the disclosed compounds a pharmaceutical compositions disclosed here can be

used and easily adapted for treating viral infections by identifying those compounds which have affinity for the ACE2 active site.

[0035] Although the invention has been described above in relation to preferred embodiments thereof, it will be understood by those skilled in the art that variations and modifications can be accomplished in these preferred embodiments without departing from the scope and spirit of the invention.

CLAIMS

1. A method for treating or limit the occurrence of viral infection, said method comprising administering a therapeutically effective amount of a pharmaceutical composition comprising formula (I)



formula (I)

wherein R and R_5 are each independently hydrogen, a hydroxy group, an alkoxy group, a rutinosyl group, and a rhamnosyl group; R_1=OH, R_2=OH, R_3=H, R_4=OH and R_6=OH; and

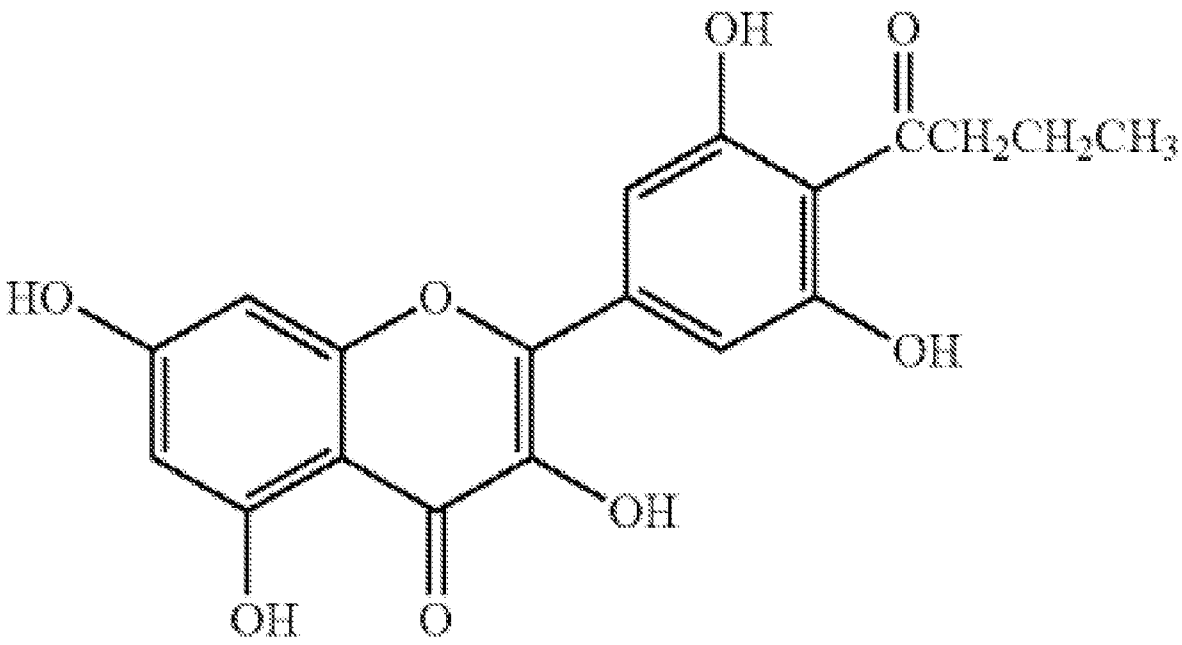
a is a single bond or a double bond; provided that at least one of R and R_5 comprises an electrophilic group chosen from aldehyde, haloalkane, alkene, butyryl, fluorophenol, sulfonamide and fluorophenyl sulfoxide,

wherein said viral infection is caused by COVID-19.

2. The method of claim 1, wherein the composition is effective for the treatment of a virus by targeting the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of infection.

3. The method of claim 2, wherein the viral invention is caused by COVID-19.

4. A method for treating or limit the occurrence of viral infection, said method comprising administering a therapeutically effective amount of a pharmaceutical composition comprising formula II

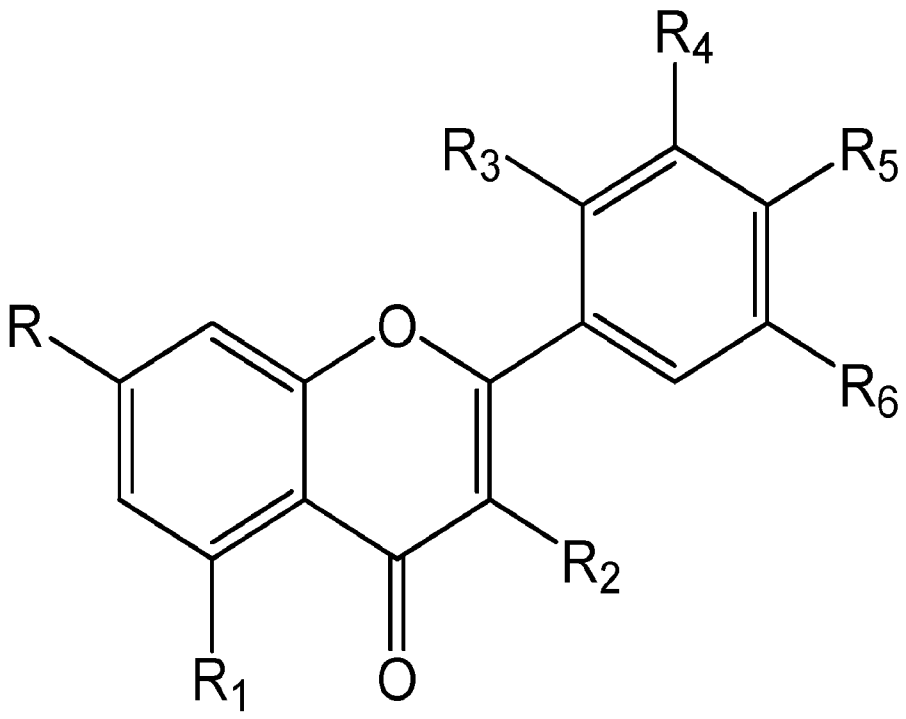


formula (II).

5. The method of claim 4, wherein the composition is effective for the treatment of a virus by targeting the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of infection.

6. The method of claim 5, wherein the viral invention is caused by COVID-19.

7. A method for treating or limit the occurrence of viral infection, said method comprising administering a therapeutically effective amount of a pharmaceutical composition comprising formula (III)



formula (III)

wherein R, R_1, R_2, R_4, R_5, and R_6 are a hydroxyl group or chlorine,

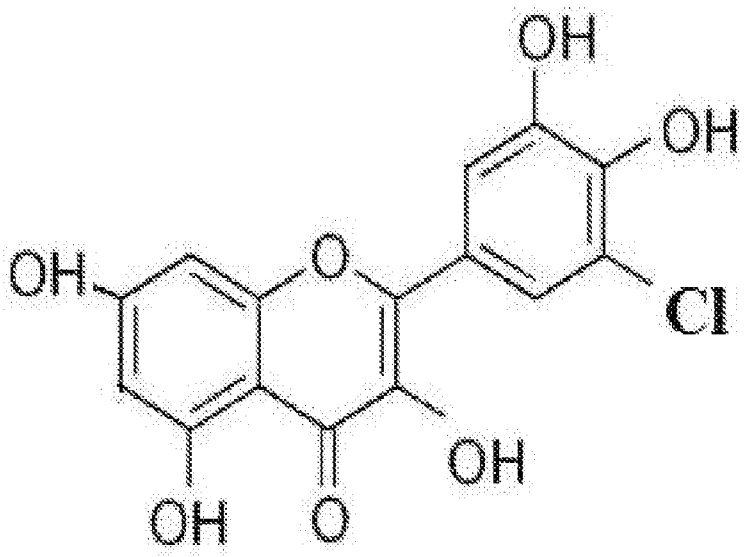
R_3 is hydrogen; and wherein, at least one of R, R_1, R_2, R_4, R_5, and R_6 is chlorine, and

wherein said viral infection is caused by COVID-19.

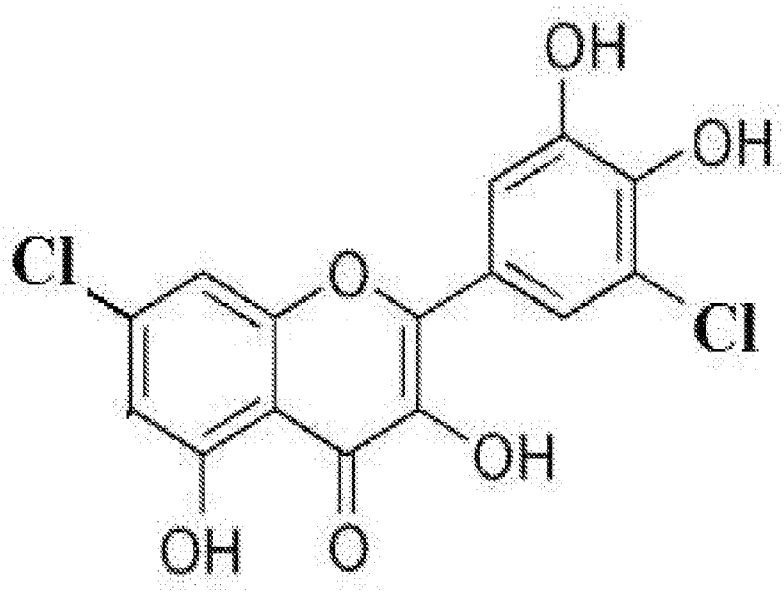
8. The method of claim 7, wherein the composition is effective for the treatment of a virus by targeting the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of infection.

9. The method of claim 8, wherein the viral invention is caused by COVID-19.

10. The method of claim 7, wherein formula 3 is selected from the compounds:



formula (IIIa) and



formula (IIIb).

11. The method of claim 1, wherein the pharmaceutical composition further comprises hesperidin and piperine.

12. A method of limiting the occurrence of, reducing the risk or severity of or treating viral infections comprising administering a composition consisting of therapeutically effective amounts of a pharmaceutical composition comprising myricetin and hesperitin to a patient at risk of or diagnosed with viral infection wherein the composition targets the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of the viral infection.

13. The method of claim 12, wherein the viral infection is caused by a coronavirus.

14. The method of claim 13, wherein the coronavirus is COVID-19.

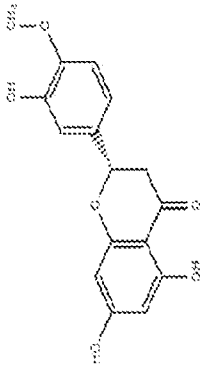
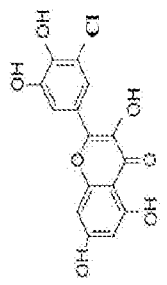
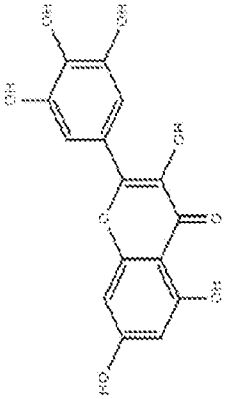
15. The method of claim 12, wherein about 300 to about 700 mg myricetin and about 100 to about 500 mg hesperitin are present in the composition.

16. The method of claim 12, wherein about 450 to about 600 mg myricetin and about 250 to about 400 mg hesperitin are present in the composition.

17. The method of claim 12, wherein about 55 to about 75% weight myricetin and about 30 to about 50% hesperitin based on the total weight of the mixture, is present in the composition.

18. The method of claim 12, wherein the ratio of myricetin to hesperitin present in the composition is about (30-60):(30-60).

Table 1

compound	α-Pinene	Hesperetin	Linalool	formula 3(a) 2-(3-chloro-4,5-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	Myricetin
structure					
ΔG kcal/mol	-5.7	-9.1	-5.5	-9.8	-8.9

FIGURE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/22538

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/352; A61K 47/16; A61K 47/22 (2021.01)

CPC - A61K 9/4858; A61K 31/4453

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2019/0365703 A1 (Global Biolife Inc) 05 December 2019 (05.12.2019); para [0009], [0043]	1-3, 7-11
A	Prajapat et al. "Drug targets for corona virus: A systematic review" Indian Journal of Pharmacology. 11 March 2020 (11.03.2020) vol 52, pg. 1-14; pg. 1, abstract, pg. 3, para 8	1-3, 7-11
A	US 2019/0343792 A1 (GLOBAL BIOLIFE INC) 14 November 2019 (14.11.2019); para [0027]	1-3, 7-11
A	US 2018/0353528 A1 (ADAERATA LIMITED PARTNERSHIP) 13 December 2018 (13.12.2018); entire document	1-3, 7-11
A	Zakaryan et al. "Flavonoids: promising natural compounds against viral infections" Archives of Virology. 25 May 2017 (25.05.2017) vol 162, pg. 2539-2551; entire document	1-3, 7-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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International application No.
PCT/US 21/22538

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 7-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/22538

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-3 and 7-11, directed to a method for treating or limit the occurrence of viral infection comprising a pharmaceutical composition comprising formula I/III, wherein said viral infection is caused by COVID-19.

Group II: Claims 4-6, directed to a method for treating or limit the occurrence of viral infection, said method comprising administering a therapeutically effective amount of a pharmaceutical composition comprising formula II.

Group III: Claims 12-18, directed to a method of limiting the occurrence of, reducing the risk or severity of or treating viral infections comprising administering a composition consisting of therapeutically effective amounts of a pharmaceutical composition comprising myricetin and hesperitin to a patient at risk of or diagnosed with viral infection wherein the composition targets the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of the viral infection.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I includes the technical feature of a method for treating or limit the occurrence of viral infection, wherein said viral infection is caused by COVID-19, which is not required by any other invention of Group II or III.

Group II includes the technical feature of a method for treating or limit the occurrence of viral infection, said method comprising administering a therapeutically effective amount of a pharmaceutical composition comprising formula II, which is not required by any other invention of Group I or III.

Group III includes the technical feature of a method of limiting the occurrence of, reducing the risk or severity of or treating viral infections wherein the composition targets the Angiotensin Converting Enzyme (ACE2) active site for the treatment, prevention or limiting occurrence of the viral infection, which is not required by any other invention of Group I or II.

Common technical features:

The inventions of Groups I-III share the technical feature of a method of treating a viral infection comprising a compound of formula I-III/myricetin and hesperitin (compounds comprising the core structure of the compound of formula I).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2019/0365703 A1 to Global Biolife Inc (hereinafter Global). Gloabl discloses treating a viral infection (para [0009]) comprising adminstering myricetin and hesperitin (para [0029]: In another embodiment, about 450 to about 600 mg myricetin; about 250 to about 400 mg hesperitin; and about 5 to about 50 mg piperine are present in the composition).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I, II or III. The inventions of Group I, II and III thus lack unity under PCT Rule 13.