Artículo de revisión

Peruvian plants of traditional use as potential sources of molecules with activity against COVID-19

Plantas peruanas de uso tradicional como fuente potencial de moléculas con actividad contra la COVID-19

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ABSTRACT

Introduction: The current situation of COVID-19 is a big issue for the human population. At present, no healing drug is available in the market. Researchers are doing their best to produce drugs to fight the disease. Various efforts are being considered based on different directions of scientific knowledge and technologies for the treatment of the disease. Unfortunately, none of these drugs works absolutely against the pandemic. Therefore, bioactive molecules from plants, animals and microorganisms could be a better option to treat COVID-19.

Objective: Review the literature about species of the flora of Peru used for the treatment of respiratory diseases and highlight the plants with potential in the production of secondary metabolites and plant lectins as an alternative against COVID-19.

Methods: A review was conducted of scientific articles related to the use of traditional medicine in Peru, China, and India for the treatment of respiratory diseases, as well as information about plant lectins and secondary metabolites potentially useful against COVID-19.

Results: A long list is presented of genera and species of the flora of Peru with great potential against COVID-19. Most of these species belong to the Asteraceae, Loranthaceae, Piperaceae, Viscaceae and Zingiberaceae families. Numerous species are endemic to Peru.

Conclusions: The flora of Peru has more than 22 000 plant species. Many of these species are traditionally used in the treatment of respiratory diseases and are potentially useful for the treatment of COVID-19.

Keywords: flora of Peru; plant lectins; respiratory diseases; SARS-CoV-2; secondary metabolites.

RESUMEN

Introducción: La situación actual de la COVID-19 es un gran problema para la población humana. En la actualidad, no hay medicamentos curativos disponibles en el mercado. Los investigadores están haciendo todo lo posible para producir fármacos con que luchar contra la enfermedad. Se están considerando varios esfuerzos basados en diferentes orientaciones del conocimiento científico y en las tecnologías para el tratamiento de la enfermedad. Desafortunadamente, ninguno de estos medicamentos funciona absolutamente contra la corriente pandémica. Por lo tanto, las moléculas bioactivas de plantas, animales y microorganismos podrían ser una mejor opción para tratar la COVID-19.

Objetivo: Revisar la literatura sobre especies de la flora del Perú utilizadas en el tratamiento de enfermedades respiratorias y destacar las plantas con posible producción de metabolitos secundarios y lectinas vegetales potencialmente útiles como alternativa frente a la COVID-19.

Métodos: Se revisaron artículos de literatura científica relacionados con el uso de la medicina tradicional en Perú, China e India para el tratamiento de enfermedades respiratorias, así como la información sobre lectinas vegetales y metabolitos secundarios con potencial utilidad contra la COVID-19.

Resultados: Se presenta una amplia relación de géneros y especies de la flora del Perú con gran potencial contra la COVID-19. La mayoría de estas especies pertenecen a las familias Asteraceae, Loranthaceae, Piperaceae, Viscaceae y Zingiberaceae. Numerosas especies son endémicas del Perú.

Conclusiones: La flora del Perú tiene más de 22 000 especies de plantas. Muchas de estas especies se utilizan tradicionalmente en el tratamiento de enfermedades respiratorias y pueden ser potencialmente útiles en el tratamiento de la COVID-19.

Palabras clave: flora del Perú; lectinas de plantas; enfermedades respiratorias; SARS-CoV-2; metabolitos secundarios.

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Introduction

Several epidemics and pandemics have afflicted humanity throughout its history causing the death of millions of people around the world. In the middle of the 14th century the Black Death or Pestilence caused by the bacterium *Yersinia pestis* killed 75-200 million people in Europe, Eurasia and North Africa, becoming the pandemic with the most deaths in human history[1] In the 20th century, three pandemics: Spanish influenza (1918-1920), Asian influenza (1957) and Hong Kong influenza (1968) reported around 80 to 100 (according to recent estimates), two and four millions of death, respectively.[2]

The identification and characterization of a novel coronavirus associated with Severe Acute Respiratory Syndrome (SARS) have renewed interest in this Coronaviridae family.[3] According to published reports, the SARS-Coronavirus 2 or SARS-CoV-2 (formerly named as 2019-nCoV) that causes the coronavirus disease 2019 (COVID-19) appeared for the first time in Wuhan (China) in December 2019 as a result of zoonotic transmission[4] with probable bat origin.[5] This disease shown a pneumonia outbreak has been declared a world pandemic by the World Health Organization,[6] and until December 2020, more than 75.5 million infected and more than 1.67 million deaths have been reported worldwide.[7]

SARS-CoV-2, belongs Nidovirales order, of the Coronaviridae family. Its virion has a single (+) stranded RNA, with symmetric helical nucleocapsid[8] that encodes several proteins including four main structural glycoproteins: spike (S); small envelope (E); membrane (M) and nucleocapsid phosphoprotein (N). Other proteins have non structural functions such as RNA dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLPro).[9] These proteases are required for processing of the viral proteins.[10] The hemagglutinin esterase (HE) is also a protein found in the SARS-CoV-2 envelope[11,12] Patiens with COVID-19 pneumonia show a histopathological spectrum distinguished by variable patterns of epithelial damage, vascular complications, fibrosis and inflammation.[13]

Since the dawn of humanity, a variety of plant have been used as alternative methods to the treatments of diseases. Respiratory illness are specially treated with medicinal plants, thus they could be a good alternative to COVID-19 treatment. Particularly in a current context where there is not specific drug or vaccine against COVID-19. Recently studies has shown antiviral activity of medicinal plant extracts against virus such as Echovirus, a serotype of enteroviruses that infected millions of people,[(14)] and Avian infectious bronchitis virus (IBV), a member of the coronavirus[(15)] For this reason, potential applications of plant biotechnology against COVID-19, such as diagnostic reagents, vaccine candidates and antiviral drugs that inhibit the viral replication cycle, have been recently emphasized.[(16)] The use of plant biomolecules, such as antibiotics and vaccines, is limited; however, an efficient combination of the synergistic antiviral effects against COVID-19 by plant-based molecules whit other potential drugs shows to be promising.[(17)] These antiviral drugs include ritonavir and lopinavir, HIV protease inhibitors; ribavirin, faviparivir, and remdesivir, nucleoside analogs; galidesivir, adenosine analogue; and azvudine (reverse transcriptase inhibitor).[(18)]

Traditional Peruvian medicine has accumulated a wide range of knowledge on the use of plants for several millennia, for the treatment of various diseases. This knowledge has been transmitted only orally and there is no documentation about the traditional medicine practices used by pre-Columbian cultures such as Mochica, Chimu, Paracas, Nazca and others, or Inca civilization. Our main in this review is to show the international scientific community the potential of plant species of the flora of Peru in the treatment of respiratory diseases and in obtaining lectins and secondary metabolites, as well as the production of vaccines, against COVID-19.

Methods

It was reviewed the literature published regarding the use of traditional medicial plants for the treatment of respiratory diseases in Peru, China and India (Ayurvedic medicine). It was highlighted the information about the isolation of plant lectins and secondary metabolites, published between 2010 to 2020, with potential utility in the treatment of COVID-19, using the combination of words “plant lectins and plant secondary metabolites against Coronavirus or COVID-19”. The inclusion criteria were: manuscripts in all languages with English abstracts and full text online available, and plants used in traditional medicine in various countries in the treatment of respiratory diseases. In most cases the Scopus database was use. Book and scientific articles about the flora of Peru and the flora of North of Peru, published between 1993 to 2010, were also considered in the present work. Finally, a comparative study between these plant species with genera and species related to the flora of Peru, was showed.

Results

Use of Peruvian medicinal plants in the treatment of respiratory diseases

A first strategy is the use of Peruvian medicinal plants to treat respiratory diseases such as asthma, bronchitis, chest pain, chills, compulsive cough, cold with high mucus, colds, cough, flu, inflammation of the lungs, lungs, phlegm, pneumonia, pulmonary disease. In Peru, traditional and complementary alternative medicine is a practice developed by ancient pre-Columbian civilizations. This activity continues today and is mainly carried out by the rural population, sellers of medicinal plants in local markets ("remedieros") and traditional healers ("curanderos"). However, there are no known studies on its application in the treatment against SARS-CoV-2.

According to a study published by Bussmann and Glenn (2010),[19] a total of 91 plant species of Northern Peru belonging to 82 genera and 48 families were documented and identified as respiratory system herbal remedies. About 30% of these species correspond to three families, Asteraceae (15 species), Lamiaceae (8 species) and Fabaceae (5 species). However, not all reported species correspond to the native flora of northern Peru but rather are introduced species: *Mangifera indica* L. (mango), *Medicago sativa* L. (purple medic), *Allium sativum* L. (garlic), *Zingiber officinale* Rosc. (gingiber), among others. Although not all species have been tested on biological activity, the population uses them in the form of oral administration such as infusions of leaves, whole plants, stems, flowers, and other parts of the plant. This form of use is extremely important because no side effects or toxicity have been reported to date. In the same year, another study carried out by Vásquez *et al*. (2010)[20] reported 130 species from Northern Peru of which 61 species (47%) are used in the treatment of respiratory diseases, highlighting the Asteraceae, Lamiaceae, and Fabaceae with 22, 6 and 6 species, respectively.[20] A comparison between Bussmann and Glenn (2010)[19] and Vásquez *et al*. (2010)[20] studies, showed a high number of genera and species of the Asteraceae family used in the treatment of respiratory diseases. However, the isolation and identification of lectins and secondary metabolites in this family against COVID-19 were not reported.[21,22,23].

Worldwide the traditional Chinese medicine (TCM) is widely applied in the treatment of various diseases. An example is a Chinese herbal mixture called

Lianhuaqinqwen or Lian Hua Qing Wen, a mixture of 11 medicinal species, gypsum, and menthol, traditionally used to treat several respiratory diseases like cough, influenza, pneumonia, and bronchitis.[24,25] Also, the Shu Feng Jie Du composition, composed of numerous plant species is used for the treatment of influenza and viral infections.[22,26] Finally, a recent study showed that about 219 plants from 83 families exhibited antiviral activity of which 149 from 71 families were screened for the identification of secondary metabolites and their possible effect against COVID-19 pandemic.[27]

Use of medicinal plants due the presence of plant lectins and secondary metabolites

A second strategy was reviewed the literature related to the identification of lectins (Table 1) and secondary metabolites, used to the treatment of COVID-19, to compare them with the species and genera that occur in the flora of Peru (Table 2).

Table 1 - Plant lectins tested for their antiviral activity against SARS-CoV-2[21, 23, 35]

[Plant/Family] [Approach effective agent: Lectins]	References
[*Allium porrum*/Alliaceae] [APA] [*Cladastris lutea*/Fabaceae] [Cladistris] [*Cymbidium hybrid*/Orchidaceae] [CA] [*Epipactis helleborine*/Orchidaceae] [EHA] [*Galanthus nivalis*/Amaryllidaceae] [GNA] [*Hippeastrum hybrid*/Amaryllidaceae] [HHA] [*Iris hybrid*/Iridaceae [IRA] [*Iris hybrid*] [IRA b] [*Iris hybrid*] [IRA r] [*Listera ovata*/Orchidaceae] [LOA] [*Morus nigra*/Moraceae] [Morniga M II] [*Narcissus pseudonarcissus*/Amaryllidaceae] [NPA] [*Urtica dioica*/Urticaceae] [UDA] [*Viscum album*/Viscaceae] [ML III]	*Keyaerts et al.* (2007)
[*Canavalia brasiliensis*/Fabaceae] [ConBr] [*C. maritima*] [ConM] [*Dioclea lasiocarpa*/Fabaceae] [DLasil] [*D. sclerocarpa*] [DSclerL]	*Gondim et al.* (2019)
[*Nicotiana benthamiana*/Solanaceae] [Nictaba]	*Yonesi and Rezazadeh* (2020)

Table 2 - Potential use of Peruvian plant species in the treatment of COVID-19. Comparison with species reported in other parts of the world for the presence of plant lectins and secondary metabolites, tested for their antiviral activity against SARS-CoV-2[21,22,23,35]

Family	Species	Peruvian species No (Endemic species)
Adoxaciae (ex Caprifoliaceae)	*Sambucus javanica* subsp. *chinensis*	3
Amaryllidaceae	*Hippeastrum hybrid*	21
Araceae	**Colocasia esculenta*	1
Betulaceae	*Alnus japonica*	(1)
Brassicaceae	*Isatis indigotica*	(1)
Dioscoriaceae	*Dioscorea rhizoma*	70
Euphorbiaceae	**Hevea brasiliensis*	6
Fabaceae	**Cannavalia brasiliensis*	12 (1)
	Cassia semen	4
	Cassia (= *Senna*)	46 (9)
	Dioclea lasiocarpa	12
	Pterocarpus santalinus	3
Gentianaceae	*Gentiana radix*	2 (1)
Lamiaceae	*Salvia miltiorrhiza*	76 (35)
	Scutellaria baicalensis	15 (5)
Lauraceae	*Cinnamomun cassia*	8 (3)
Linaceae	*Linum usitatissimum*	5 (1)
Moraceae	*Artocarpus integrifolia*	2
	Morus nigra	3
Myricaceae	*Myrica faya*	3
Plantaginaceae	*Veronica linariifolia*	6
Poaceae	**Phragmites australis*	1
Polygonaceae	*Polygonum* sp.	11 (1)
Solanaceae	*Nicotiana benthamiana*	15 (6)
	**N. tabacum*	1
	**Solanum lycopersicon* (= *Lycopersicon esculentum*)	8 (2)
Urticaceae	*Urtica dioica*	7 (1)
Zygophyllaceae	**Tribulus terrestris*	3

*Species of the flora of Peru.

Plant lectins

Plant lectins are a unique, natural, heterologous and ubiquitous group of proteins or carbohydrate-binding proteins with the ability to recognize and reversible bind to sugar structures present on the cell Surface.[21,28,29] They are found in a wide range of organisms, from viruses to humans.[30] In the pioneering study made by Keyaerts et al. (2007)[21] thirty-three plants lectins isolated from 27 species of plants were tested for their antiviral activity against SARS-CoV and FIPV (Feline Infectious Peritonitis Virus). Among the total of plant lectins, the Mannose-specific agglutinins were highlighted. Other lectins are ML III, Nictaba and HHA, isolated from *Viscum album* L. “mistletoe” (Viscaceae), *Nicotiana tabacum* L. “tobacco” (Solanaceae) and *Hippeastrum hybrid* Hort. (Amaryllidaceae), respectively.[21] The most potent lectins against the SARS-CoV were the plant lectin APA–isolated from *Allium porrum* L., the plant lectin UDA isolated from *Urtica dioica* L., and the plant lectin Nictaba isolated from *N. tabacum*.[21] Mistletoe lectins (ML I, ML II and ML III), isolated from *V. album* (European mistletoe), enhance immune responses to intranasally co-administered herpes simplex virus glycoprotein D2.[31] In *U. dioica, Urtica dioica* agglutinin (UDA), was isolated showing efficacy on the replication of different SARS-CoV strains.[32]

In the flora of Peru, no species of the *Viscum* genus have been reported, however numerous species of the *Dendrophthora* and *Phoradendron* genera, belonging to the Viscaceae family, have been reported. These genera have 23 species each, as well 3 and 6 endemic species, respectively,[33] and new studies allowed the incorporation of new species for both families, Loranthaceae, and Viscaceae, especially of the genus *Phoradendron*[34] (Table 3).

Table 3 - Some families and genera of the flora of Peru with the greatest potential in plant lectins content for the treatment of COVID-19[33, 34]

Amaryllidaceae [25 (3)] 135 +4 (54)	Solanaceae [42] 538 +78 (162)	Loranthaceae [11] 60 +3 (16)	Santalaceae [3] 11 (7)	Viscaceae [2] 46 + 26 (19)
Hippeastrum 21	*Nicotiana* 15 (6)	*Actanthus* 6 (3)	*Arjona* 1	*Dendrophthora* 23 + 8 (13)
	Solanum (= *Lycopersicon*) 8 + 34 (2)	*Cladocolea* 2 +1	*Cervantesia* 3 (2)	*Phoradendron* 23 + 18 (6)
		Gaidendron 1	*Quinchamalium* 7 (5)	
		Ixocactus 1		
		Ligaria 3		
		Oryctantus 5 (1)		
		Phthirusa 3 +1		
		Psittacanthus 20 (4)		
		Struthanthus 11 +1 (4)		
		Tripodanthus 1		
		Tristerix 7 (4)		

+ (No), addition of new species.[34]
[Number of genera (Endemic genera)].
Number of species, (Endemic species).
Genus (Number of species by genus).

Also, in the flora of Peru, 15 species of the genus *Nicotiana*, including *N. tabacum*, have been reported, of which 5 are endemic, as well as 538 species of Solanaceae with 162 endemic species. On the other hand, although *H. hybrid* has not been reported in the flora of Peru, there are 21 species of this genus as well as 135 species of Amaryllidaceae and 54 endemic species[33] (Table 3). In the Urticaceae family, the flora of Peru registers the species *U. dioica* and 6 other species and one endemic, but no species of the *Allium* genus are reported[33] (Table 2).

In a recent study, the antiviral activity of 4 lectins extracted and purified from the Northeastern Brazilian flora, from four Fabaceae species: *Canavalia brasiliensis* Mart. Ex. Benth. (ConBr), *C. maritima* Thouars. (ConM), *Dioclea lasiocarpa* Benth. (DLasiL) and *D. scleroparpa* Ducke (DSclerL) was reported. The lectins DSclerl y DLasilL showed potent antiviral activity against HIV-1 and respiratory sencitial virus (RSV), and ConBr and ConM against influenza A virus strain H3N2 and influenza B virus.(35) In the flora of Peru, although only *C. brasilienses* have been reported, there are 12 species of the *Canavalia* genus with one endemic species and 12 species of the *Dioclea* genus (Table 2).(33)

Secondary metabolites

In the last decade (2010-2020) the scientific literature has been abundant in the discovery of numerous secondary metabolites with antiviral activity against SARS-CoV-2. This is the case of myricetin and scutellarein, which inhibited 90% of the ATPase activity of the SARS-CoV helicase (Nsp13), one of the non-structural proteins.(36) Myricetin is a flavonoid with antioxidant properties, present in numerous plant species, and scutellarein is a flavone isolated in *Scutellaria laterifolia* L. (Lamiaceae) as well as in the fern *Asplenium belangeri* (Bory) Kunze (Aspleniaceae). In the flora of Peru, 15 species of *Scutellaria* have been reported and 5 species are endemic,(33) as well as 65 species of *Asplenium* and 2 endemic species.(37)

Other objectives has been the discovery of natural products as ACE2 (Angiotensin-converting enzyme 2)-blockers, and targeting the TMPRSS2 (Transmembrane serine protease, serine 2), papain-like proteinase (PLpro) and chymotrypsin-like protease [3CL(pro)].(22)

In the case of ACE2-blockers, several species were identified such a *Berberis integerrima* Bunge (Berberidaceae), *Crataegus microphylla* K. Koch (Rosaceae), *Onopordum acanthium* L. (Asteraceae) and *Quercus infectoria* Olivier (Fagaceae),(38) as well as *Rheum officinale* Baill. and *Polygonum multiflorum* Thunb., both Polygonaceae species that produce emodin, an anthraquinone that significantly blocked the S protein and ACE2 interaction,(39) and inhibit the 3a ion channel of SARS-CoV and HCoV-OC43.(40) Of these species in the flora of Peru, only the genera *Berberis* with 32 species and 18 endemic, *Crateagus* with 1 species and *Polygonum* wih 11 species and 1 endemic have been recorded.(33)

Referent to targeting the TMPRSS2, several secondary plant metabolites have been identified. Thus, the flavonoides kaempherol, luteolin and quercetin, the most common flavonoids found in plants, such as olives, grapes, cauliflower, and others,(41) significantly suppressed TMPRSS2 expression.(42) Addittionally, sulforaphane [1-isothiocyanato-4-(methylsulfinyl)-butane], isolate from broccoli (*Brassica oleraceae* L.),(43) downregulate the TMPRSS2 expression,(44) and cryptotanshinone, the main active component in the root of *Salvia miltiorrhiza* Bunge (Lamiaceae)[45,46] also shows anti-TMPRSS2 activity.[47] In the flora of Peru *B. oleraceae* is not a native species although there are 4 reported native species of this genus, and although *S. miltiorrhiza* is not recorded there are 76 species of the genus *Salvia* with 35 endemic species.[33]

In the case of targeting papain-like proteinase (PLpro) six cinnamic amides were isolated from fruits from *Tribulus terrestris* L. (Zygophyllaceae), and among these terrestrimine showed the best inhibitory activity of SARS-CoV PLpro.[48] Seven bioactive transhinones were isolated from *S. miltiorrhiza*, and the results showed that cryptotanshinone, tanshinone I and rosmariquinone were the most potent inhibitors of SARS-CoV PLpro.[49] Likewise, nine diarylheptanoids were isolated from *Alnus japonica* (Thunb.) Steud. (Betulaceae), and among these hirsutenone showed the most significant inhibitory effect against SARS-CoV PLpro.[50] In the flora of Peru, the Zygophyllaceae family registers 6 genera with 12 species and the *Tribulus* genus with 3 species: *T. cistoides*, *T. longipetatalus* and *T. terrestris* (Table 3). The Betulaceae family with a single genus (*Alnus*) and a single species, *A. acuminata* Kunth, and as already indicated, the *Salvia* genus registers 76 species with 36 endemic species.[33]

Referent, to targeting chymotrypsin-like protease [3CL(pro)] alkylated chalcones, specifically xanthoangelol E, isolated from *Angelica keiskei* (Miq.) Koidz., showed to be the most potent SARS-Co-V- 3CL(pro) inhibitor.[51] Likewise, several tanshinones isolated from *S. miltiorrhiza*, specifically dihydrotanshinone I, showed the most potent SARS-Co-V- 3CL(pro) inhibitory effect[52] Both plant species have also shown significant inhibitory effect against SARS-CoV PLpro.

Additionally, the effect of numerous flavonoids towards SARS-CoV-3CL(pro) was evaluated, observing that pectolinarin (isolated from *Cirsium chanroenicum* Nakai (Nakai), Asteraceae) showed the higher inhibitory effect.[53] Only the *Cirsium vulgare* (Savi) Ten. species has been reported in the flora of Peru.[33]

In traditional Indian medicine (Ayurvedic and Siddha medicinal system) as well as in traditional Chinese medicine, numerous plant species used in the treatment of various diseases of the respiratory tract and of potential use against SARS-CoV-2 are reported.[54] Among these species the following are mentioned: *Piper nigrum* L. and *P. betle* L. (Piperaceae), *Cinchona officinalis* L. (Rubiaceae), *Zingiber officinale* (Zingiberaceae), and others. Most of these species are not found in the flora of Peru. However, in the genus *Piper* 429 species have been registered with 302 endemic species, in the genus *Cinchona*, native to America, 18 species and 3 endemic species (*C. delessertiana*, *C. glandulifera* and *C. nitida*) and although *Z. officinalis* is not a native species, in the flora of Peru it is they have registered 6 genera of this family, 44 species and 7 endemic species (Table 4).[33] In addition, in recent years new species of *Peperomia* (7), *Piper* (12) and *Cinchona* (8) have been added to the flora of Peru, highlighting the Rubiaceae family with a significant increase of 212 new species (Table 3).[34] In the genus *Piper*, hundreds of secondary compounds have been isolated and identified showing different beneficial biological activities and medicinal properties.[55,56] In *C. officinalis*, chloroquine, a synthetic form of quinine, isolated from cinchona bark, has been tested for its antiviral properties against SARS-CoV-1,[21] and the *Z. officinalis* showed several chemical constituents, especially volatile oils, with antimicrobial activities for various bacteria, virus and fungus.[57]

Table 4 - Some families and genera of the flora of Peru with the greatest potential in plant secondary metabolites content for the treatment of COVID-19[33, 34]

Asteraceae [222 (14)] 1432 (729)	Piperaceae [3] 811 + 19 (528)	Rubiaceae [97 (1)] 579 + 212 (165)	Zingiberaceae [6] 44 (7)	Zygophyllaceae [6] 12
Baccharis 70 (20)	*Peperomia* 381 + 7 (226)	*Cinchona* 18 + 8 (3)	*Alpinia* 1	*Bulnesia* 1
	Piper 429 +12 (302)	*Isertia* 5 (1)	*Costus* 23 (3)	*Fagonia* 1
	Sarcorhachis 1		*Dimerocostus* 2	*Kallstroemia* 4
			Hedychium 1	*Larrea* 1
			**Monocostus* 1 (1)	*Porlieria* 2
			Renealmia 16 (3)	*Tribulus* 3

+ (No), addition of new species.[34]
[Number of genera (Endemic genera)].
Number of species, (Endemic species).
Genus (Number of species by genus).
*Endemic genus.

In the study by *Bhuiyan et al*. (2020)[27] a wide list of species and genera that have potentially efficient secondary metabolites against SARS-CoV-2 is reported. About 68% of these species and genera are found in the flora of Perú,[33] specifically the genera *Baccharis*, *Capparis*, *Maytenus*, *Cyperus*, *Euphorbia*, *Acacia* (*Vachellia*), *Geranium*, *Strychnos*, *Ficus*, *Phyllanthus*, *Prunus* and *Viola*, with more than 16 species/genus, as well as numerous endemic species. A special reference is for the *Baccharis* genus, widely distributed in the Neotropics with around 400 to 500 species, highlighting *B. latifolia* used in traditional medicine in Latin America for its anti-inflammatory properties.[58] Other *Baccharis* species such as *B. latifolia*, *B. genistelloides*, and *B. vacciniifolia* are widely used in traditional Peruvian medicine as anti-inflammatory and in the treatment of respiratory diseases.[20] As already indicated in the flora of Peru, 70 species of *Baccharis* have been registered with 20 endemic species.

In recent years, among the numerous secondary metabolites identified with activity against SAR-CoV-2, which have received more attention are: glycyrrhizin, baicalin, scutellarin, hesperetin, nicotinamide and quercetin that could have antiviral effect for their capacity for binding ACE2.[59] The flavonoid glycyrrhizin is the major component in roots from licorice (*Glycyrrhiza glabra* L. and *G. uralensis* Fischer, Fabaceae), used in the traditional Chinese medicine for the treatment of bronchitis, with anti-oxidant and anti-inflammatory properties, and have been proven to inhibit infection of human respiratory syncitial virus (HRSV).[60] Baicalin is a flavone glucoronide isolated from *Scutellaria baicalensis* Georgi (Lamiaceae), used in the Chinese medicine for its therapeutic effects, having exhibited antiviral activities for SARS coronavirus, and with potential to inhibit ACE in *in vitro* conditions.[61] Recently it was reported that the extract of this species inhibited 3CLPro activity of the SARS-CoV virus-2 *in vitro*.[62] Scutellarin is a glycosyloxyflavone isolated from *Erigeron breviscapus* (Vaniot) Hand. (Asteraceae) with broad pharmacological effects and widely used in Chinese medicine[63] observing that it reduces the expression and activity of ACE in brain tissue *in vivo* and consequently could inhibit ACE2.[64] Hesperetin, and to a lesser extent aloe emodin, are two phenolic compounds isolated from *Isatis tinctoria* var. *indigotica* L. (Brassicaceae) that inhibit cleavage activity of the 3CLPro of SARS-CoV-2.[65] Hesperetin is a bioflavonoid abundant in *Citrus aurantium* L. and Citri Reticulate Pericarpium (Rutaceae, CRP), commonly called as Chenpi and widely used in traditional Chinese medicine.[59] Quercetin is a flavonoid widely distributed in several species of *Allium* (Amaryllidaceae) such as onion (*A. cepa* L.), garlic (*A. sativum*) and leek (*A. porrum*) and in the latter species a significant potential in inhibition of ACE2 enzymes, has been observed, therefore of potential use against SARS-CoV-2.[66] Other secondary metabolites such as betulinic acid, triterpenoid isolated from *Betula pubescens* Ehrh. (Betulaceae), showed the highest inhibitory effect on enzymatic activity of 3CLPro of SARS-CoV-2,[67] and homoharringtonine, an alkaloid derived from *Cephalotoxus fortuei* Hook. (Cephalotaxaceae) showed potent antiviral activities against certain viruses such as rhabdovirus and coronavirus.[68]

Conclusions

The flora of Peru is one of the richest and most varied in the world and with a high degree of endemism. Numerous species are used by traditional Peruvian medicine in the treatment of respiratory diseases. Species of the genera *Baccharis* (Asteraceae), *Cinchona* and *Isertia* (Rubiaceae) and *Dendrophthora* and *Phoradendron* (Viscaceae), are some that can be used against COVID-19, due to the potential presence of plant lectins and secondary metabolites.

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Conflict of interests

The authors declare that there is no conflict of interest

Authors' contributions

Guillermo E. Delgado-Paredes: General design of the study. Interpretation and discussion of results.

Paulo R. Delgado-Rojas: Preparation of tables. Interpretation and discussion of results.

Consuelo Rojas-Idrogo: General design of the study. Interpretation and discussion of results.