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PHYTOTHERAPY: A POTENTIAL REMEDY AGAINST INFECTIOUS CORONAVIRUS DISEASE (COVID-19)

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Abstract: A novel Coronavirus disease (COVID-19) caused by SARS-Cov-2 has emerged as one of the most infectious diseases of the present century. It has caused a serious threat and global health crisis. Although the vaccines and some drugs approved, the pandemic goes on. Lack of medicines accessible to population and hasty increase of cases, mainly due to omicron variant, have focused the attention towards phytotherapy as a promising alternative to curtail and eradicate the overall impact of this infectious *disease*. In this context, questions arise: can plants contribute to disease control against viruses? Which species can be used as an alternative and/or complement therapeutic against COVID-19? Thus the objective of present review is to evaluate the medicinal plant species already validated for the treatment of common colds and other respiratory problems besides that published in the monographs of the World Health Organization, as well as studies carried out on already certified antiviral activities. To contribute towards the treatment of COVID-19, it is essential to identify the species with a potential for validation studies, containing clinical and pre-clinical trials. It is suggested that species already indicated for antiviral activity against HIV should be selected for pre-clinical trials. Species including *Echinacea angustifolia* DC (roots), *Echinacea pallida* (Nutt.) Nutt. (roots), *Echinacea purpurea* (L.) Moench (shoots), and *Andrographis paniculate* (Burm. F.) Ness. should be considered for clinical trials in cases of COVID-19.

Keywords: Medicinal plants, Plant derived natural compounds, Respiratory diseases, SARS-CoV-2, selection tool.

INTRODUCTION

Historically, plants for medicinal purposes have been used since the beginnings of human civilization. It is a practice that has been passed on through successive generations, representing an important cultural heritage (de Oliveira et al., 2016; Firmo et al., 2012). Over time this popular therapeutic practice has been going through different phases, being the first and, for many years, the only therapeutic option to treat and prevent diseases, and then to occupy a marginalized position with predominant use in the less favored social classes, without access to health services. However, at the end of the 20th century, herbal medicine returned as an important therapeutic tool in modern society in both developed and developing countries (Bruning et al., 2012; Ribeiro, 2019).

The importance of phytotherapy at present is justified by several factors, such as the difficult access for a large part of the population to health services, especially in poor countries; the high cost of synthetic drugs, in addition to their ineffectiveness for several diseases of global prevalence and finally the recognition of the pharmaceutical industry of the importance of vegetables as a source of new drugs due to the increase in scientific research demonstrating and proving pharmacological actions of many plants (Pereira et al., 2015).

In addition to phytotherapy, plants also contribute to therapy through isolated active principles, such as substances that have never been synthesized yet and that are obtained exclusively from plant sources such as morphine and cardiotonic glycosides and also contributing to obtaining synthetic derivatives such as all steroidal drugs (Robbers et al., 1997).

The validation of plants for medicinal use consists of the scientific confirmation of therapeutic properties, used in folk medicine, through ethno-directed, pharmaco-gnostic, chemical, pre-clinical pharmacological, and toxicity studies, and clinical trials, in addition to pharmaceutical development of

formulations (Fatima; Nayeem, 2016).

Although the scientific evolution does not allow setbacks and should guarantee the use of plants in a rational manner, supported by scientific methods, miraculous healing by herbal formulations is often reported, especially in Brazil, a country with a great biodiversity and cultural diversity (Balbino and Dias, 2010; Brazil, 2020; Figueredo et al., 2014).

We can certainly say that, contrary to the information that has been propagated, it is extremely important to verify the scientific evidence of these plants, thorough pre-clinic and clinical studies. guaranteeing their safety in their use. However, certainly, using well-established selection criteria it is possible to direct efforts and resources towards bioprospecting studies in an attempt to identify plant species that are likely to contribute to public health worldwide in the medium or long term.

Thus, this work was carried out with the objective of evaluating medicinal plant species already validated for the treatment of common colds and other respiratory problems published in the monographs of the World Health Organization (WHO, 1999, 2002, 2007 and 2009), as well as studies on already certified antiviral activity, in order to identify species with a potential for validation studies, containing clinical and pre-clinical trials and aiming to contribute to the treatment of COVID-19.

MEDICINAL PLANTS AND COVID-19

The COVID-19 outbreak was first documented on December 31, 2019, in China and the infection is called COVID-19. This virus is from a large family of zoonotic viruses that can cause from a common cold to a severe respiratory affection. The infection has been spreading all over the world quickly and currently affects countries in the six continents (Xu et al., 2020).

Although many vaccines of different brands have been approved by drug surveillance agencies in practically all countries, they are still not able to prevent contamination by SARS-Cov-2. It is clear that these vaccines have been shown to reduce the severity of symptoms but there is still a lot to be researched to get out of this pandemic. Also, although there are already registered drugs for the treatment of COVID-19, these are still inaccessible to the majority of the population because they are expensive, such as antiviral drug (rendesivir, ritonavir, nirmatrelvir), monoclonal antibodies (regkirona, casirivimabe-imdevimabe, balanivimabe-etesevimab), IL-6 inhibitors (tocilizumab, sarilumab) and others (WHO, 2021).

It is important to report that since the cases were confirmed in China, thousands of people have died, the new variants and despite the advances already made, the search for alternative methods of controlling or preventing COVID-19 has been growing around the world. In several countries, Integrative and Complementary Practices have been used for the treatment of COVID-19 as well as the control of sequelae known as post-Covid syndrome (Ruela et al., 2021). Among these countries, China stands out, which since 2020, The Guidelines of Diagnosis and Treatment for COVID-19 included TCM therapies such as acupuncture and the use of medicinal plants (PRC, 2020; Chamarro, 2021).

During the SARS outbreak in 2003, several clinical trial with herbal products were performed. The most of them showed that these products from plants used together with conventional treatment to SARS had some beneficial effect as decrease the mortality and relief the symptons, however these results are not conclusive due to some methodologics

issues (Leung, 2007; Liu et al., 2004).

Information as potential of herbal products against infection, associated with the historical curative power of plants since the dawn of human civilization and the need for studies to evidence effective and safe drugs against the current pandemic, arouses interest in investigating species that can be used to auxiliary to fight the COVID-19. In this scenario, science is the only tool that can indicate the path of therapeutic efficacy and safety (Yang et al., 2020).

Considering the importance of plants for therapy, this work reports plant species, selected by the WHO in its monograph guides, that are used for the treatment of cold and respiratory problems, as well as demonstrating the plants, present in these guides, which already have proven antiviral activity as subsidies to support the selection of plant material for further validation studies aiming the Research & Development of bioproducts to fight the SARS-CoV-2 and/or symptoms of the infectious disease COVID-19.

BRIEF HISTORY OF WHO PLANT MONOGRAPHS

In the 4th International *Conference of Drug Regulatory Authorities* (ICDRA) in 1986, it was suggested that WHO produced a publication to standardize information on the most important medicinal plants traditionally used in various countries where this practice is common by gathering information to support its therapeutic use. Thus, in 1999, the volume 1 of the "*WHO monographs on selected medicinal plants*," containing 28 monographs (WHO, 1999), was released, and then the volumes 2 (WHO, 2002), 3 (WHO, 2007) and 4 (WHO, 2009) were subsequently published.

In these monographs, plants were selected due to their use in traditional practices in different countries with enough scientific studies to determine their effectiveness and safety. Thus, all plants have validation for some medicinal use, but it is worth mentioning that not all of their popular therapeutic indications have been scientifically proven. Thus, in the monographs, in addition to various information on pharmacopoeial quality control parameters, pharmacological and pre-clinical and clinical toxicity trials, there are medicinal indications for each species. These indications are divided into three categories: plant species with clinical evidence, plant species listed in pharmacopoeias, traditional medical systems and official documents from various WHO member countries, and plant species with indications for popular use only, therefore without pre-clinical and clinical scientific information.

In the first category, plant species have indications validated by documented clinical studies performed according to the rules of good practice, that is, controlled, randomized, double blind *clinical trial*. In the second category of therapeutic indication are plant species with actions established in many countries, included in pharmacopoeias or official documents of those countries, composed of uses of species that have already been scientifically studied but that require complementary studies to validate the therapeutic use. In the third category of plant species for medicinal use, there is a focus on popular use without scientific evidence, therefore without guarantee of efficacy and safety.

By analyzing the editions of the WHO monographs, we found that the titles of these three categories changed over time. In this work, we used the description of categories used from the volume 3 (WHO, 2007), in which there were changes in categories 2 and 3. Category 1 remained with the same title "Use supported by clinical data" Category 2 included indications of plant species included in pharmacopoeias documented in official

codes (*Use described in pharmacopoeias and well established documents*), and the third category was used only in traditional medicine (*Used described in traditional medicine*), maintaining the lack of scientific evidence in the latter category (WHO, 1999, 2009, 2007, 2002).

PLANTS TO TREAT COLD AND RESPIRATORY INFECTIONS FROM WHO MONOGRAPHS

In this chapter, we first present the plant species that are mentioned in these monographs with medicinal use to treat cold, highlighting species with corroborative clinical trials already carried out (category 1); those in pharmacopoeias and documents recognized with some performed pre-clinical trial but requiring a complete validation (category 2); and those indicated only due to traditional or popular use in countries and which do not have a proven safety or efficacy (category 3) (Table 1). Table 2 shows the plant species listed in the WHO monographs for respiratory disorders, also referenced according to the categories above. It is important to highlight that these species are distributed in these three categories only regarding therapeutic indication for cold and respiratory diseases.

In this analysis, we found that for some plant species that are used to treat common cold there are already clinical studies proving their use. The species include *Echinacea*

CATEGORY OF MEDICINAL USE	SPECIES/PART OF PLANT	REFERENCE
1 - Uses supported by clinical data	*Echinaceae angustifolia* /Roots	(WHO, 1999)
	Echinaceae purpurea /Aerial parts	(WHO, 1999)
	Ephendra sinica /Branches/Aerial parts	(WHO, 1999)
	Chamomilla recutita / Flowers	(WHO, 1999)
	Andrographis paniculata /Aerial parts	(WHO, 2002)
2- Uses described in pharmacopoeias and well established documents	*Astragalus membranaceus* /Roots	(WHO, 1999)
	Bupleurum falcatum/Roots	(WHO, 1999)
	Platycodon grandiflorum / Roots	(WHO, 1999)
	Thymus vulgaris/Leaves and Flowers	(WHO, 1999)
	Zingiber officinale /Rhizomes	(WHO, 1999)
	Sambucus nigra /Flowers	(WHO, 2002)
	Commiphora molmol /Branches oil-resin	(WHO, 2007)
	Achillea milefolium/Flowers/ aerial parts	(WHO, 2009)
	Salix alba / Young branches	(WHO, 2009)
3- Uses described in traditional medicine	*Valeriana officinalis* /Underground parts	(WHO, 1999)
	Cephaellis ipecacuanha /Roots rhizomes	(WHO, 2007)
	Trigonella foenum-graecum /Seeds	(WHO, 2007)
	Momordica charantia./Fruit	(WHO, 2007)

Table 1. Plant species indicated to the treatment of cold that appear in WHO monographs, according to the categories 1- Uses supported by clinical data 2- Uses described in pharmacopoeias and well established documents 3- Uses described in traditional medicine

angustifolia D.C. (roots), *E. pallida* (Nutt.) Nutt. (roots), *E. purpurea* (L.) Moench (aerial parts), *Ephedra sinica* Stapf (branches and aerial parts), *Chamomilla recutita* (L.) Rauschert (flowers), and *Andrographis paniculata* (Burm. F.) Nees (aerial parts). Regarding the use to treat respiratory diseases, plants with clinical trials are the same as plants mentioned for common flu, except for *Ephedra sinica* Stapf. (see table 2)

Ephedra sinica Stapf is used for the treatment of common flu. It is emphasized that this use is restricted to decongestant and bronchodilator activity, as confirmed by clinical trials (WHO, 1999). This plant species is distributed in Asia, Central and North Americas, and the Mediterranean. Its branches and aerial parts are widely used in traditional medicine to treat diseases of the central nervous, cardiovascular, and respiratory systems (Ibragic and Sofić, 2015). A recent study by Ren et al., 2020 has stated that this species is part of the traditional Chinese medicine, constituting one of the components of the Qingfei Paidu decoction (QPD), which has shown good results in controlling COVID-19 in China. Its chemical composition stands out for the presence of alkaloids such as ephedrine, pseudoephedrine and norephedrine (Ibragic and Sofić, 2015). Its use as a decongestant and bronchodilator was reported for ephedrine (Brunton et al., 2018). Ephedrine, due to activation of adrenoceptors in the lungs, also causes vasoconstriction and blanching when used nasally. This action was more significant with ephedrine than with epinephrine. According to that study, both ephedrine and pseudoephedrine can be used orally as nasal decongestants in some diseases such as allergic rhinitis. However, it seems that, for cold, it is not very effective to treat nasal congestion (Brunton et al., 2018). Numerous other pre-clinical and clinical trials have been carried out on this species, but we emphasize that these studies aimed to evaluate the effects on the control of obesity (Kim et al., 2012). Besides the medicinal uses of *E. sinica* and several clinical trials (Al Dhamen et al., 2019) in a review study, have demonstrated that the use of this species is associated with many adverse effects, such as liver problems, nephritis and cardiac toxicity, including some deaths.

Species of *Echinacea*, originating in the United States and Canada, are also used in different regions of the world for the treatment of various diseases. *Echinacea agustifolia* D.C. var. *angustifolia* (roots), *E. pallida* (Nutt.) Nutt. (roots) and *E. purpurea* (aerial parts) are widely used for the treatment of common flu or other respiratory problems based on pre-clinical and clinical trials. These species are characterized by the presence of phenolic substances, such as derivatives of caffeic acid (echinacoside, cynarine, and chicoric acid) (Mengs et al., 1991), with immune system-stimulating activity and antiviral activities already reported by several *in vitro* and *in vivo* studies (Hudson; Vimalanathan, 2011; Hudson, 2011; Senchina et al., 2010).

Randomized controlled trials (RCTs) studies compared with placebo group in patients with upper respiratory infection treated with tincture of *E. pallida* roots showed improvement in the disease treatment, with a decrease in disease time from 13 to 9.8 days for bacterial infections and from 12.9 to 9.1 days for viral infections (Bräunig, 1993). Clinical studies on *E. purpurea* have already been conducted to treat respiratory problems, showing excellent resultes (Isbaniah et al., 2011; Rahmati et al., 2012; Rauš et al., 2015). Lind et al. (2001) carried out a survey on systematic reviews on several medicinal plants and demonstrated that more than thirty clinical trials were performed using preparations of *Echinacea* (*E. purpurea*, *E. pallida* and *E. angustifolia*), suggesting that

these preparations have a beneficial effect mainly if used at the beginning of common colds. These species are not indicated for patients with tuberculosis, multiple sclerosis, AIDS, and autoimmune diseases, and the use should not exceed eight weeks (German Commission E Monograph, 1992).

Chamomilla recutita (L.) Rauschert (synonym: *Matricaria chamomilla* L.) is popularly known as German chamomile. Its flowers have a blue essential oil due to the presence of chamazulene (1-15%), considered the major component. The flowers also have flavonoids, especially apigenin. Although the use of this species by inhalation has been reported in the volume 1 of the WHO monographs (1999) against respiratory tract irritations in common colds with evidence from clinical trials, in our survey, we only obtained results from clinical trials for dermatological problems (Hashempur et al., 2018), problems in the oral cavity (Aghamohamamdi, Hosseinimehr, 2016), and anxiety (Zick et al., 2011). Miraj and Alesaeidi (2016) carried out a systematic review of the therapeutic uses of this species considering pre-clinical and clinical trials and concluded that the species can be used effectively and safely.

Andrographis paniculate (Burm. F.) Nees is a common species in Asia, whose shoots are rich in lactonic diterpenes, such as andrographolide. In the volume 2 of the WHO monographs (2002), this species is indicated for the prophylaxis and treatment of upper respiratory infections such as common flu. *In vitro* studies have reported anti-HIV-1 activity (Basak et al., 1999; Kumar et al., 2012; Ribeiro et al., 2010), in addition to stimulating activity of the immune system evidenced in *in vitro* and *in vivo* tests (Puri et al., 1993). A double-blind, placebo-controlled clinical study with extract of shoots of this plant in patients with common flu showed a significant decrease in symptoms (such as sore throat, tiredness, muscle pain and malaise) on the 4th day of treatment compared to the placebo group (Hancke et al., 1995). In a similar study, the same type of extract, tested in patients with initial symptoms of common flu and uncomplicated sinusitis, showed improvement in the treated group compared to the placebo group (Linde et al., 2001). Another randomized, double-blind, clinical study investigated the prophylactic effects of the extract of shoots of *A. paniculata* against influenza on school children for three months, with evaluation by doctors. There was a test group (200 mg of the extract) and a placebo group. In the first two months, there was no difference between the two groups regarding the onset of the flu. However, after the third month of treatment, there was a significant decrease in the incidence of colds in the treated group (30%) compared to the placebo group (62%) (Caceres et al., 1997). In a randomized study with 152 adult patients with pharyngotonsillitis, one group received powder from shoots of *A. paniculata* at a dose of 6 g/day, another group a dose of 3 g/day, and the other received paracetamol. There was no difference among the groups (Chantrakul et al., 1991).

Regarding the species indicated for use against common flu with some type of scientific evidence, there are also *Astragalus membranaceus* (roots), *Bupleurum falcatum* (roots), *Platycodon grandiflorum* (roots), *Thymus vulgaris* (leaves and flowers at the top), *Zingiber officinale* (rhizome), *Sambucus nigra* (flowers), *Commiphora molmol* (oil-resin from branches), *Achillea milefolium* (flowers and shoots), and *Salix alba* (young branches) (Table 1).

For the species mentioned against respiratory conditions with some scientific studies, there are *Platycodon grandiflorum* (roots), *Thymus vulgaris* (top leaves and

flowers), *Allium sativum* (bulbs), *Eucalyptus globulus* (leaves), *Mentha* x *piperitha* (leaves), *Sambucus nigra* (flowers), *Polygala senega* (roots), *Pimpinella anisum*. (essential fruit oil), and *Foeniculum vulgare* (fruits) (Table 2).

Among them, some plant species with pre-clinical trials on respiratory disorders are worth mentioning. The roots of *Platycodon grandiflorum*., a common species in North Asia, are used for problems of upper respiratory infections. Its decoction evidenced an expectorant action in *in vivo* trials. Platycodins (triterpene saponins) are the possible active components of this species (Takagi; Lee, 1972; Zhu, 1958). The flowers and leaves of *Thymus vulgaris* (thyme) have an essential oil whose major components are thymol and carvacrol, that are used to treat respiratory tract infections due to antiseptic (Abu-Darwish et al., 2012), antitussive (Gavliakova et al., 2013; Reiter; Brandt, 1985), and expectorant actions (Fig.1) (Marzian, 2007).

The fruits of *Foeniculum vulgare* (anethol doux), which present trans-anethole, (+)-fenchone and estragole as major components of its essential oil, are reported for use as an expectorant in mild inflammation of the upper respiratory tract, an action that has been proven in *in vivo* trials (Müller-Limmroth; Fröhlich, 1980).

The essential oil from fruits of *Pimpinella*

CATEGORY OF MEDICINAL USE	SPECIES/PART OF PLANT	REFERENCE
1- Uses supported by clinical data	*Echinaceae angustifolia* DC/Roots	(WHO, 1999)
	Echinaceae purpurea (L.) Moench/Aerial parts	
	Chamomilla recutita (L.) Rauschert (Flowers)	
	Andrographis paniculata (Burm. F.) Nees (Aerial Parts)	
2- Uses described in pharmacopoeias and well established documents	*Platycodon grandiflorum* (Jacq.)A. DC./Roots	(WHO, 1999)
	Thymus vulgaris L./Leaves and Flowers	(WHO, 1999)
	Allium sativum L./Bulbs	(WHO, 1999)
	Eucalyptus globulus Labill/Leaves	(WHO, 2002)
	Mentha x *piperita* L./Leaves	(WHO, 2002)
	Sambucus nigra L./Flowers	(WHO, 2002)
	Polygala senega L./Roots	(WHO, 2002)
	Pimpinella anisum L./Fruit essential oil	(WHO, 2007)
	Pimpinella anisum L./Fruits	(WHO, 2007)
	Foeniculum vulgare Will/fruits	(WHO, 2007)
3- Uses described in traditional medicine	*Ammi visnaga* (L.) Lam. /fruits	(WHO, 2007)
	Carthamus tinctorius L./flowers	(WHO, 2007)
	Punica granatum L./pericarp	(WHO, 2009)
	Magnolia officinalis Rehler and Wilson/ Branches, Root bark and Steam	(WHO, 2009)

Table 2. Plant species indicated for medicinal use for the treatment of respiratory conditions that appear in the monographs of the World Health Organization, according to the categories 1- Uses supported by clinical data 2- Uses described in pharmacopoeias and well established documents 3- Uses described in traditional medicine

anisum has trans-anethole as the major compound. It is classified by the WHO for use against mild inflammation of the respiratory tract and pre-clinical *in vivo* studies showed expectorant action (Boyd, 1970; Boyd; Sheppard, 1970). The trans-anethol was investigated in rats and showed no carcinogenic action. However, hepatotoxic action was evidenced (Truhaut et al., 1989). According to the WHO (WHO, 2007), the application of the essential oil of *Pimpinella anisum* must be only as inhalation.

The essential oil of leaves of *Eucalyptus globulus*, as well as other species of *Eucalyptus* whose essential oil contains 1,8-cineole as the major substance, is used against respiratory tract disorders because it is antiseptic (Nahaei et al., 2016; Pereira et al., 2014; Salari et al., 2006), antitussive (Misawa; Kizawa, 1993), and expectorant (Boyd; Sheppard, 1968).

The leaves of *Mentha x piperita* L. (peppermint) have been described for mild inflammatory problems of the upper respiratory tract. Pre-clinical studies show antibacterial (McKay; Blumberg, 2006) and antiviral action against rinderpest virus (McKay; Blumberg, 2006). Clinical trials with this species have shown the effectiveness on digestive problems, highlighting irritable bowel syndrome (Jailwala et al., 2000; Pittler; Ernst, 1998). There is a double-blind, controlled clinical study to verify the action of aromatic plants on respiratory problems. It was verified that a nasal preparation containing five plants (*Eucalyptus citriodora*, *E. globulus*, *M. piperita*, *Origanum syriacum*, and *Rosmarinus officinalis*), administered five times for three days, modified the severity of symptoms such as sore throat, hoarseness and cough when compared to the placebo group (Ben-Arye et al., 2011).

Considering the need to discover low-cost drugs for COVID-19, we suggest that clinical studies on patients with this disease should be carried out using the species validated by clinical trials on cold and other respiratory conditions which appear in the WHO monographs. Among these species with some clinical validation from these monographs, we recommend that *Efendra sinica* should not be recommended due to its high toxicity as well *Matricaria recutita* due to the insufficiency of studies to certify its effectiveness in the treatment of respiratory problems. Thus, *Echinacea* medicinal species and *Andrographis paniculata*, in addition to studies proving their effectiveness in the clinical treatment of respiratory tract disorders, demonstrate a stimulating action on the immune system with no evidence of use risks and can be used in clinical trial to evaluate for prevention and early infection of COVID-19. When the use of other drugs against COVID-19 begins, the use of plants must be well evaluated because there are no studies that prove its safe use with other drugs, taking precautions with the possible interactions between plant-drug.

PLANTS WITH ANTIVIRAL ACTIVITY FROM WHO MONOGRAPHS

Twenty-five species included in the WHO medicinal plant monographs have antiviral activity against different types of viruses. They were object of pre-clinical and/or clinical trials, with predominance of tests carried out against HIV and herpes simplex viruses, mainly type 1.

The plant species with anti-HIV action in pre-clinical and/or clinical trials, according to WHO data, are *Andrographis paniculata* (shoots), *Calendula officinalis* (flowers), *Syzygium aromaticum* (flower bud), *Terminalia chebula* (fruits), *Scutellaria baicalensis* (roots), *Hypericum perforatum* (top flowers and shoots), *Achilleamille folium* (flowers and shoots with flowers), and *Momordica charantia* (fruits).

Many of these plants with antiviral action act by inhibiting proteases. Shaghaghi (2020) has cited that the most important therapeutic strategy to control COVID-19 is through the synthesis of chemical compounds capable of inhibiting proteases from these virus and this also can be researched among natural products derived from plants. In theses tests, rendesivir, already approved to treat COVID-19, can be being used as a positive control (Khaerunnisa et al., 2020).

Thus, there are some plants that have secondary metabolites with potential against proteases according to the molecular docking studies (Liu; Wang, 2020). *Andrographis paniculata* (Burm. F.) Ness is a species composed mainly of diterpene lactones. Its main representatives are andrographolide and its derivatives (WHO, 2009). A study demonstrated through molecular docking the potential action of these substances for the treatment of COVID-19 given their ability to bind to the 3CLpro protein, which is essential for the maturation of the virus (Wu et al., 2020)

The species *Calendula officinalis* L. and *Terminalia chebula* Retz have flavonoids in their chemical composition: quercetin, isoquercetin and rutin (Vidal-Ollivier et al., 1991; WHO, 2009, 2002). These are compounds that have already been shown to have a binding affinity to the SARS-CoV-2 protease in a similar or even superior way than nelfinavir, a HIV-1 protease inhibitor, active against SARS-CoV (Adem et al., 2020; Khaerunnisa et al., 2020; Xu et al., 2020).

Momordica charantia L. and *Hypericum perforatum* L., have in addition to quercetin, isoquercetin and rutin, catechins in their chemical composition (Grinter; Zou, 2014; Nahrstedt; Butterweck, 1997; WHO, 2002). Catechins also showed a potential activity against SARS-CoV-2 protease according to this docking *in silico* approach (Khaerunnisa et al., 2020).

The potential of these secondary metabolites, according to these evidences from these studies using molecular docking as well as their biologically safety profile, reinforces the suggestion that plant species with validation studies against HIV, such as those emphasized in this review, can be prioritized for preclinical studies on models against SARS-CoV-2.

CONCLUSION

The purpose of this review is not to carry out a complete survey of all scientific studies already carried out on the mentioned plant species but to indicate species that can be selected for validation studies aiming their use in pre-clinical and clinical trials in mild cases of COVID-19 or to prevent it.

We suggest for pre-clinical trials, species that are already indicated for antiviral activities against HIV should be selected, emphasizing species with a potential signaled by molecular docking studies. For clinical trials, the species *Echinacea angustifolia* DC (roots), *Echinacea pallida* (Nutt.) Nutt. (roots), *Echinacea purpurea* (L.) Moench (shoots), and *Andrographis paniculate* (Burm. F.) Ness. should be considered to prevent or treat the onset of infection.

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