Therapeutic approach for COVID-19: The power of herbal medicine Abordagem terapêutica para COVID-19: O poder da medicina herbal Enfoque terapéutico para COVID-19: El poder de la medicina herbal

Received: 09/30/2020 | Reviewed: 10/04/2020 | Accept: 10/13/2020 | Published: 10/14/2020

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### Abstract

The objective of this work was to evaluate whether medicinal plants as active ingredients of herbal, homeopathic and floral medicines marketed in Brazil, had potential use as a therapeutic strategy for prevention, treatment and cure for COVID-19. This study took into account products marketed and regulated by Brazilian legislation with claims such as: immunomodulators, antivirals and improvement of symptoms related to respiratory system deficiency, which were calculated the absolute (n) and relative (%) frequencies. In addition, PubMed®, Web of Science® and SciVerse Scopus® databases were used to search the literature in order to obtain the scientific claims of plants found in the formulations of the evaluated products, taking into account the typical symptoms of COVID-19. 113 products were found, of which 65% were herbal medicines, 27% homeopathic medicines and 7% floral. There were 13 medicinal plants with an absolute frequency  $\geq$  5, in which scientific evidence was found regarding their medicinal use, as a complementary therapy in the treatment of symptoms related to COVID-19.

**Keywords:** Medicinal plants; Homeopathics; Florals; SARS-CoV-2; Complementary treatment.

#### Resumo

O objetivo deste trabalho foi avaliar se as plantas medicinais, como princípios ativos de medicamentos fitoterápicos, homeopáticos e florais comercializados no Brasil, têm potencial uso como estratégia terapêutica para prevenção, tratamento e cura do COVID-19. Este estudo considerou produtos comercializados e regulamentados pela legislação brasileira com reivindicações como: imunomoduladores, antivirais e melhora de sintomas relacionados à deficiência do aparelho respiratório, sendo calculadas frequências absolutas (n) e relativas (%). Além disso, os bancos de dados PubMed®, Web of Science® e SciVerse Scopus® foram utilizados em busca na literatura para obter afirmações científicas das plantas encontradas nas formulações dos produtos, dos quais 65% eram fitoterápicos, 27% medicamentos homeopáticos e 7% florais. Houve 13 plantas medicinais com frequência absoluta  $\geq$  5, nas quais foram encontradas evidências científicas quanto a seu uso medicinal como terapia complementar no tratamento dos sintomas relacionados à COVID-19.

Palavras-chave: Plantas medicinais; Homeopáticos; Florais; SARS-CoV-2; Tratamento complementar.

### Resumen

El objetivo de este trabajo fue evaluar si las plantas medicinales como ingredientes activos de los medicamentos herbales, homeopáticos y florales comercializados en Brasil, tenían un uso potencial como estrategia terapéutica para la prevención, tratamiento y cura del COVID-19. Este estudio tomó en cuenta productos comercializados y regulados por la legislación brasileña con reclamos tales como: inmunomoduladores, antivirales y mejoría de síntomas relacionados con la deficiencia del sistema respiratorio, los cuales se calcularon las frecuencias absolutas (n) y relativas (%). Además, se utilizaron las bases de datos PubMed®, Web of Science® y SciVerse Scopus® para buscar en la literatura con el fin de obtener los reclamos científicos de las plantas que se encuentran en las formulaciones de los productos, de los cuales el 65% eran medicamentos a base de hierbas, el 27% medicamentos homeopáticos y el 7% florales. Fueron 13 plantas medicinales con una frecuencia absoluta ≥ 5, en las que se encontró evidencia científica sobre su uso medicinal, como terapia complementaria en el tratamiento de síntomas relacionados con COVID-19.

**Palabras clave:** Plantas medicinales; Homeopáticos; Florales; SARS-CoV-2; Tratamiento complementario.

### **1. Introduction**

The world health organization (WHO) has reported the presence of COVID-19 in 215 countries. In they the number of cases exceeds over a million and the number of deaths exceeds over 250 thousand (WHO, 2020). The form of transmission that occurs from human to human, by aerosol, or by contact with contaminated objects. The virus can survive for two hours to a few days on the surface or on the floor, but that this is not the main course of the infection (Aanouz et al., 2020; Ali & Alharbi, 2020). Environmental factors, such as temperature, can affect the epidemiological dynamics of many infectious diseases. This happen especially in tropical regions, as observed in infections by influenza viruses, which are more present during winter. Countries like Brazil, were one of the countries most affected by the disease, taking into account this factor (Prata et al., 2020; Shi et al., 2020).

Human coronaviruses are predominantly concomitant with diseases of the upper respiratory tract. They ranging from mild to moderate, in which the main initial symptoms are fever, cough, shortness of breath and fatigue. They can progress to respiratory failure and

multiple organ failure (Ho et al., 2020; Vellingiri et al., 2020; Zhai et al., 2020). In addition, researchers have chosen risk groups, whose symptoms may be aggravating, which include elderly, children and patients with other health problems, such as lung, heart disease, diabetes and cancer, for example (Ali & Alharbi, 2020).

In view of the risk of contamination and the proliferation of symptoms in patients, prevention and health management can provide relief from the symptoms of COVID-19, because there is no precise treatment. One approach to prevent symptoms or contamination is the use of medicinal plants as an alternative therapy. They can influence the immune system and attenuate primitive symptoms related to the disease, as research on traditional Chinese medicine (Ang et al., 2020; Ho et al., 2020).

However, it is observed that Chinese medicine, which uses medicinal plants as basis of treatment, has strong relationship and may come to be used as therapeutic aid. In this sense, the objective of this work was to evaluate whether medicinal plants as active ingredients of herbal, homeopathic and floral medicines marketed in Brazil, had potential use as a therapeutic strategy for prevention, treatment and cure for COVID-19.

### 2. Materials and methods

### 2.1 COVID-19 x Herbal medicine

The mapping of the relationship between the coronavirus and the use of medicinal plants as complementary treatment was carried out by co-occurrence analysis using VOSviewer software (https://www.vosviewer.com/). The bibliographic research was carried out between March and May 2020, with study published until May 18, in the SciVerse Scopus® database (Elsevier Properties SA, USA). The words used for consultation were "COVID-19" and "Herbal medicine", with publication dates from 1975 to 2020. Titles, abstracts and bibliographic information of the returned articles were exported to a text file. A thesaurus file was used to merge synonyms and exclude general expressions (for example, objective, area of study and conclusion).

### 2.2 Product search strategy

The data were collected between March and May 2020 on the Brazilian website of manufacturers, compounding pharmacies, drugstores and health food stores. This study took

into account products marketed and regulated by Brazilian legislation, being herbal, homeopathic and floral medicines, with claims such as: immunomodulators, antivirals and improvement of symptoms related to respiratory system deficiency (BRAZIL, 2009, 2014, 2018a, 2018c). Information on the plant presence, the types of product and the claims on the labels and patient information leaflets were collected. And the values of absolute (n) and relative (%) frequency were calculated, so that for the table construction, only medicinal plants with an absolute frequency of  $n \ge 5$  were considered. The other ingredients and their absolute and relative frequencies can be seen in the supplementary material in table A.

### 2.3 Collection of functional and scientific claim data

A comprehensive literature search was carried out in the following databases: PubMed® (US National Library of Medicine, USA), Web of Science® (Thomson Reuters, USA) and SciVerse Scopus® (Elsevier Properties SA, USA) for studies published until May 18, 2020. Cited references to the retrieved articles and previous reviews were also manually checked to identify any additional studies that were eligible. All citations were imported into a bibliographic database (Mendeley, https://www.mendeley.com) and duplicates were removed. The eligible articles were related to the scientifically proven function of the medicinal plants found in commercial products, provided that they had claims related to antiviral, immunomodulatory activities and treatment of symptoms related to respiratory tract deficiencies, including typical symptoms of COVID-19, such as fatigue, muscle pain, sneezing, sore throat, dry cough, high fever, breathing problems, etc., with some severe cases including pneumonia, severe respiratory syndrome, kidney failure and even death.

### 2.4. Data analysis

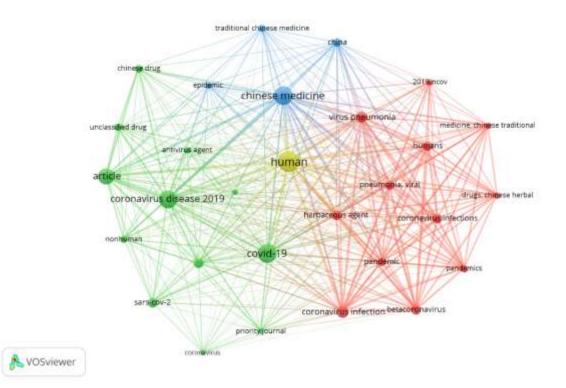
The mean, standard deviation, variation range and frequency distribution of the studied variables were calculated. The probability plots and the Kolmogorov–Smirnov test were used for assessing the normality of the data. Statistica 12.0 (StatSoft Inc.,Tulsa, United States of America, 2013) was used for data analysis.

### 3. Results and Discussion

### 3.1 Co-occurrence: COVID-19 x Herbal medicine

The query "COVID-19" and "Herbal medicine" returned 67 articles, until May 18 of 2020, when using the Scopus database, with a minimum of 10 occurrences, as a limit for the inclusion of terms in the analysis. It resulted in 1088 terms, of which 35 were selected based on a relevance score. The co-occurrence map identified four groups that express different research fronts (Figure 1). Cluster 1, identified by the color blue, is mainly driven by the application of Chinese medicine, as a traditional form of treatment, in addition to its use in epidemics. This is demonstrated by the terms that appear "epidemic" and "traditional chinese medicine". Cluster 2, in green, shows that the vast majority of terms are related to COVID-19 diseases, by the term "coronavirus disease 2019", where there is no medication and treatment directed to this disease, despite the attempt to use antiviral drugs against the virus, the terms "antivirus agent", "unclassified drug", demonstrate this relationship.

**Figure 1.** Network map of co-occurrence of terms. Labels and circle sizes are proportional to the number of occurrences. The lines identify the main links between the terms and the line thickness represents the association strength. The distance between the terms also reflects the association strength. Some term labels are not displayed due to the scale (for example, the circle for the term "infection prevention").



Source: Authors (2020).

Opposite to cluster 2, cluster 3 appears, in red color, which does not have a factor highlighted, but related by the terms "coronavirus infections" with one of its most serious medical consequences, "viral pneumonia", as well as researches related to the use of medicinal plants as direct agent for its treatment. For cluster 4, central and yellow, it was observe that all the clusters in the co-occurrence map come into congruence with the COVID-19 and its consequences, as well as its relationship with the human being. However, it was observe that Chinese medicine, which uses medicinal plants as the basis of treatment, has strong relationship and may come to be used as therapeutic aid.

## 3.2 Frequency of ingredients in herbal, homeopathic and floral products

The search and use of natural plant compounds is promising approach in the development of new therapeutic agents. In view of this context, a total of 113 products were identified, among 33 different national manufacturers. Of the 113 products 66% were herbal medicines, 27% homeopathic medicines and 7% floral. It was observed that these medicinal products used for alternative therapies had diversified composition, being possible to list 123 different ingredients, of which medicinal plants, minerals, amino acids and vitamins were present. Table 1 shows the absolute and relative percentage distribution of the main medicinal plants and associated natural products, such as propolis, with  $n \ge 5$ .

**Table 1.** Absolute frequency (n) and relative frequency (%) of the main medicinal plants and associated products declared on the labels and patient information leaflets of the commercial products ( $n \ge 5$ ).

Compounds	Homeopathics (n = 31)		Herbal medicine (n = 74)		Florals (n = 8)		- All (n = 113)
	Absolute (n)	(%)	Absolute (n)	(%)	Absolute (n)	(%)	(%)
Echinacea purpurea	0	0	21	28.38	0	0	18.58

Research, Society and Development, v. 9, n. 10, e6789108907, 2020 (CC BY 4.0)   ISSN 2525-3409   DOI: http://dx.doi.org/10.33448/rsd-v9i10.8907							
Mikania glomerata Spreng.	0	0	15	20.27	0	0	13.27
Propolis	0	0	13	17.57	0	0	11.50
Astragalus propinquus	0	0	10	13.51	0	0	8.85
Gelsemium sempervirens	8	25.81	0	0	0	0	7.08
Curcuma longa	0	0	7	9.46	0	0	6.19
Eupatorium perfoliatum	6	19.35	0	0	0	0	5.13
Bryonia alba	6	19.35	0	0	0	0	5.31
Allium sativum L.	4	12.90	1	1.35	1	12.50	5.31
Uncaria tomentosa	0	0	6	8.11	0	0	5.31
Zingiber officinale	0	0	6	8.11	0	0	5.31
Carapichea ipecacuanha (Brot.) L. Andersson	4	12.90	1	1.35	0	0	4.42
Panax ginseng	0	0	5	6.76	0	0	4.42
Atropa belladonna	5	16.30	0	0	0	0	3.54

### Source: Authors (2020).

Among the 123 ingredients found in the composition of the evaluated products, it was observed that some medicinal plants were more present in these formulations. The medicinal plant that appeared most among the products was *Echinacea purpurea*, with frequency of 18.58%. This herb was considered "sensation herb of the moment" in the herbal medicine industry in the United States and can be found in several pharmaceutical forms, such as capsules, extracts, tinctures and teas. The reason why this plant appeared more frequently

among the Brazilian herbal medicines, since it is a plant of North American origin, is because there are more scientific and ethnopharmacological data published, as well as quality and safety control protocols for non-native plants than for natives. The same can be observed for ingredients such as *Astragalus propinquus*, *Gelsemium sempervirens*, *Eupatorium perfoliatum*, *Bryonia alba*, *Allium sativum*, *Zingiber officinale*, *Panax ginseng* and *Atropa belladonna* (Carvalho et al., 2018; Flora do Brasil 2020 em construção, 2020; World Flora Online, 2017).

### 3.3 Herbal medicines

The definition of herbal medicines can be interpreted in several ways, depending on the country in question. The Brazilian legislation defines it as products obtained from active vegetable raw material, when the active comes from a single or more than one plant species (BRAZIL, 2014). In addition, the practice of using medicinal plants began in 1988, when phytotherapy was implemented in the health service, as well as procedures and routines related to its practice in medical assistance units (BRAZIL, 2006). However, in some countries, herbal preparations may contain active ingredients from non-vegetable sources, such as minerals and animal components. In the United States, these products are classified as botanicals and/or dietary supplements, unlike the European Union and New Zealand, which the definitions become Herbal medicinal products and Herbal remedies, respectively (BRAZIL, 2018a, 2018b). Summary of the ingredients with frequency of  $n \ge 5$ , in addition to the claims that manufacturers make available on the label and functional claims based on scientific studies can be seen in Table 2.

**Table 2.** Medicinal plants with absolute frequency of  $n \ge 5$  and their functional and scientific claims.

Herb	Popular name	Category	Label claim	Part used	Functional and scientific claim	Reference
					Clinical: improved the non-specific immune response in common cold.	
Echinacea purpurea	Conical purple flower; Purple comet; Echinacea	Herbal medicine	Antiviral activity; Immunomodulatory activity; Treatment of respiratory system infections	Root; Leaf	(↑ white globes, neutrophil monocytes, NK cell); Modulation of cytokines. Viral activity against SARS CoV, influenza A and B, Rhinoviruses.	(Carvalho et al., 2018; Fusco et al., 2010; Goel et al., 2005; Hudson, 2012)
Mikania glomerata Spreng.	Copper grass; Guaco; Cipo-catinga	Herbal medicine	Treatment of respiratory system infections	Leaf	Fever; Respiratory tract diseases associated with bronchoconstriction	(de Moura et al., 2002; Oliveira et al., 2013)
Propolis	-	Herbal medicine	Antiviral activity; Immunomodulatory activity; Treatment of respiratory system infections	-	Dose-dependent immune response (IgG and IgM production); Viral activity against influenza A.	(Freitas et al., 2011; Shimizu et al., 2008)
Astragalus propinquus	Huang-Qi; Siberian ginseng	Herbal medicine	Antiviral activity; Immunomodulatory activity	Root	Mild headaches; IL-2 inducing activity by plant phytochemicals (immunostimulant)	(Chang et al., 2014; Pistelli, 2002; Yesilada et al., 2005)

Gelsemium sempervirens	Yellow Jasmin	Homeopathic	Immunomodulatory activity	Root	Fever; Dry cough; Antiviral action against Influenza	(Dutt et al., 2010; Jin et al., 2014; Moore, Michael; Chesner, 1997)
Curcuma longa	Saffron; Yellow Ginger	Herbal medicine	Immunomodulatory activity	Root	Antiviral against influenza A - Inhibits replication; Anti-inflammatory and immunomodulatory: Reduction of infection in the lungs (↓ MCP-1 and TNFα); Fever.	(Dao et al., 2012; Han et al., 2018; Sharif et al., 2018)
Eupatorium perfoliatum	Common boneset	Homeopathic	Antiviral activity; Immunomodulatory activity; Treatment of respiratory system infections	Leaf	Antiviral activity against Influenza A and Dengue Virus (DENV)	(Derksen et al., 2016; Teixeira, 2010)
Bryonia alba	White Bryony	Homeopathic	Antiviral activity; Treatment of respiratory system infections	Root	Antiviral activity against Chikungunya Virus; Anti-inflammatory activity: Reduction of lungs inflammation	(Nayak et al., 2014; Vellingiri et al., 2020)

Allium sativum L.	Garlic; Wild garlic	Herbal medicine; Homeopathic; Floral	Antiviral activity; Treatment of respiratory system infections; Physical and mental exhaustion: Homeostasis.	Root	Antiviral: inhibits the synthesis of viral nucleoproteins and polymerase activity; Inhibits the enzyme 5-lipoxygenase relationship with asthma and chronic obstructive pulmonary disease (COPD)	(Chavan et al., 2016; Pearson et al., 2007; Prasad et al., 2004)
Uncaria tomentosa	Cat nail; Yellow tick; Hawk claw	Herbal medicine	Immunomodulatory activity	Bark; leaf	Phytotherapy for allergic asthma: by immunomodulatory activity through the inhibition of IL-6 and TNF-α; Antiviral activity against dengue virus (DENV), by immunomodulation.	(Azevedo et al., 2018; Reis et al., 2008)
Zingiber officinale	Ginger; Mangarataia; Mangaratiá	Herbal medicine	Treatment of respiratory system infections	Root	Immunomodulatory activity: ↑ cytokines TNF-α - Activation of macrophages; Antiviral activity against influenza A; Antiemetic	(Carvalho et al., 2018; Imanishi et al., 2006; Kim et al., 2014; Park, Kap Joo; Lee, 2005)
Carapichea ipecacuanha (Brot.) L. Andersson	Ipeca; Poaia; Ipecaccuanha; Brazilian Root	Herbal medicine; Homeopathic	Immunomodulatory activity; Treatment of respiratory system infections	Whole plant	Treatment of inflammation of respiratory tract disorders	(de Albuquerque et al., 2007; Ferreira Júnior et al., 2012)

Panax ginseng	Ginseng; Five leaves; Panacea	Herbal medicine	Immunomodulatory activity; Treatment of respiratory system infections	Root	Immunomodulatory and adaptogenic: Reduction of gene expression of Interleukins (IL-6 and IL-8)	(Hong & Lyu, 2011; Irfan et al., 2020; Lee et al., 2014)
Atropa belladonna	Belladonna; Night Shadow; Devil's Cherries	Homeopathic	Treatment of respiratory system infections	Root	Treatment of respiratory system infections: asthma, chronic lung diseases; Antiviral activity against dengue virus (DENV)	(Teixeira, 2010; Vellingiri et al., 2020)

NK: natural killer cell; IgG: immunoglobulin G; IgM: immunoglobulin M; IL-2: Interleukin 2; IL-6: Interleukin 6; IL-8: Interleukin 8; MCP-1: monocyte chemoattractant protein-1; TNFα: tumour necrosis factor-alpha. Source: Authors (2020).

One of the medicinal plants that was most found among the evaluated products was *Echinacea purpurea*, being herbaceous, flowering plant, belonging to the genus *Echinacea*. This herb has its origin known in North America so that when the colonizers arrived in the American prairies, the use of this herb became commonplace and it was popularized in the old world. In the United States, in 2009, it was the third most popular herbal medicine, and its sales, annually, reach more than 100 million dollars. Primarily, this medicinal plant was used to treat various infections and the preparation of this plant started to be investigated, so that they observed improvement in the nonspecific immune response, in addition to causing the elimination of free radicals, it may have led to faster resolution of symptoms of the common cold (Goel et al., 2005).

More recent reviews have summarized the studies on SARS-CoV and SARS-CoV-2 infections and addressed the mechanism of infection and the important role of the innate immune response. The proposed infection mechanism and its consequences for this new virus is based on the other viruses in the coronavirus family. Therefore, the knowledge of these mechanisms provides evidence for the development of new drugs and vaccines. In view of this, several viruses have already been shown to be susceptible to extracts of *Echinacea purpurea* and the review by Hudson (2012) suggests, based on the mechanisms of infection, in addition

to the anti-inflammatory and virucidal properties, that this medicinal plant could be useful against coronavirus disease and its pathogen (Vellingiri et al., 2020).

It was observed throughout this session that although herbal medicines are not used as main treatment for diseases, they can come to assist in the symptoms of COVID-19, coming in common with the objective of the Research Program for Medicinal Plants in Brazil, which aims to contribute to the development of an alternative and complementary therapy, with scientific basis (BRAZIL, 2006).

### **3.4 Homeopathics**

Homeopathy is a natural and holistic treatment system that considers the human being as a whole, instead of treating only the problem or symptoms of the disease. Homeotherapy uses homeopathic medicines, whose composition is derived from substances of animal, mineral and vegetable origin. This practice was developed by Samuel Hahnemans, in the 18th century, after studies and reflections based on observation and clinical tests. As a result, it has become the second most widely used disease treatment method on the planet, with over 200 million users worldwide, as it has been included in the national health systems of several countries, such as India, Switzerland, Chile, Mexico, for example. In Brazil, the clinical practice of homeopathy was added to the table of procedures of the Unified Health System (SUS) in 1999 and only in 2003, after the World Health Organization defined traditional and complementary/alternative medicine, the National Policy Integrative and Complementary Practices (PNPIC) was added (Brazil, 2006; WHO, 2001).

It is not new that homeopathic medicines are being used in an endemic state. Despite its use, scientific evidence from clinical studies indicates that homeopathic medicines has no reasonable mechanism of action (Ali & Alharbi, 2020). In Table 2, it is possible to observe compounds that were used in the formulation of some homeopaths, so that it shows only 5 ingredients with frequency  $n \ge 5$  in this category, where *Gelsemium sempervirens* appeared most frequently among these.

*Gelsemium sempervirens* belongs to the genus Gelsemium which is commonly found in the United States, mainly in the south, from Virginia to Florida. Its homeopathic use is known in the treatment of several diseases, such as neuralgia, migraines, uterine pain, rheumatism, flu, nausea, whooping cough, asthma, whooping cough, hysteria and epilepsy, besides being an important remedy for influenza. In addition, reported more than 190 phytochemicals present in *Gelsemium sempervirens*, including alkaloids and iridoids, which are considered to be the

two active groups most likely to be responsible for the observed pharmacological effects (Jin et al., 2014).

As well as preventive hygiene practices, sports and dietary practices, which aims to maintain the homeostasis of the biological and psychological functions of the human being, individualized homeopathic treatment, in addition to curing, can be considered as prophylactic instrument for disease facilities. However, scientific studies are needed to support homeopathy against COVID-19, despite the potential claims.

## **3.5 Floral**

Florals in general are called alternative pseudo-therapies, that has grown over the years, because they have the ability to restore harmony and balance the changes in the mood and personality, which can lead to physical and real illnesses, like stress, for example. Its mechanism of action is linked to subtle biochemical and molecular reactions, acting on the limbic system or directly on the hypothalamus, due to the essences used in its composition (Resende et al., 2014). Plants and their parts contain various bioactive compounds with various effects on the physical, emotional and psychological effects of the human body, mainly flower essence (Chiru et al., 2020). In Table 2, it is possible to see compounds that were used in the formulation of the florals, so that it shows only one ingredient with frequency  $n \ge 5$ , it is presented in this category.

In the context of body and mind balance that flower therapies employ, garlic (*Allium sativum* L.), one of the ingredients found in the evaluated products, demonstrated that raw garlic homogenate can improve anxiety and depression behavior in a study conducted with rats, possibly by attenuating oxidative stress and increasing antioxidant defense (Rahmani et al., 2020).

Although there are no studies relating the direct action of florals with COVID-19, mainly with *A. sativum* L., an ingredient found among the products, researches has observed that since the pandemic was installed, 16-28% of the examined individuals demonstrated symptoms of anxiety and depression, which may be linked to economic disturbances, health expenses, and especially, to mortality and morbidity (Lal et al., 2020; Rajkumar, 2020). Therefore, potentially, this type of alternative treatment may infer over the psychological symptoms. However, these alternative approaches require critical investigations to promote objective and concrete information, in the face of so much adverse data.

### 4. Conclusions

In the current global context, COVID-19 has become a pandemic, for which there are still no proven strategies for prevention, treatment and cure. In Brazil, there are guidelines available in the Unified Health System (SUS) that include herbal and homeopathic medicines and even regulate remedies, as the main or complementary therapy for diseases. Why not use these existing measures to combat symptoms of COVID-19, since the plants available on the market have proven to have antiviral actions, immunomodulatory activity, in addition to acting against typical symptoms caused by SARS-CoV-2 Therefore, these drugs are indicated as complementary therapy, due to their potential.

### Acknowledgement

The authors acknowledgement the Federal University of Lavras for technical and structural support. This work was financial by Coordination of Improvement of Higher Education Personnel (CAPES) and Research Support Foundation of the State of Minas Gerais (FAPEMIG) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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