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Brazilian essential oils as source for the discovery of new anti-COVID-19 drug: a review guided by in silico study

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Abstract The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China and its spread worldwide has become one of the biggest health problem due to the lack of knowledge about an effective chemotherapy. Based on the current reality of the SARS-CoV-2 pandemic, this study aimed to make a review literature about potential anti-coronavirus natural compounds guided by an in silico study. In the first step, essential oils from native species found in the Brazilian herbal medicine market and Brazilian species that have already shown antiviral potential were used as source for the literature search and compounds selection. Among these compounds, 184 showed high antiviral potential against rhinovirus or picornavirus by quantitative structure–activity relationship analysis. (*E*)-α-atlantone; 14-hydroxy-α-muurolene; allo-aromadendrene epoxide; amorpha-4,9-dien-2-ol; aristochene; azulenol; germacrene A; guaia-6,9-diene; hedycaryol; humulene epoxide II; α-amorphene; α-cadinene; α-calacorene and α-muurolene showed by a molecular docking study the best result for four target proteins that are essential for SARS-CoV-2 lifecycle. In addition, other parameters obtained for the selected compounds indicated low toxicity and showed good probability to achieve cell permeability and be used as a drug. These results guided the second literature search which included other species in addition to native Brazilian plants. The majority presence of any of these compounds was reported for essential oils from 45 species. In view of the few studies relating essential oils and antiviral activity, this review is important for future assays against the new coronavirus.

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Introduction

In December 2019, for the first time the new coronavirus (SARS-CoV-2) was isolated from patients with acute pneumonia in Wuhan (China) (Guarner 2020). In February 2020, the World Health Organization (WHO) characterized this situation as a pandemic, and the new virus has already infected more people than its two predecessors, SARS-CoV (Severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) (Guarner 2020). In preliminary studies, the reason for the higher infectivity of the new coronavirus compared to the previous ones has been related to the greater affinity for binding to human proteins and because it is potentially more stable and able to survive higher temperatures (Chu et al. 2020; He et al. 2020).

The growing number of infections and deaths resulting from the Coronavirus Disease 2019 (COVID-19) pandemic highlights the need for an accelerated search for effective treatments. Drug repositioning, also known as redirecting, repurposing, and reprofiling, is defined as a different application of the drug than the one that it was initially produced and emerges as an effective and quick possibility to combat COVID-19 (Serafin et al. 2020). Several drugs already in use have been tested against SARS-CoV-2 and, among them, the majority drugs are antivirals (Sanders et al. 2020).

Essential oils have important pharmacologic proprieties, such as broad-spectrum antibacterial, antifungal, antiviral action and immunomodulation, in addition to few adverse effects (Raut and Karuppayil 2014; Valdivieso-Ugarte et al. 2019). Thus, essential oils show great efficacy and speed of action, and they can represent an important source for the development of COVID-19 treatments. In this way, this study aimed to evaluate the potential of compounds present in essential oils from Brazilian species. Brazil hosts more than 20% of the biodiversity in the world, with more than 46,000 species of plants, algae and fungi that were already identified and cataloged (Dutra et al. 2016; Filard et al. 2018). These numbers become even more impressive when considering that the knowledge about the country's entire biodiversity is incomplete, and researchers are still working on building of this information (Filard et al. 2018). Therefore, Brazilian flora has a rich chemical variety that makes it a potential source for drug discovery (Valli and Bolzani 2019).

Despite all this diversity and vast use by the population, few species are licensed as pharmaceutical ingredients (Carvalho et al. 2018). This occurs because there is little published scientific and ethnopharmacological data, or protocols for quality and safety assurance for native plants (Cavalho et al. 2018). Clinical trials involving native Brazilian plants, extracts, essential oils or their active ingredients are even smaller, although there is a solid traditional use by the local population (Carvalho et al. 2018; Dutra et al. 2016). One of the reasons for the few studies involving native plant species is the strict Brazilian standards for access to biodiversity, and the lack of adequate documentation for the use and regulation of these species (Carvalho et al. 2018; Dutra et al. 2016). This fact justifies the need for further studies focused on the native Brazilian flora (Carvalho et al. 2018; Dutra et al. 2016).

Several reviews have been published about natural products as possible drugs against SARS-CoV-2. However, in the face of this pandemic for which no specific drug has yet been approved, it is essential to increasingly expand studies in search of effective treatment. Therefore, this review included essential oils from native Brazilian species with previously reported antiviral activity, as well as native species licensed in Brazil found in the herbal medicine market, aiming to involve natural products accessible to the population. These Brazilian species were used as a source of chemical diversity. In addition, in order to deepen this research, other species apart from the native ones were also investigated and indicated in the second stage of this review. An illustrative summary of the methods and results obtained can be found in Fig. 1.

Essential oils from Brazilian native species

In the first part of the review, literature indexed in PubMed concerning natural compounds present in essential oils from native plant species licensed in Brazil was selected for the research. The species

"*Ananas comosus*", "*Anadenanthera colubrina*", "*Bacopa monieri*", "*Brosimum gaudichaudii*", "*Caesalpinia ferrea*", "*Carapichea ipecacuanha*", "*Cereus jamacaru*", "*Cereus peruvianus*", "*Cordia curassavica*", "*Croton heliotropiifolius*", "*Dorstenia aritoflia*", "*Erythrina velutina*", "*Erythrina verna*", "*Himatanthus lancifolius*", "*Lantana camara*", "*Maytenus ilicifolia*", "*Mikania glomerata*", "*Myroxylon balsamum*", "*Operculina hamiltonii*", "*Passiflora alata*", "*Paullinia cupana*", "*Schinus terebinthifolia",* "*Senna alexandrina*", "*Solanum paniculatum*", "*Stryphnodendron adstringens*", "*Trichilia catigua*", and "*Uncaria tomentosa*" were used as query keywords (Carvalho et al. 2018). This research was carried out in PubMed database considering articles from January 1st 2005 to March 31th 2020. Studies related only to biological assays, review works, and manuscripts in a non-English language were excluded. The natural compounds reported in studies on chemical characterization of essential oils were tabulated and repeated references to the same compound were also excluded. The same research pattern was also used for essential oils from Brazilian species that have already shown antiviral action: "*Aloysia gratissima*", "*Ayapana triplinervis*", "*Eupatorium patens*", "*Heterothalamus alienus*", "*Hyptis mutabilis*", "*Lippia alba*", "*Lippia origanoides*", "*Ocimum campechianum*", "*Pectis odorata*", and "*Tessaria absinthioides*" (Silva et al. 2020).

From this research, among the 27 licensed native species previously reported, seven species had already their essential oils chemically characterized and the compounds for each species are informed in the Table S1, Supplementary material. In addition, the constituents present in the essential oils evaluated as antiviral agent were also reported (Table S1, Supplementary material), except for the *Pectis odorata*. All compounds were considered to the in silico assays, regardless of their concentration, since Brazilian species were used as a source of chemical diversity.

These licensed species used in the Brazilian traditional medicine are: (1) *Cordia curassavica,* used as anti-inflammatory; (2) *Croton heliotropiifolius,* stimulant; (3) *Lantana camara* and (4) *Mikania glomerata,* expectorant; (5) *Passiflora alata,* as anxiolytic, sedative and expectorante; (6) *Schinus terebinthifolia,* anti-infective and healing; (7) *Solanum paniculatum,* cholagogue, choleretic and hepatoprotective (Carvalho et al. 2018).

Regarding antiviral activity, this action was not reported yet for essential oils from these species, but studies indicate the activity of their extracts. The aqueous extract from *Lantana camara* leaves has shown action against white spot syndrome virus in shrimp (Balasubramanian et al. 2007). In addition, the aqueous extract from *Mikania glomerata* and *Solanum paniculatum* leaves had antiviral activity against Suid Herpesvirus (SuHV-1) (Kaziyama et al. 2012). The hydroethanolic extract from *Schinus terebinthifolia* stem bark also inhibited *Herpes simplex* virus type 1 strains (HSV-1) (Nocchi et al. 2017). On the other hand, no antiviral action has been reported in the literature for *Cordia curassavica*, *Croton. heliotropiifolius* and *Passiflora alata.*

Based on the few studies of antiviral activity for licensed species, other Brazilian species that have already shown action against any virus were added to the research in order to increase the search source for compounds with potential activity against the new coronavirus. In the study performed by García et al. (2003), different essential oils were screened for virucidal property and *Aloysia gratissima* and *Tessaria absinthioides* showed potent inhibition on junin virus (JUNV) and HSV-1, whereas *Eupatorium patens* was active against HSV-1 and dengue virus type 2 (DEN-2). In this same way, *Heterothalamus alienus* essential oil was also able to inhibit JUNV, HSV-1, and DEN-2 viruses (Duschatzky et al. 2005). Inhibitory effect in the early stages of infection by other herpes virus (HSV-2) was also observed after treatment with essential oils from *Hyptis mutabilis* and *Ocimum campechianum* (Brand et al. 2016).

Recently, the outbreak of the Zika virus also raised concerns for the scientific community due to the severe disorders caused by this infection and the absence of an approved drug to combat it. However, essential oils like the one obtained from *Ayapana triplinervis* prove to be a potent phytocompound against this virus (Haddad et al. 2019). In addition, it is worth highlighting the great potential of essential oils extracted from *Lippia* genus as an antiviral agent. *Lippia origanoides* has already shown action against yellow fever virus and the same property was demonstrated for *Lippia alba* (Gómez et al. 2013; Meneses et al. 2009), which was also effective against four dengue viruses (DENV-1, DENV-2, DENV-3, and DENV-4) (Ocazionez et al. 2010). All these results show the broad-spectrum antiviral action of essential

Table 1 Species containing at least one of the selected compounds (1–14) as top five constituent in their essential oil

Species	Local	Part	Compound	Concentration (%)	References
Annona muricata	Ghana	Fruit Pulp and Leaves	14^{MS}	10.64	Gyesi et al. (2019)
Artabotrys insignis	Ivory Coast	Leaves	$7^{MS;FID;NMR}$	17.10	Gooré et al. (2017)
Athanasia brownii	Madagascar	Aerial Parts	$10^{MS;FID}$	5.10	Rasoanaivo et al. (2013)
			$13^{MS;FID}$	0.20*	
			$14^{MS;FID}$	0.20*	
Baccharis dracunculifolia	Uninformed	uninformed	14^{MS}	6.74	Chaaban et al. (2018)
Baccharoides lilacina	India	Aerial Parts	12^{MS}	6.10	Joshi (2013)
Calamintha nepeta	Italy	Aerial Parts	$3^{MS;FID}$	11.40	Mancini et al. (2013)
			$13^{MS;FID}$	0.60*	
			$12^{MS;FID}$	0.60*	
			$5^{MS;FID}$	0.60*	
Callicarpa americana	USA	Leaves	10^{MS}	13.90	Tellez et al. (2000)
			14^{MS}	0.20*	
			13^{MS}	t*	
			12^{MS}	t*	
Carum carvi	Austria	Steam	$7^{MS;FID}$	14.1–18.2	Chizzola (2014)
		Inflorescence	$7^{MS;FID}$	2.80–6.90	
		Leaves	$7^{MS;FID}$	1.70*–10.70	
Cedrus deodara	India	Wood Chips	1^{MS}	8.60	Chaudhary et al. (2009)
Chamecyparis formosensis	Taiwan	Heartwood Chips	14^{MS}	7.00	Chen et al. (2015)
			13^{MS}	1.80*	
Cionura erecta	Iran	Roots	14^{MS}	3.58	Mozaffari et al. (2014)
Cistus creticus	Greece	Aerial Parts	12^{MS}	6.50	Demetzos et al. (1997)
			13^{MS}	0.40*	
			11^{MS}	2.00*	
Cupressus sempervirens	Tunísia	Mature cones and leaves	$11^{MS;\ FID}$	2.3–3.1	Hamrouni-Aschi et al. (2013)
Cyanthillium cinereum	Ivory Coast	Root	$7^{MS;NMR}$	7.10	Boué et al. (2018)
Cymbopogon validus	South Africa	Leaves	$9^{MS;FID}$	5.40	Rungqu et al. (2016)
			$14^{MS;FID}$	1.00*	
		Flowers	$9^{MS;FID}$	7.60	
			$14^{MS;FID}$	1.20*	
Diplotaenia cachrydifolia	Iran	Uninformed	$13^{MS;FID}$	9.34–25.2	Khajeh (2012)
Elytropappus rhinocerotis	South Africa	Aerial Parts	7^{MS}	0.00–15.60	Hulley (2019)
Helichrysum gymnocephalum	Madagascar	Leaves	$11^{MS;FID}$	5.10	Afoulous et al. (2011)
Hypericum perforatum	Iran	Flowers and Fruits	11^{MS}	12.12	Akhbari et al. (2012)
Myrtus communis	Sardinia	Fruits	10^{MS}	0.32*–15.40	Usai et al. (2018)
			13^{MS}	0.15*–0.71*	
			3^{MS}	0.05*–10.70	
Nectandra leucantha	Brazil	Leaves	$7^{MS;FID}$	7.34	Grecco et al. (2015)
Nepeta erecta	India	Aerial Parts	10^{MS}	1.70	Bisht et al. (2012)

Table 1 continued

Species	Local	Part	Compound	Concentration (%)	References
Pelargonium graveolens	Taiwan	Leaves	8^{MS}	20.10	Lin et al. (2016)
			14^{MS}	t*	
Phebalium stellatum	Australia	Aerial Parts	9^{MS}	4.50*–9.80	Palá-Paúl et al. (2009)
Phebalium sylvaticum	Australia	Aerial Parts	9^{MS}	7.40–9.70	Palá-Paúl et al. (2009)
Phoebe bournei	Uninformed	Leaves	14^{MS}	7.32	Ding et al. (2018)
Piper aduncum	Brazil	Leaves	7^{MS}	13.33	Silva et al. (2019)
			14^{MS}	1.09*	
Piper nigrum	India	Green Pepper Corn	$9^{MS;FID}$	6.70–9.10	Orav (2004)
Polyalthia jucunda	Vietnã	Leaves	11^{MS}	6.50	Dai et al. (2014)
Psidium guajava	Brazil	Leaves	$3^{MS;FID}$	14.70	Silva et al. (2018)
			$10^{MS;FID}$	1.40*	
Ruilopezia bracteosa	Venezuela	Aerial Parts	8^{MS}	4.40	Alarcón et al. (2015)
Rydingia michauxii	Iran	Aerial Parts	10^{MS}	4.56	Karami et al. (2015)
			13^{MS}	0.09*	
Senecio mudicaulis	India	Uninformed	10^{MS}	21.25	Sharma et al. (2015)
Seseli rigidum	Serbian	Roots	$14^{MS;FID}$	0.00*–8.10	Marčetić et al. (2013)
			$13^{MS;FID}$	0.00*–0.73*	
			$3^{MS;FID}$	0.00*–1.79*	
Stachys benthamiana	Iran	Aerial Parts	10^{MS}	10.70	Karami et al. (2015)
Stachys officinalis	Italy	Flowers	10^{MS}	9.20	Giuliani et al. (2017)
Swietenia macrophylla	Brazil	Terminal Shoots	7^{EAD}	6.89	Soares et al. (2003)
		Mature Leaves	7^{EAD}	5.29	
		Senescent Leaves	7^{EAD}	4.68	
Tetradenia riparia	Brazil	Leaves	$3^{MS;FID}$	14.00	Melo et al. (2015)
			$14^{MS;FID}$	0.50*	
Teucrium montanum	Serbia	Aerial Parts	13^{MS}	4.97	Vukovic et al. (2007)
			14^{MS}	1.73*	
Teucrium persicum	Iran	Aerial Parts	12^{MS}	9.70	Miri et al. (2012)
			14^{MS}	1.10*	
			13^{MS}	0.10*	
Thapsia garganica	Sicily	Flower	10^{MS}	9.00	Casiglia et al. (2016)
Ugni myricoides	Costa Rica	Leaves	$10^{MS;FID}$	4.20	Quintão et al. (2010)
			$3^{MS;FID}$	0.30*	
Vernonia cinerea	India	Roots	14^{MS}	30.70	Joshi (2015)
			5^{MS}	3.50*	
Zanthoxylum dissitum	China	Roots	$10^{MS;FID}$	29.40	Wang et al. (2015)
Zingiber collinsii	Vietnam	Rhizome	$10^{MS;FID}$	9.00	Huong et al. (2020)
Zingiber zerumbet	India	Rhizomes	10^{MS}	2.50	Rana et al. (2012)
			14^{MS}	t*	
Zingiber zerumbet	China	Rhizomes	$10^{MS;FID}$	7.30	Wu et al. (2017)

(**1**) (E)-α-Atlantone; (**2**) 14-Hydroxy-α-muurolene; (**3**) allo-Aromadendrene epoxide; (**4**) Amorpha-4,9-dien-2-ol; (**5**) Aristochene; (**6**) Azulenol; (**7**) Germacrene A; (**8**) Guaia-6,9-diene; (**9**) Hedycaryol; (**10**) Humulene epoxide II; (**11**) α-Amorphene; (**12**) α-Cadinene; (**13**) α-Calacorene; (**14**) α-Muurolene *not majority. ^{MS}GC-MS (coupled gas chromatography—mass spectrometric detection); ^{NMR}NMR (nuclear magnetic resonance); ^{FID}GC-FID (coupled gas—flame ionization detection; ^{EAD}GC-EAD (coupled gas chromatography—electroantennographic detection)

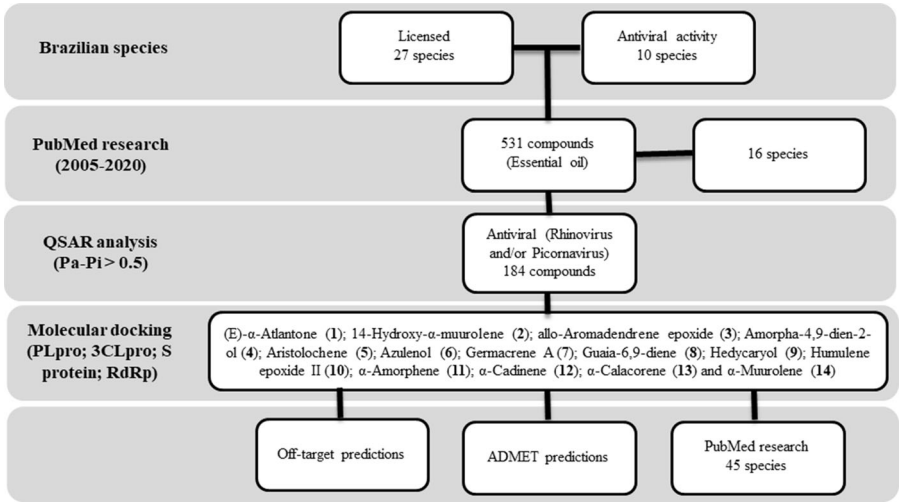

Fig. 1 Workflow scheme. The work is divided into four main parts: (1) Search of natural compounds present in essential oils from Brazilian native species; (2) QSAR analysis and selection of compounds with high antiviral potential; (3) Molecular docking analysis and selection of top 14 compounds with the highest binding energies values for papain-like protease (PLpro), 3-Chymotrypsin-like protease (3CLpro), spike glycoprotein (S protein), and RNA-dependent RNA polymerase (RdRp); (4) Search of species containing at least one of selected compounds as top 5 constituent in their essential oil

oils and, therefore, their potential should be investigated against to COVID-19.

Anti-COVID-19 potential

Although the antiviral activity of essential oils from native plant species licensed in Brazil has not been tested, they have other pharmacological properties and may have the potential to treat SARS-CoV-2, as indicated by other drug repositioning studies. In addition to drug repositioning, other alternatives can accelerate the research for COVID-19 treatments. The virtual screening (in silico) is an important tool to guide both in vitro and in vivo research, minimizing the assays cost, improving chances of finding the desired drug candidates and generating results in a shorter time (Pinzi and Rastelli 2019). In this way, the compounds reported in essential oils from these species were subjected to quantitative structure–activity relationship (QSAR) analysis using the program Prediction of Activity Spectra for Substances (PASS online). The aim of this test was to predict the antiviral potential of these compounds. Their structure was compared with substances that are active against viruses and are available in the database. The action specifically on rhinovirus and picornavirus was selected due the fact of that these two species belong to the same Coronavirus group [(+)ssRNA − Group IV] (Fernández-Miragall et al. 2009; Schrauf et al. 2009; Kim et al. 2012; Zhu et al. 2020b, c). The probabilities of each compound to be active (Pa) and inactive (Pi) were reported and the compounds with Pa–Pi $\geq$ 0.5 were classified as high potential (Seibert et al. 2019).

In the first step, 531 compounds were identified from research papers published that had investigated the composition of essential oils, among which 184 had high potential (Pa–Pi $\geq$ 0.5) against rhinovirus and/or picornavirus in the analysis performed by PASS online (Table S2, Supplementary material).

Human rhinovirus and picornavirus belong to the Picornaviridae family, which are nonenveloped viruses with a positive ssRNA genome (Schrauf et al. 2009; Fernández-Miragall et al. 2009). Although SARS-CoV-2 is a β-coronavirus and belongs to a different family, Coronaviridae, it has non-segmented positive-sense RNA, as well as previous viruses (Zhu et al. 2020a). Thus, these three virus contain the same genome classification, belonging to the same group [(+)ssRNA − Group IV].

In addition, phylogenetic analysis has demonstrated that viruses belonging to Picornaviridae and Coronaviridae families can be classified into the picornavirus-like supercluster and a same compound may have therapeutic potential targeted to multiple viruses

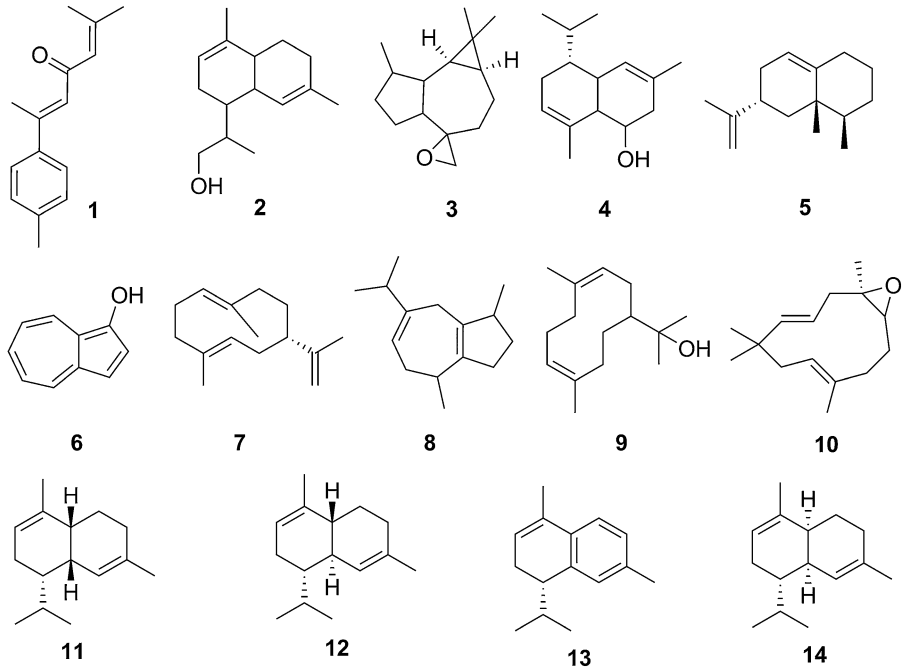

Fig. 2 (**1**) (*E*)-α-Atlantone; (**2**) 14-Hydroxy-α-muurolene; (**3**) allo-Aromadendrene epoxide; (**4**) Amorpha-4,9-dien-2-ol; (**5**) Aristochene; (**6**) Azulenol; (**7**) Germacrene A; (**8**) Guaia-6,9-diene; (**9**) Hedycaryol; (**10**) Humulene epoxide II; (**11**) α-Amorphene; (**12**) α-Cadinene; (**13**) α-Calacorene; (**14**) α-Muurolene

in this supercluster (Kim et al. 2012). Furthermore, there are studies suggesting that results can be extrapolated between different viruses. Muller et al. (2018) found that the natural compound silvestrol, a flavagline isolated from plants of the genus *Aglaia*, presents antiviral activity against coronavirus and picornavirus. The target of silvestrol is the eIF4A helicase required to unwind stable RNA secondary structures in 5′ UTRs of capped mRNAs to create a binding platform to initiate protein synthesis (Chu et al. 2016; Hinnebusch et al. 2016). Silvestrol increase the affinity of eIF4A to RNA impairing the activity of the eIF4F complex (Sadlish et al. 2013). This translation mechanism occurs in coronavirus, such as MERS-CoV and HCoV-229E and this fact justifies Muller et al. (2018) findings. However, the authors also found silvestrol activity in picornavirus (human rhinovirus A1 and poliovirus type 1). It is known that picornavirus, although utilizing a different mechanism for viral translation (IRES-dependent mechanism), still require eIF4A helicase activity for efficient translation initiation (Bordeleau et al. 2006). Kuo et al (2009) also presented molecules that act in both groups of viruses. Those molecules act inhibiting the proteases 3Cpro and 3CLpro in picornavirus (CVB3, EV71 and RV14) and coronavirus (SARS-CoV and CoV-229E), respectively. Therefore, the potential action against rhinovirus and picornavirus were selected to perform the compound screening effective to SARS-CoV-2, since there are few studies on the new coronavirus, which would make the QSAR analysis unfeasible.

This strategy was based on non-specific antiviral properties and broad spectrum mechanisms of action of essential oils on viruses that can be related to their complex chemical composition. Morphological alteration is an example of mode of action of these natural products since they can destroy or mask the virus which affects viral attachment and influences its adsorption in the host cells (Ma and Yao 2020). However, the viral structure is very simple, being basically composed by genetic material surrounded by a protein wrap (Böhme et al. 2013). In this way, genome-related sites can be a target of essential oils but the protein inhibition is a promising alternative to treat the COVID-19 (Mori et al. 2016; Sharma and Kaur 2020). According to Wu et al. (2020), the main therapies are related to inhibition of viral life cycle and

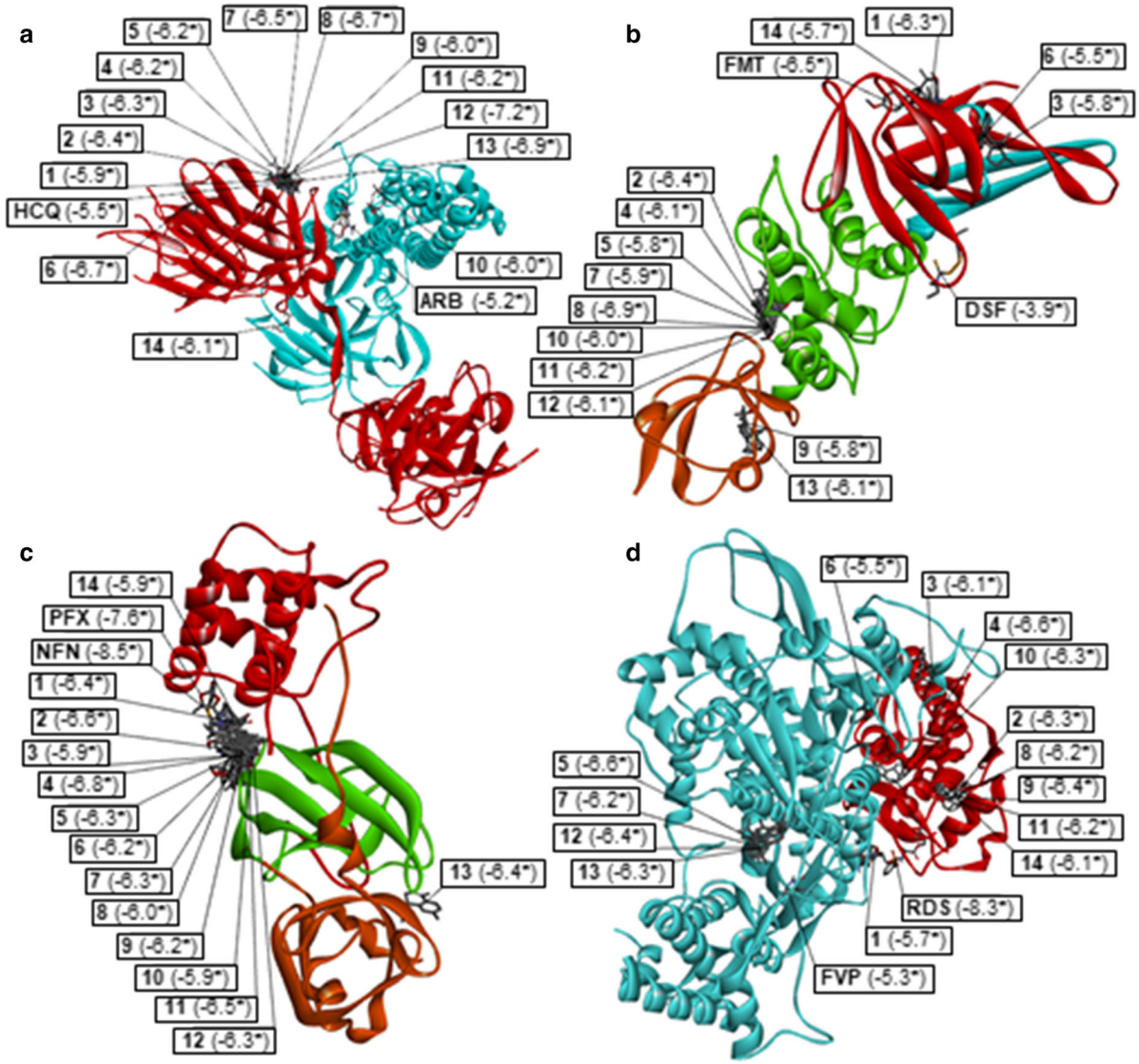

Fig. 3 3D diagram showing the superimposed binding site of compounds from essential oils and controls with **a** spike glycoprotein (S protein), **b** papain-like protease (PLpro), **c** 3-Chymotrypsin-like protease (3CLpro) and **d** RNA-dependent RNA polymerase (RdRp). (**1**) (*E*)-α-Atlantone; (**2**) 14-Hydroxy-α-muurolene; (**3**) allo-Aromadendrene epoxide; (**4**) Amorpha-4,9-dien-2-ol; (**5**) Aristochene; (**6**) Azulenol; (**7**) Germacrene A; (**8**) Guaia-6,9-diene; (**9**) Hedycaryol; (**10**) Humulene epoxide II; (**11**) α-Amorphene; (**12**) α-Cadinene; (**13**) α-Calacorene; (**14**) α-Muurolene; (**HCQ**) hydroxychloroquine; (**ARB**) arbidol; (**FMT**) formoterol; (**DSF**) disulfiram; (**PFX**) prulifloxacin; (**NFN**) nelfinavir; (**RDS**) remdesivir and (**FVP**) favipiravir. [a]Energy binding energy values in kcal/mol (unnormalized)

inhibition of structural proteins. Based on these data, proteins involved to maturation and infectivity of the virus such as papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro) as well as spike glycoprotein (S protein) and RNA-dependent RNA polymerase (RdRp) that act in the cell cycle of the virus were selected for next analysis.

Thus, the previous compounds that showed high potential against at least one of the viruses (rhinovirus or picornavirus) were subjected to molecular docking studies. This analysis was carried out by AutoDock Vina tool using PyRx software in order to understand the interaction between these compounds and the targets proteins to combat the novel coronavirus

infection (Dallakyan and Olson 2015). Crystal structures of SARS-CoV-2 (2019-nCoV) PLpro (Protomer PDB ID 6W9C), main protease, also called 3CLpro (PDB ID 6Y2F), S protein (Protomer PDB ID 6VSB) and RdRp (PDB ID 6M71) were obtained from the protein database (PDB). 3D structures of the compounds were obtained by the PubChem database. The files were converted to the appropriate format (*.pdb) using the Biovia Discovery Studio software (San Diego, USA). For which target, a grid box was defined in order to comprise the entire protein. Then, AutoDock Vina algorithm was used to calculate the binding energies between the targets and the compounds in the PyRx docking tool. Drugs that were already indicated by previous studies as potential anti-COVID-19 with the same proteins as molecular targets were included as positive controls: formoterol, disulfiram. nelfinavir, prulifloxacin, hydroxychloroquine, arbidol, remdesivir and favipiravir (Arya et al. 2020; Lin et al. 2018; Qamar et al. 2020; Fantini et al. 2020; Zhu et al. 2020; Wang et al. 2020; Chen et al. 2020). The binding energies were expressed in kcal/mol and converted to inhibition constant (K_i) in μM (Table S3, Supplementary material).

Dimercaprol and mechlorethamine were chosen as negative control since they are clinically established drugs without antiviral activity (Kadioglu et al. 2020). With exception of disulfiram, the positive control drugs revealed binding energies $\leq$ -5.2 kcal/mol and inhibition constant $\leq$ 153.5 μM, while negative control drugs bound with affinities $\geq$ -3.3 kcal/mol and inhibition constant $\geq$ 3798.5 μM to the four targets (Table S3, Supplementary material). Disulfiram has a reactive sulfur group that could bind covalently to cysteine proteases as PLpro and such strong binding is not commonly accounted in docking protocols, which helps to explain such high energy binding (− 3.9 kcal/mol) when compared to others positive control drugs (Lin et al. 2018). This distinction between positive and negative controls is maintained even when the binding energy values energies are normalized by the number of heavy atoms (N) (Normalized binding energy = binding energy/$N^{1/3}$) (Table S4, Supplementary material). This normalization strategy normally is employed as an attempt to mitigate the contribution of the compound size to the energy score as many scoring functions tend to favor compounds with higher molecular weight due to a larger sum of van der Waals atom pairs interactions (Pan et al. 2003; Hancock et al. 2005).

The 14 compounds that showed the best results for the four analyzed targets were: (*E*)-α-atlantone (**1**); 14-hydroxy-α-muurolene (**2**); allo-aromadendrene epoxide (**3**); amorpha-4,9-dien-2-ol (**4**); aristolochene (**5**); azulenol (**6**); germacrene A (**7**); guaia-6,9-diene (**8**); hedycaryol (**9**); humulene epoxide II (**10**); α-amorphene (**11**); α-cadinene (**12**); α-calacorene (**13**) and α-muurolene (**14**) (Table S3, Supplementary material) (Fig. 2). All these compounds exhibited lower binding energy values (stronger affinity) than the negative controls, even after normalization as these controls have relatively low molecular weight (Table S4, Supplementary material). When compared to the positive controls, in general, the selected compounds showed favorable binding energies, even having lower molecular weight than these reference drugs which makes them more druglike (Table S4, Supplementary material).

Most of the top 14 compounds are cyclic sesquiterpenes, except the **6** which is a cyclic monoterpene. Sesquiterpenes are among the main classes of secondary metabolites with antiviral properties (Reichling 2018). These compounds had been tested against different herpesviruses, rhinovirus and hepatitis B (Astani et al. 2011; Gu et al. 2019).

The selected compounds were identified in the essential oils from *Aloysia gratissima*, *Cordia curassiava*, *Lantana camara*, *Lippia alba, Lippia origanoides* and *Schinus terebinthifolia* in the first research step. Among these, the native licensed species *Lantana camara* has the greatest potential in which seven compounds were identified: **3**, **6**, **7**, **8**, **10**, **13** and **14**. In addition, *Lippia alba* (compounds **2**, **3**, **7**, **9**, **11** and **14**) and *Lippia origanoides* (compounds **5**, **10**, **11**, **12**, **13** and **14**) also present great potential, in which six compounds were identified. Therefore, the molecular docking results suggest that these three essential oils would have potential to inhibit SARS-CoV-2 and these natural products may be indicated for future in vitro trial studies.

The proteins analyzed by molecular docking are essential for the SARS-CoV-2 lifecycle (Sanders et al. 2020). The S protein is involved in the first step of the viral replication cycle, since it mediates the virus attachment to the surface of respiratory cells, using the angiotensin-converting enzyme-2 (ACE-2) as an entry receptor (Fantini et al. 2020). This transmembrane

protein forms homotrimers protruding from the viral surface and each single protomer is made up of two functional subunits S1 and S2 (Walls et al. 2020; Wrapp et al. 2020). S1 is divided into 2 subdomains: N-terminal domain and receptor-binding domain (Wrapp et al. 2020).

The compounds **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **11**, **12** and **13** are predicted to bind to the N-terminal domain of the S1 subunit, as well as the hydroxychloroquine control. The proposed mechanism of action of the hydroxychloroquine includes the inhibition the entry step of SARS-CoV-2 (Liu et al. 2020). The binding of this drug with the N-terminal domain, which is conserved among clinical isolates worldwide, inhibits the interaction between S protein and the host cell receptor (ACE-2) (Fantini et al. 2020). Thus, bonding of the mentioned compounds to the same region of hydroxychloroquine, could inhibit the interaction with ACE-2 and consequently the entry of the virus into the cell. The binding energy (unnormalized and normalized) and inhibition constant values of these compounds indicate stronger affinity with S protein than the control hydroxychloroquine (Fig. 3a and Table S4). This drug, worldwide used for the treatment of malaria and rheumatological conditions, showed anti-SARS-CoV-2 effects both in vitro and in vivo and was recommended by several national guidelines for treatment of patients with COVID-19 (such as Belgian, Italian and Chinese guidelines) (Singh et al. 2020). However, the effectiveness of this drug has not been proven by clinical trials and its serious adverse effects especially on the heart and eyes cause concern (Zou et al. 2020). Therefore, most countries no longer recommend this drug for the treatment of COVID-19.

Arbidol (umifenivir) is another antiviral drug included in clinical trials that act inhibiting the virus entry. This agent is approved in China and Russia for treating influenza, SARS, and Lassa viruses and showed clinical efficacy superior to lopinavir/ritonavir in treating COVID-19 (Zhu et al. 2020b). This drug binds in the S2 subunit and it can effectively block or impede the trimerization of the S protein (Vankadari 2020). The compound **10** bound near to the binding region of arbidol and, therefore, it may present a similar mechanism of action. This compound exhibited better binding energy (unnormalized and normalized) and inhibition constant than arbidol (Fig. 3a and Table S4). On the other hand, the compound **14** bound to other region of the S2 subunit and despite the low binding energy, there is no evidence in the literature that binding at this site leads to inhibition (Fig. 3a).

In addition to S protein, PLpro and 3CLpro are enzymes also considered as promising targets, since they are cysteine proteases which mediate the proteolytic processing of maturation and infectivity of the virus (Arya et al. 2020; Qamar et al. 2020). The PLpro monomer consists of four domains: palm, thumb, and finger domains which form an extended right-hand architecture, and the N-terminal ubiquitin-like (Ubl) domain (Ratia et al. 2006). The PLpro active site is located at the bottom of the palm and thumb domains, where the control disulfiram bound (Fig. 3b). Disulfiram, an approved drug to treat alcohol dependence considered a therapeutic option for COVID-19, acts forming a covalent adduct at the active site of SARS-CoV PLpro, thus it is a competitive inhibitor (Lin et al. 2018; Li and Clercq 2020). None of the analyzed compounds indicated the same mechanism of action than disulfiram, since they did not bind to the PLpro active site.

Although they do not bind to this active site, the analyzed compounds can interfere with the PLpro functions by binding into allosteric sites with a low general inhibition constant (< 92.5 uM) (Fig. 3b), which reinforces the potential of these selected compounds as anti-coronavirus agent. The compounds **2**, **4**, **5**, **7**, **8**, **10, 11** and **12** bound between the Ubl and thumb domains. The compounds **9** and **13** bound only in Ubl (Fig. 3b). The Ubl domain is not required for PLpro catalytic activity, but it is necessary for its interferon (IFN) antagonist activity, which is one viral strategy to disable the host's innate immune response (Frieman et al. 2009). Another PLpro function involved in modulating the innate immune response is deubiquitinating. PLpro recognizes and cleaves ubiquitin, a protein that regulates a number of cellular pathways, including many processes associated with combating viral infection (Ratia et al. 2014). The region between the palm and fingers domains is important for this ubiquitin recognition (Ratia et al. 2014). The compounds **1**, **3**, **6** and **14** mainly bound in this region, as well as the formoterol control (Fig. 3b). Formoterol is a bronchodilator used in the management of chronic obstructive pulmonary disease (COPD) and asthma, and it has shown potential to inhibit the viral PLpro activity (Arya et al. 2020). Formoterol may reduce human coronavirus replication by inhibiting receptor expression and/or endosomal

function and modulating airway inflammation after infection (Yamaya et al. 2020).

Along with PLpro, 3CLpro is essential for processing the polyproteins that are translated from the viral RNA and its inhibitors are unlikely to be toxic, since no human protease with similar cleavage specificity is known (Zhang et al. 2020). The protomer of this enzyme is divided in the domains I, II and III (Zhang et al. 2020). The compound **13** interacts with one of the amino acid residues of the catalytic site (HIS41, domain I), which might interfere with substrate entering (Fig. 3c) (Zhang et al. 2020). Binding to the 3CLpro active site, this compound may have an mechanism of action similar to ritonavir and liponavir, two anti-HIV drugs, which have been reported to be active against SARS and MERS (Nutho et al. 2020).

Others compounds (**1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** and **14**) were predicted to bind in the region between domains II and III, important for 3CLpro dimer formation (Zhang et al. 2020). Similarly, the controls nelfinavir and prulifloxacin, considered the best drugs targeting SARS-CoV-2 3CLpro that could be used for the treatment of COVID-19, do not interact either with the 3CLpro catalytic site residues (Qamar et al. 2020). They bound between domains II and III, as well as the most of the analyzed compounds (Fig. 3c).

In relation to the mechanisms of action of these positive controls, experiments demonstrated that nelfinavir, a very safe and widely prescribed drug in the treatment of HIV-infected patients, exerts its effect not at the entry step, but at the post-entry step of SARS-CoV infection, involving partial 3CLpro block (Yamamoto et al. 2004). The nelfinavir effectiveness in inhibiting SARS-CoV-2 replication in vitro was higher than nine HIV-1 protease inhibitors including lopinavir (Yamamoto et al. 2020). Similar to nelfinavir, prulifloxacin also inhibits the 3CLpro SARS-CoV-2 interrupting the dimer formation (Li et al. 2020). The compounds **1**, **3**, **6**, **7**, **8**, **9**, **10**, **12** and **14**, probably have the same mechanism of action than nelfinavir and prulifloxacin, since they bound to the same region. None of the analyzed compounds showed binding energy and inhibition constant values lower than these positive controls (Fig. 3c). However, after binding energy normalization, compounds **2**, **4**, **5**, **6**, **7**, **11**, **12**, **13** showed to be more promising than these reference drugs, because their normalized binding energy overcome it due to their lower molecular weight (Table S4, Supplementary material).

The enzyme RdRp (also known as nsp12) catalyzes the synthesis of viral RNA and plays a central role in the replication and transcription viral cycle. Thus, RdRp can also be target to SARS-CoV-2 therapy as demonstrated in treatment with remdesivir and favipiravir (Wang et al. 2020; Chen et al. 2020). The structure of the RdRp contains a polymerase domain (fingers, palm and thumb domains) and a nidovirus-unique N-terminal extension domain (NiRAN). These two domains are connected by an interface domain (Gao et al. 2020).

The compounds **1**, **3**, **5**, **6**, **7**, **12** and **13** were predicted to bind in the polymerase domain: **1** is located in the RdRp active site, in the palm domain; **3** and **6** in the interface domain and **5**, **7**, **12** and **13** in the fingers domain (Fig. 3d). The binding to this polymerase domain might interfere with the viral RNA synthesis (Velthuis et al. 2014). On the other hand, the compounds **2**, **4**, **8**, **9**, **10, 11** and **14** were predicted to bind to the RdRp NiRAN domain (Fig. 3d). This domain is not part of the RdRp catalytic site, but it is essential for the virus due to potential functions that may include nucleic acid ligation, mRNA capping and protein-primed RNA synthesis (Lehmann et al. 2015).

The compound **1** did not show binding energy stronger than the controls, but it bound in the same region than remdesivir. Thus, the compound **1** probably has a mechanism of action similar to the control remdesivir, since it also bounds in the RdRp active site, which can inhibit the virus by synthesis inhibiting of viral nucleic acid (Wu et al. 2020). Remdesivir has broad-spectrum activity against members of several virus families (Ebola, SARS-CoV and MERS-CoV) and showed clinical improvement in 68% of patients with severe COVID-19 in a clinical study (Grein et al. 2020).

The compounds **5**, **7**, **12** and **13** exhibited binding energy (unnormalized and normalized) and inhibition constant values lower than favipiravir and they bound near to the binding region of this control, suggesting a similar mechanism of action (Fig. 3d). Favipiravir (T-705), a guanine analogue approved for influenza treatment, can effectively inhibit the viral RdRp and an in vitro study reported its activity against SARS-CoV-2 (Wang et al. 2020; Li and Clercq 2020). One clinical trial already reported that among patients with COVID-19, favipiravir significantly improved the latency for relief of pyrexia and cough when compared to arbidol (Chen et al. 2020).

Off-target, drug-like and toxicity predictions

During the new drugs discovery, in addition to the interest targets, it is also important to evaluate the possibly off-targets bindings. Off-target binding comprises the binding of a compound to a protein other than its primary target of therapeutic interest, which can lead to side-effects (Xie et al. 2011). The selected compounds **1**–**14** were submitted to SwissTargetPrediction, one of the standard tools of computational off-target prediction methods with 2092 *Homo sapiens* targets (Daina et al. 2019). The results indicated a low probability ($\leq$ 16%) of affinity with the targets for the compounds, indicating a low potential of off-target competition, except for the compound **2**. This compound showed 33% of probability of interaction with LXR-alpha (Table S5, Supplementary material). The LXR-alpha (nuclear liver X receptor alpha) is involved in the cholesterol metabolism and lipid biosynthesis. In addition, it is a regulator of inflammatory cytokines and suppressor of hepatic glucose production, being a potential drug target for treatment of diabetes (Steffensen and Gustafssonet 2004). However, the anti-diabetes effect of the compound **2** is not yet reported in the literature and its probability of affinity (33%) can be considered low.

Absorption, distribution, metabolism, excretion and toxicity (ADMET) profile has a great importance in drug discovery and development. Focusing on off-target actions, the selected compounds **1**–**14** were evaluated for their possible toxic effects (cardiotoxic, hepatotoxic and mutagenic) through the web-based tool ADMETlab (Dong et al. 2018). The inhibition of the hERG potassium channel may result in QT interval prolongation and causes severe cardiac side effects, which is the foremost problem in clinical studies of drug candidates (Wang et al. 2012). Regarding hepatotoxicity, drug-induced liver injury is a major cause for drug withdrawal from the market (Chen et al. 2011). Ames test, the most widely used assay for testing the mutagenicity (Xu et al. 2012), was used for this parameter prediction. Interestingly, compounds **1–14** were not highly likely for these important toxicity endpoints (except hepatotoxicity for compound **4**), forecasting their security (Table S6, Supplementary material). Several in vivo studies have already demonstrated that many essential oils can be used safely (Altaei 2012; Hoff Brait et al. 2015; Cruz et al. 2017; Mishra et al. 2018). Furthermore, clinical trials have confirmed the good tolerability of essential oils use for humans (Lillehei and Halcon 2014; Hammer 2015; Han et al. 2017). Although the compound **4** has presented a prediction for hepatotoxicity, it is one constituent of *Aloysia gratissima* essential oil which did not cause side effects on fish when used as an anesthetic (Benovit et al. 2015).

However, it is worth highlight that some essential oil constituents can be allergens (Groot and Schmidt 2016). Therefore, in addition to the major toxicological endpoints of concern, such as acute toxicity genetic toxicity, carcinogenicity, reproductive toxicity, and developmental toxicity, allergenic potential tests must be carried out in order to determine safe doses and routes of administration before the clinical use.

In addition, the drug-likeness based on Lipinski's rule was also predicted, on ADMETlab platform. According to Lipinski's rule, a molecule should present molecular weight $\leq$ 500 Dalton, number of H-bond donors $\leq$ 5, number of H-bond acceptors $\leq$ 10 and LogP $\leq$ 5 to be considered as an ideal drug molecule (Lipinski 2004). The results indicated that none of **1** to **14** compounds violated the Lipinski's parameters (except LogP for compound **7**), showing good probability to achieve cell permeability and be considered as a drug candidate (Table S6, Supplementary material).

Potential anti-COVID-19 essential oils

All considered, the in silico results point out to the potential of the compounds **1**–**14** to be explored as anti-coronavirus agent. Essential oils are complex mixtures and this chemical diversity guarantees their different therapeutic properties. However, the major compounds, usually consisted by one to five substances, are mainly responsible for their biological effects (Bakkali et al. 2008). Based on this prediction, the second research step was based in the selection of essential oils that presented at least one of these compounds as major (at the top five) constituents in order to indicate possible natural products for future in vitro and in vivo trials against COVID-19.

This search was performed at PubMed literature on these natural compounds and potential essential oils in which they were present (Query keywords: "(*E*)-α-Atlantone"; "14-Hydroxy-α-muurolene"; "allo-

Aromadendrene epoxide"; "Amorpha-4,9-dien-2-ol"; "Aristochene"; "Azulenol"; "Germacrene A"; "Guaia-6,9-diene"; "Hedycaryol"; "Humulene epoxide II"; "α-Amorphene"; "α-Cadinene"; "α-Calacorene"; "α-Muurolene" and "essential oil"). In addition, synonymous for these compounds described in PubChem were used in parallel as a search query keyword.

According to Table 1, 45 species were selected and it is worth highlighting that the *Athanasia brownii, Calamintha nepeta, Callicarpa Americana, Chamecyparis formosensis, Cistus creticus, Cymbopogon validus, Myrtus communis, Pelargonium graveolens, Piper aduncum, Psidium guajava, Rydingia michauxii, Seseli rigidum, Tetradenia riparia, Teucrium montanum, Teucrium persicum, Ugni myricoides, Vernonia cinerea* and *Zingiber zerumbet* species presented more than one of the compounds of interest in their constitution.

Among the species selected, antiviral potential has already been reported for *Baccharis dracunculifolia*. This species is a native plant from Brazil and it is important in the green propolis production. Study performed by Búfalo et al. (2009) showed a low viral (poliovirus type 1) quantification by real-time PCR after treatment with *Baccharis dracunculifolia* essential oil. In addition, this species has been considered safe, since it showed no cytotoxicity against HEp-2 cells, as well as it was classified as category 5 through in vivo toxicity assays by Globally Harmonized Classification System (GHS) for Chemical Substances and Mixtures (Búfalo et al. 2009, 2010; Massignani et al. 2009). Thus, *Baccharis dracunculifolia* essential oil stands out as a potential alternative for the treatment of COVID-19.

Additionally, as reviewed by Silva et al (2020), compounds **4** and **14** have already been identified as major compounds in essential oils with antiviral activity. *Santolina insularis* essential oil (12.7% of compound **4**) presented high activity against herpes simplex type 1 and type 2, accompanied by low cytotoxicity (Logu et al. 2000). *Fortunella margarita* essential oil (10.3% of compound **14** in leaves and 5.5% in fruits) presented activity against avian influenza-A virus (Ibrahim et al. 2015).

Essential oils in clinical trials

Essential oils have been shown to be effective in clinical trials against respiratory virus infections. A double blind randomized controlled trial using essential oils from different species (*Coridothymus capitatus*, *Origanum dictammus* and *Salvia fruticos*a) to treat upper respiratory tract infection was performed by Duijker et al. (2015). Among the virus-positive patients, human rhinovirus, H1N1 influenza, human metapneumovirus and human coronavirus strains were identified by specific RT-qPCR. The severity and duration of symptoms of these patients were lower in the treated group compared to placebo group and the use of the essential oils was safe, since hepatic or renal function showed no changes. In this same way, randomized study performed by Shayeganmehr et al. (2018) showed that *Zataria multiflora* essential oil reduced H9N2 influenza replication, as well as clinical symptoms.

Regarding non-respiratory virus infections, double-blind randomized trial was performed to confirm the action of *Myrtus communis* against human papillomavirus (HPV). Herbal vaginal suppositories containing 0.5% of myrtle essential oil were prescribed for the intervention group and showed greater number of negative HPV tests (92.6%) after treatment when compared to the placebo group (62.6%). In addition, an improvement in the size of the cervical lesion was also observed (Nikakhtar et al. 2018).

In a controlled clinical trial to evaluate the reducing of HSV-1 virus (*Herpes simplex* virus, Type 1) found in saliva, infected patients were treated with a commercially available mouth rinse or sterile water as control group. The antiseptic was composed of eucalyptol, thymol, and menthol terpenes, which are found in different essential oils. The samples were analyzed at different times (30 s, 30 min and 60 min) after the treatments and it was possible to observe that the group containing terpenes was efficient at the first time, since viruses were not detected after 30 s, whereas for the group containing only water, the virus concentration was not changed (Meiller et al. 2005). *Melaleuca alternifolia* essential oil has also shown activity against HSV and a randomized, placebo-controlled, investigator-blinded study was performed to evaluate its efficacy. The results showed that patients treated with oil gel (6% tea tree essential oil) have median time to re-epithelialization and

median duration of culture positivity (9 days and 3 days, respectively) lower than placebo group (12.5 days and 4 days, respectively) (Carson et al. 2001).

All these data indicate some benefit of essential oil for the treatment of virus infections; however, studies relating to this purpose (essential oils and clinical trials) still represent a small portion among the approach of new viral agents. The results presented in this work reinforce the antiviral potential of compounds found in essential oils and direct the species reported in the Table 1 for in vitro and in vivo assays. On the other hand, the low performance and the difficulty of isolating these components justify the use of essential oils instead of just one active compound. In addition, the complex chemical composition of essential oils allows the occurrence of a synergistic effect between their components and, consequently, greater action against viruses, as well as decreases the probability of developing resistant strains (Schnitzler 2019).

Conclusions and future perspectives

Therefore, this review shows that essential oils have potential to inhibit SARS-CoV-2 and, based on their physical–chemical characteristics, their administration may be an alternative to treat and control the COVID-19 symptoms. Furthermore, this study provides valuable information on which essential oils should be prioritized for in vitro and in vivo studies in order to confirm these results and afford a potential drug in the fight against COVID-19.

In addition, the few studies referring to antiviral potential of essential oils should be highlighted, since in a PubMed literature search less than 0.08% of works identified using the antiviral as query keyword also referred to essential oils ("antiviral" "essential oil"). This reality reinforces the importance of the present work and encourages new studies to evaluate the action of essential oils against dangerous classes of viruses.

Another important point is that the essential oils production is affected by several biotic and abiotic factors, and the qualitative and quantitative constitution of these metabolites can be altered in the same species, changed its biological effect (Gobbo-Neto and Lopes 2007). In this same way, many essential oils exist in the form of several different chemotypes and for that it is important to ensure the correct identification of the natural product. Thus, we suggest that essential oils should be chemically characterized before screening biological studies to confirm the presence of the compounds indicated (**1**–**14**) in our research. In addition, we also believe that this work can be used as a reference in the research and evaluation of other oils that have not been identified in the PubMed literature or that have not yet been reported.

Supplementary material

Tables of the compounds reported in the species and QSAR, molecular docking, off-target, drug-like and toxicity predictions.

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Decalrations

Conflict of interest All authors declare that they have no conflict of interest.

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