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ORIGINAL PAPER

Less COVID-19 deaths in southern and insular Italy explained by forest bathing, Mediterranean environment, and antiviral plant volatile organic compounds

Valentina Roviello[1] · Giovanni N. Roviello[2]

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Abstract
The coronavirus disease 2019 (COVID-19) is causing major sanitary and socioeconomic issues, yet some locations are less impacted than others. While densely populated areas are likely to favor viral transmission, we hypothesize that other environmental factors could explain lower cases in some areas. We studied COVID-19 impact and population statistics in highly forested Mediterranean Italian regions versus some northern regions where the amount of trees per capita is much lower. We also evaluated the affinity of Mediterranean plant-emitted volatile organic compounds (VOCs) isoprene, α-pinene, linalool and limonene for COVID-19 protein targets by molecular docking modeling. Results show that while mean death number increased about 4 times from 2020 to 2021, the percentage of deaths per population (0.06–0.10%) was lower in the greener Mediterranean regions such as Sardinia, Calabria and Basilica versus northern regions with low forest coverage, such as Lombardy (0.33%) and Emilia Romagna (0.29%). Data also show that the pandemic severity cannot be explained solely by population density. Modeling reveals that plant organic compounds could bind and interfere with the complex formed by the receptor binding domain of the coronavirus spike protein with the human cell receptor. Overall, our findings are likely explained by sea proximity and mild climate, Mediterranean diet and the abundance of non-deciduous Mediterranean plants which emit immunomodulatory and antiviral compounds. Potential implications include 'forest bathing' as a therapeutic practice, designing nasal sprays containing plant volatile organic compounds, and preserving and increasing forest coverage.

Keywords SARS-CoV-2 · COVID-19 · Pandemics · Immunomodulatory compounds · Forest bathing · Mediterranean vegetation · Volatile organic compounds · Plant therapeutics · Angiotensin-converting enzyme 2 · Spike · Receptor binding domain

Introduction

The COVID-19 (coronavirus disease 19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing enormous difficulties around the globe from both a sanitary and socioeconomic perspective (Dai et al. 2021; Bashir et al. 2020a; Caterino et al. 2021). With the world still waiting for an effective mass vaccination using the developed anti-COVID-19 vaccines (Costanzo et al. 2021; He et al. 2021) and despite the efforts by pharmaceutical companies and the scientific community to develop effective therapies through drug repurposing (Borbone et al. 2021; Costanzo et al. 2020; Kumawat et al. 2021; Khan et al. 2021), herbal medicine (Vicidomini et al. 2021b) and other recently proposed approaches (Vicidomini et al. 2021a; Wang et al. 2020b), SARS-CoV-2 and its mutations remain a major global issue leaving our future unclear. COVID-19 has also had an environmental impact on the planet, and while initial data from ESA (European Space Agency) and NASA (U.S. National Aeronautics and Space Administration) seemed to suggest that pollution in the first epicenters of COVID-19 such as the Hubei region of China, Italy, Spain and the USA had reduced significantly (up to 30%) (Muhammad et al. 2020), in the subsequent phases of the pandemic, an increasing pollution trend was recorded

✉ Giovanni N. Roviello
giroviel@unina.it; giovanni.roviello@cnr.it

[1] Department of Chemical, Materials and Industrial Production Engineering (DICMaPI), University of Naples Federico II, Piazzale V. Tecchio 80, 80125 Naples, Italy

[2] Istituto Di Biostrutture E Bioimmagini, IBB–CNR, Via Mezzocannone 16, 80134 Naples, Italy

globally (Wang et al. 2020a; Zheng et al. 2021; Shehzad et al. 2021). Of equal importance, there has also been an increase in plastic pollution (Gorrasi et al. 2020; Ufnalska and Lichtfouse 2021) due to face masks, gloves and other single-use COVID-19-related plastics that are posing a major risk for marine ecosystems and aquatic organisms (Aragaw 2020). Environmental degradation is not only one of the worrying effects of the COVID-19 pandemic, but it is also at its origin (Paital and Agrawal 2020; Chen et al. 2021) as shown by several studies that associate air pollution with higher rates of the disease as well as more significant risk factors for acute respiratory infections. This is due to the damaging effects that pollutants have on the body's immune system as well their ability to carry potentially harmful microorganisms (Cai et al. 2007; Susanne Becker 1999; Sun et al. 2016; Xie et al. 2019). Since environmental pollutants are in strong correlation with COVID-19 severity (Bashir et al. 2020b; Zhu et al. 2020), with particulate matter (PM) in combination with humidity significantly increasing the risk of COVID-19 incidence (Jiang et al. 2020), air pollution control could likely reduce the harmful consequences of the SARS-CoV-2 infection (Bashir et al. 2020b).

Several studies sustained the hypothesis of a direct proportionality between COVID-19 severity and levels of fine particulate matter (PM) in urban areas (Conticini et al. 2020). In fact, PM could play a role in spreading the virus in the air (Setti et al. 2020) and is also linked to respiratory illnesses in turn causing higher COVID-19 mortality rates (Dutheil et al. 2020; Kutralam-Muniasamy et al. 2021). Inside the respiratory system, PM can exacerbate respiratory distress leading to inflammatory responses, as well as pulmonary and cardiovascular problems. Remarkably, the highest number of COVID-19 victims in Italy was found in the areas of the country endowed with PM concentrations of $\geq 50\ \mu g/m^3$ as PM_{10} daily averages (Setti et al. 2020). On the other hand, it is well known that trees play a beneficial role in the fight against air pollution (Grzędzicka 2019) and, in particular, urban trees exert an important action of air purification not only by absorbing nocive gases through their leaf stomata, but also by intercepting the PM on leaves and other plant surfaces (Nowak et al. 2014, 2018).

Among the environmental factors able to influence the impacts of COVID-19, air quality had a stronger effect on the number of confirmed cases of COVID-19 in the temperature range of 10–20 °C, while the air quality-associated relative risk of SARS-CoV-2 transmission was more pronounced in the relative humidity range of 10–20%, leading to the hypothesis that air quality has a greater impact on the spread of the virus under low relative humidity conditions (Xu et al. 2020). Southerly latitude was previously associated with lower hospitalization and mortality rates for COVID-19 worldwide due to multiple factors. These include a higher availability of endogenously produced vitamin D (which is endowed with well-recognized immunomodulatory properties, following sunlight/low ultraviolet skin exposure) as well as higher relative humidity and temperature conditions disfavoring the SARS-CoV-2 survival outside the human body (Panarese and Shahini 2020; Maha and Talal 2021). Indeed, the pandemic has been found to have graver consequences the more one travels northward on the European map while several Mediterranean countries have experienced a much milder impact with lower mortality rates linked to the SARS-CoV-2 infection (Panarese and Shahini 2020). This was initially thought to be due to the rigorous control measures taken by local governments who seemed to have arrested the SARS-CoV-2 inexorable spread (Frogoudaki 2020; Saglietto et al. 2020). During the second year of the pandemic however, it became clear that the coronavirus had practically reached all the most remote places of the world without sparing those Mediterranean areas that previously seemed protected from any significant COVID-19 impacts. Nevertheless, the effects of the pandemic in Mediterranean countries, even if highly increased, remained less burdensome than in northern countries. This is most likely thanks to the above-cited protective effects provided by geographical location and climate, the availability of endogenous vitamin D, lower air pollution, as well as other environmental factors together with the Mediterranean diet (Cena and Chieppa 2020). During the first year of the COVID-19 pandemic, Italy showed significant regional differences on the impact of the coronavirus; where it was much more dramatic in the North when compared to the south and insular Italy (Signorelli et al. 2020). We previously associated this difference to factors such as, among others, the different evergreen forest coverage in the examined territories and the consequent more durable plant emission of bioactive volatile organic compounds (VOCs)(Roviello and Roviello 2021). Evergreen trees have the benefit of not only mitigating air pollution, and this even during the winter, but they also act as emitters of VOCs with ascertained immune system bolstering effects. From previous screenings of native Mediterranean plant species for emissions of C5 and C10 hydrocarbons, isoprene and monoterpenes in different habitats, more than 30 VOCs were observed in the emissions from these plants. Among the different Mediterranean plants, the evergreen oak (*Quercus ilex L.*) is able to emit a large number (19) of different VOCs, while Spanish broom (*Spartium junceum L.*, Fig. 1) emissions are dominated by isoprene, with, at lesser concentrations, other VOCs like α-pinene, linalool and limonene. These four compounds (Fig. 1) are the most representative VOCs from Mediterranean plants that are categorized according to their main emitted compound as isoprene, α-pinene, linalool and limonene emitters (Owen et al. 2001).

In the present work, we studied the impact of COVID-19 on highly forested areas of Italy during the period ranging

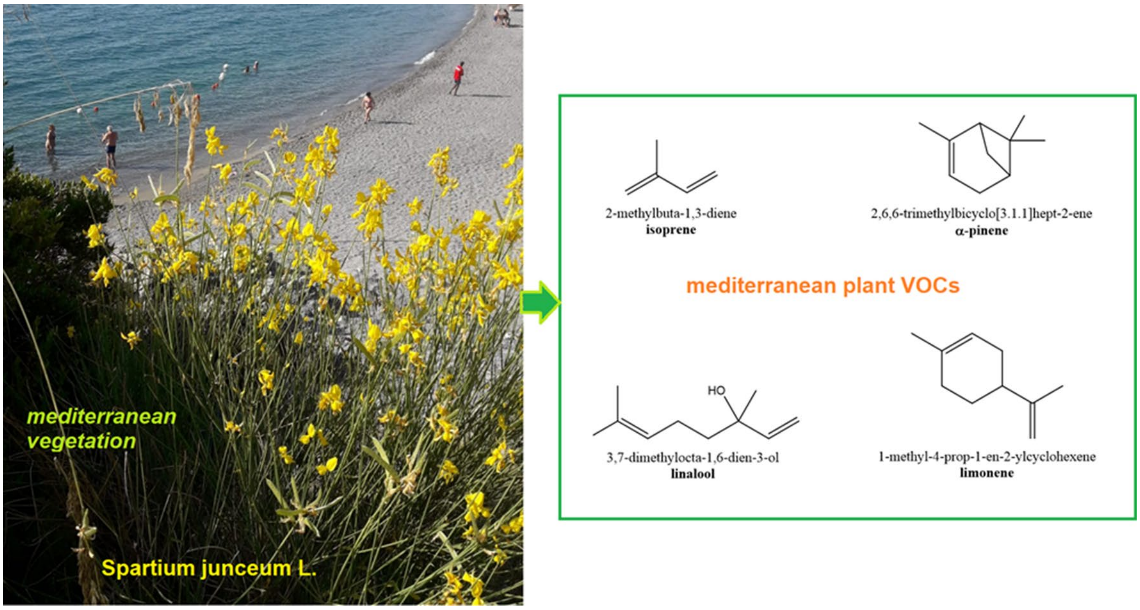

Fig. 1 Spanish broom (*Spartium junceum L.*) in a coastal area of Calabria, South Italy (photo taken by G.N. Roviello on June 04, 2021) and schematic representation of some of the most representative volatile organic compounds (VOCs) emitted by Mediterranean plants. Note how Spanish broom is one of the main emitters of isoprene and, at a lower extent, also of α-pinene, linalool and limonene, that were studied in this work (Owen et al. 2001)

from fall 2020 to spring 2021, comparing it to the situation recorded during the previous year and confirmed lower pandemic effects on Mediterranean forest-rich areas of the country. We also compared COVID-19 data, population density and average age of the greenest regions from Northern (Aosta Valley) and Mediterranean (Sardinia) Italy which demonstrated that the lower SARS-CoV-2 impact in Mediterranean green areas cannot be merely explained in terms of lower population density or median age. It is thus most likely that other environmental effects, such as Mediterranean plant VOCs emission, play a key role as we hypothesize and explain in the following sections.

Experimental

Estimation of forest composition and other parameters mentioned in this work

COVID-19 data in Table S1 were obtained from the link https://www.emergenza.com/17-maggio-2021-aggiornamento-casi-covid-19/ (accessed on June 29, 2021) or were available in our previous work, together with those on regional forested areas that in turn were obtained from data released by Italian National Forest Service (INFC). Prevalence of deciduous vs. evergreen forestal species in Aosta valley and Sardinia (Results and Discussion) was estimated by using the data furnished by INFC, available at the link below: https://www.sian.it/inventarioforestale/caricaDocumento?idAlle=421 (accessed on July 9, 2021).

Population density and median age data for Italian regions were found at the links: https://www.tuttitalia.it/regioni/densita/ and https://ugeo.urbistat.com/AdminStat/it/it/classifiche/eta-media/regioni/italia/380/1 (both accessed on June 29, 2021).

Histograms were realized in Meta Chart https://www.meta-chart.com/histogram (link accessed on June 29, 2021), while chemical structures shown in Fig. 1 were realized by ChemDraw 12.0 program.

Molecular docking

Blind molecular docking was performed with SwissDock using as receptor the ACE2-RBD (angiotensin-converting enzyme 2-receptor binding domain) complex (Protein Data Bank [PDB] ID: 6M0J) whose three-dimensional structure was obtained from Protein Data Bank (Berman et al. 2002), and as ligands the structures of isoprene, α-pinene, linalool and limonene that were found in SwissDock database or downloaded as 3D files from Pubchem (https://pubchem.ncbi.nlm.nih.gov/, accessed on June 29, 2021) and saved as Mol2 files by UCSF Chimera that was used also in complex visualizations. More details on SwissDock docking platform and on the docking software EADock DSS, as well on the procedures for docking experiments can be found at http://www.swissdock.ch/ (accessed on June 29, 2021).

The docking method was validated using ellagic acid as a reference compound that in our blind docking experiment bound spike protein portion of ACE2-RBD complex and whose binding energy (BE) was comparable to that reported for spike protein with the same PDB entry (6M0J) in the literature (Gowrishankar et al. 2021); moreover, we analyzed the top-ranked poses for the complexes predicted by SwissDock according to the FullFitness and ΔG scores provided by the program as explained in the Results and Discussion section and realized the 2D protein–ligand interaction diagrams shown in Fig. 4 by the software Discovery Studio 2021.

Prediction of pharmacokinetic properties and vapor pressures

The logarithms of the partition coefficients (cLogP), blood–brain barrier (BBB) permeability, pan-assay interference compounds (PAINS) score, and druggability properties shown in Table S3 were predicted for the four Mediterranean plant VOCs by SwissADME (http://www.swissadme.ch/index.php accessed on July 8, 2021). Vapor pressures (at 20 °C) were calculated by UManSysProp http://umansysprop.seaes.manchester.ac.uk/tool/vapour_pressure (accessed on July 8, 2021), using the 'Nannoolal 2008' vapor pressure method and the 'Joback and Reid 1987' Boiling point method. BBB permeability properties predicted from SwissADME were compared with those calculated by LightBBB (http://bioanalysis.cau.ac.kr:7030/ accessed on July 8, 2021).

Results and discussion

Comparison of COVID-19 impact in Italian regions with different forest cover areas in winter-spring 2020 and autumn 2020-spring 2021

Comparing data reported for the pandemic impact on Italy during the critical period of the first year (i.e., winter 2020-spring 2020) with those corresponding to the period ranging from autumn 2020 to spring 2021, we noticed that COVID-19 impact increased in the entire country, including the Mediterranean regions of Italy during the second year, as it can be observed by the higher numbers of COVID-19 victims (both absolute numbers and normalized values) and test positivity rates (Table S1, Fig. 2), but it was still possible to observe a more favorable trend in the Mediterranean forest-rich areas (with ≥ 0.34 forest hectars/capite).

Comparing the number of COVID-19 fatalities with rates of forest area per inhabitants in the different Italian regions (Table S1), we found there to be generally less victims in the regions having ≥ 0.34 hectares of forest/number of inhabitants. Interestingly, all the Italian regions which recorded from the beginning of the pandemic to date (as of May 17, 2021) less than 2,500 COVID-19 fatalities (Table S1) are endowed with about an acre of forest per capita or more (Table S1). Normalizing the number of victims by total population, we observed that 6 out of 9 regions with ≥ 0.34 hectares of forest/number of inhabitants presented a COVID-19 deaths/total population rate lower than the median value for the country (0.21%). If one exclude in this estimation the

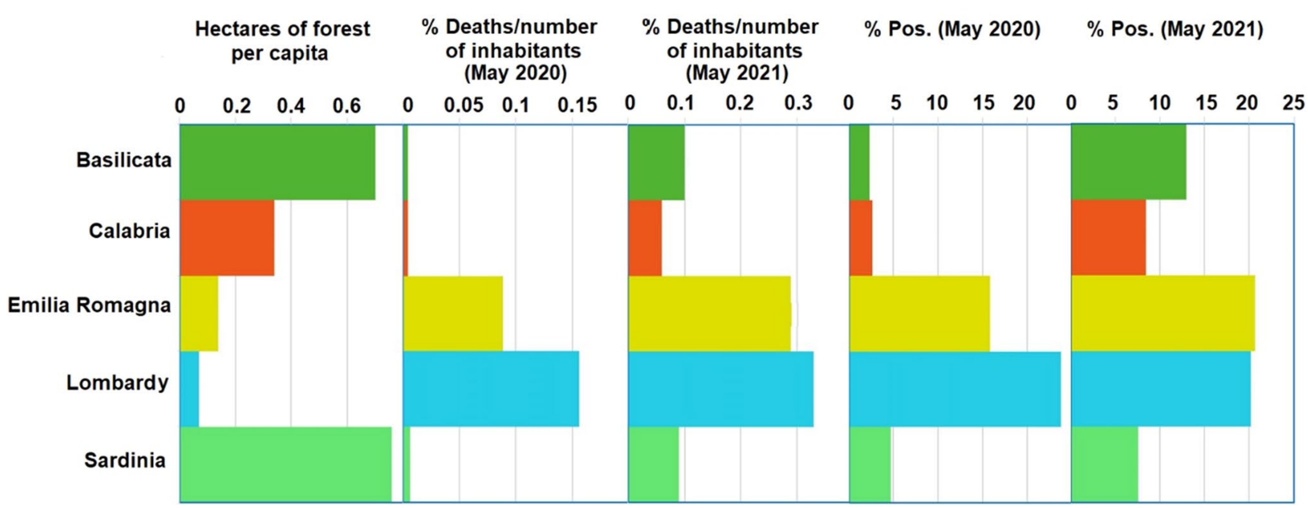

Fig. 2 Bar graphs showing the forest coverages per capita (left) as well as some parameters (mortality and test positivity rates [abbreviated as % Pos.]) useful to describe the COVID-19 impact during the first and second year of pandemic on local populations within five representative regions of Italy. Note the higher coronavirus impact on regions like Emilia Romagna and Lombardia which have less than 0.2 hectares of forest per capita when compared to the significantly more favorable situation within the regions where the above ratio was higher than 0.34 hectares/inhabitant

forested regions of North Italy, where Mediterranean vegetation is uncommon, 100% (6 out of 6) green regions have a normalized COVID-19 mortality less than 0.21%.

Interestingly, the three Italian regions with the lowest mortalities due to COVID-19 (0.06–0.10% COVID-19 deaths/total population rates, Fig. 2), i.e., Sardinia, Calabria and Basilicata, are Mediterranean Italian regions with high ratios of hectares of Mediterranean forest/number of inhabitants: 0.76, 0.34 and 0.70, respectively. Examining the same aspects for northern Italy, we found that Lombardy, having the lowest forest area per capita within northern Italy, was not only the region with the highest number of COVID-19 victims (higher than 33,000, Table S1), but it also had one of the highest rates of test positivities (higher than 20%, Table S1 and Fig. 2). Within the greener northern regions, this rate (18.8–22.0%) was similar to that found for Lombardy and significantly higher than the greener regions of southern and insular Italy (7.1–13.0%, Table S1). As an example, South Tyrol (~520,000 inhabitants, northern Italy) is endowed with a forest area per capita (~0.7 Ha/person) similar than Basilicata (~560,000 inhabitants, southern Italy), but a ~2 times higher COVID-19 mortality rate and also a significantly higher test positivity rate for both years of pandemic (Table S1). This could be associated with several environmental factors including differences in latitude, proximity to coast, climate and the local diet. Nevertheless, as we hypothesized in our previous work, the Mediterranean vegetation present in the southern and insular regions of the country could be playing a protective role. Interestingly, Aosta Valley, despite a very high ratio of hectares of forest (but with a large predominance of winter-dormant deciduous trees)/number of inhabitants (0.89 Ha/person), presents a COVID-19 death rate per total population (0.38%) that is more than 6 times higher than that of Calabria (0.06%, Table S1).

Peculiar features including proximity to the coast of the largest cities, particularly mild weather, presence of cultivated areas with Mediterranean orchards and Mediterranean wild shrubland with promising effects on air pollution mitigation, could all account for the favorable outcome of Calabria and other forested Mediterranean regions of Italy.

Comparison between Aosta Valley and Sardinia forest compositions, COVID-19 impact, population density and median age

Forest-rich regions are generally scarcely populated, and thus, we wondered if lower COVID-19 impact observed on regions like Sardinia, Calabria and Basilicata was merely a question of low population density. To this scope, we compared in more detail the data of Aosta Valley and Sardinia, as representative regions. The former is a northern (not-Mediterranean) region, rich in forests formed prevalently by deciduous trees, with the lowest population density of Italy, and a median population age lower than other Italian regions including Sardinia, with this latter being, instead, a Mediterranean region of insular Italy, endowed with evergreen Mediterranean forests dominated by *Quercus ilex L.* and *Quercus suber L.* Interestingly, Sardinia has a population density ~ two times than that in Aosta Valley, and thus, one expects that transmission of SARS-CoV-2 was more probable in Sardinia (but also in Calabria and Basilicata following a similar reasoning) than Aosta Valley considering the population density (Fig. 3). On the other hand, Aosta Valley population is younger than that of Sardinia, and thus, COVID-19 mortality, generally higher in case of older patients, could be expected more significant for Sardinia. However, in both pandemic waves under investigation, COVID-19 impact was always higher in Aosta Valley than Sardinia (Fig. 3).

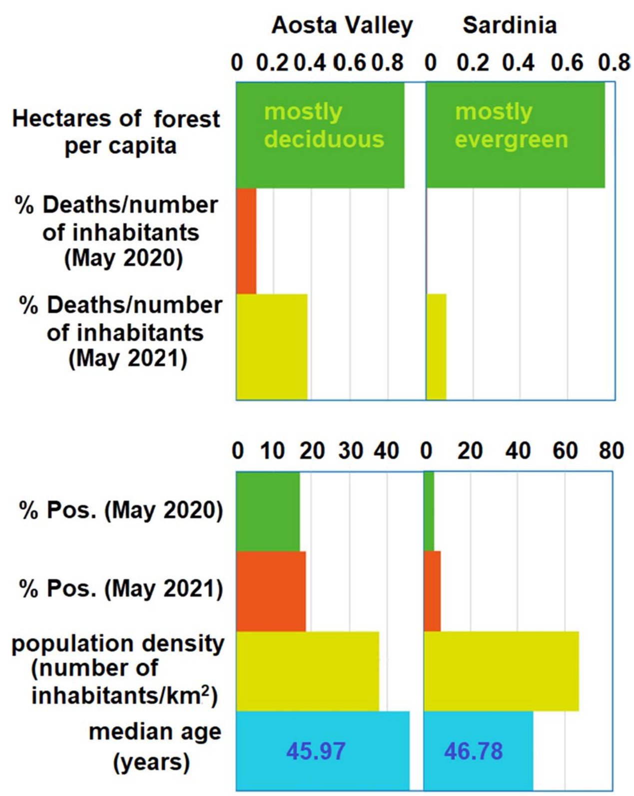

Fig. 3 Bar graphs showing the abundance of forest areas as well as some parameters useful to describe the COVID-19 impact on populations of Aosta Valley and Sardinia. These include the percentage of COVID-19 fatalities/number of inhabitants (data as of May 2020 and May 2021, upper panel) and the test positivity rates (abbreviated as % Pos., data as of May 2020 and May 2021, lower panel). Note the higher coronavirus impact on Aosta Valley which has high forest coverage with mostly deciduous trees when compared to the significantly more favorable situation of Sardinia, where the territorial forestal coverage is dominated by evergreen species, notwithstanding the higher local population density and median age

Thus, we suggest the importance of environmental protective factors in Sardinia, and more in general in Mediterranean areas of Italy and possibly other countries, like:

- Climate/higher sunlight exposure at lower latitudes. Sunlight exposure is important for vitamin D production in human body and UV antiviral action with a protective role against COVID-19 (Carleton et al. 2021; Radujkovic et al. 2020);
- Mediterranean diet (rich in polyphenols and phytochemicals that could exert protective effects)(Maiorino et al. 2020);
- Abundance in southern and insular Italy of Mediterranean plants (both cultivated and spontaneous trees/shrubs) and their emitted biogenic VOCs, immunomodulatory and antiviral volatile molecules, inhaled all year round (Roviello and Roviello 2021).

In this context, it should be noted that several plants belonging to the class of Mediterranean vegetation such as the holm oak (*Quercus ilex* L.), particularly abundant in Sardinia, and other evergreen trees, are able to cleanse the atmosphere trapping polycyclic aromatic pollutants (Sgrigna et al. 2015; Gratani and Varone 2013; Fellet et al. 2016) and that air quality improvement achieved by forests decreasing concentrations of particulates and other pollutants can also contribute to reducing the pandemic impact (Fares et al. 2020).

Mediterranean trees as sources of biogenic volatile organic compounds with immunomodulatory and antiviral activities

To collect information on the utility of inhaling plant-emitted volatile organic compounds (VOCs) for their immunomodulatory and antiviral properties, we performed a literature research and found that the practice indicated in Japan as 'forest bathing'(Mao et al. 2012), consisting in visiting a green area walking under the canopy of trees to obtain health benefits, especially on the body immune system (Li 2009), has effects that can last for more than 7 days after the trip (Li et al. 2008). The VOCs benefits on human immune function were scientifically proven and quantified including the increase in natural killer (NK) activity, with consequent effects against virus-infected cells (Li 2009). Moreover, several biogenic VOCs and in particular some volatile terpene compounds emitted by trees elicit an anti-inflammation response on respiratory system reducing airway inflammation (Kim et al. 2020).

Additionally, plant VOCs have been shown to have anti-asthmatic activity, (Kim et al. 2020), beneficial properties in case of chronic obstructive pulmonary disease and asthma (Worth and Dethlefsen 2012; Juergens 2014), and lung inflammation (Chen et al. 2014). In particular, α-pinene was effective for treatment of allergic rhinitis (Nam et al. 2014), while limonene and linalool have immunomodulatory and anticancer properties (Jin et al. 2008; Chiang et al. 2003; Zhao et al. 2021). Even though the literature on the benefits of isoprene on human health is scarce, this VOC is one of the most powerful plant-emitted antioxidants, and in plants, it stabilizes cells by protecting cell membrane by quenching ozone (Jin et al. 2008). In general, biogenic VOCs are emitted in larger amounts by trees during spring and summer than during fall and winter. However, significant amounts of these bioactive compounds are detectable in Mediterranean ecosystems during the cold season. For example, β-caryophyllene winter emission from *Cistus monspeliensis* L. is similar to that found during spring and ~ 6 times higher than summer (Rivoal et al. 2010). Among the Mediterranean trees, the Mediterranean oak, i.e., *Quercus ilex* L. (also known as holm oak), is a strong monoterpene emitter able to release in the air a considerable number of biogenic VOCs (Owen et al. 2001). Besides the most common VOCs, such as isoprene, α-pinene, linalool and limonene, numerous other volatile compounds are found in lesser amounts in Mediterranean plants (D'Auria and Racioppi 2015).

Remarkably, Mediterranean vegetation emits biogenic VOCs able to bolster human immune system but is also a source of compounds with antiviral and virucidal potential. Thus, Mediterranean plants of culinary use find application in the herbal medicine of different countries to treat numerous disorders including viral infections (Loizzo et al. 2008). More in detail, *Laurus nobilis* L oil, rich in VOCs like α -pinene, β -pinene, β-ocimene, and 1,8-cineole, is endowed with antiviral activity against SARS-CoV-1 (with an IC_{50} of 120 µg/ml and a selectivity index of 4.16) (Loizzo et al. 2008), thus gaining great attention in regard to its potential therapeutic use against the genetically similar SARS-CoV-2. Other Mediterranean plants have antiviral potential, such as *Onopordum illyricum L.* that shows activity against human immunodeficiency virus 1 (HIV-1) (Sanna et al. 2018), and *Daucus virgatus* that is active against RNA viruses like *Coxsackievirus B* (Snene et al. 2017).

In silico studies on ACE2-RBD complex binding by isoprene, α-pinene, linalool and limonene

From a molecular point of view, plant-derived compounds can act as antivirals by interfering with virus-relevant proteins, blocking, for example, the viral (RNA or DNA) polymerase, several proteases, or modulating the host–virus biomolecular recognition processes at the origin of the infection.

Owing to SARS-CoV-2 infection, a powerful biomedical strategy for viral inhibition consists in the blockade of the proteins responsible for the coronavirus entry into human cells. In particular, receptor binding domain (RBD) of SARS-CoV-2 spike protein, playing a critical role in virus and human angiotensin-converting enzyme 2 (ACE2) receptor fusion, is a very relevant target for SARS-CoV-2 inhibition. More in general, inhibiting the overall RBD-ACE2 interaction is a valid anti-COVID-19 therapeutic approach to decrease SARS-CoV-2–host cell binding, cellular internalization or release of the pathogen (Unal et al. 2021).

Considering that Mediterranean forests release the four representative biogenic volatile organic compounds (VOCs) isoprene, α-pinene, linalool and limonene, whose emission is significant especially in periods like fall during which COVID-19 impacts heavily populations, we explored by molecular docking the interaction of these molecules with RBD-ACE2 complex (Protein Data Bank [PDB] ID: 6M0J), evaluating the predicted affinities for the protein target of these biogenic compounds in comparison with a reference compound (ellagic acid). In fact, examining the affinity of a given ligand for the 6M0J structure is typically used to evaluate its effect on both the SARS-CoV-2 spike and human ACE2 binding (Unal et al. 2021). Thus, we analyzed the putative best docking poses for the top-ranked complexes corresponding to the most favorable FullFitness (Fig. 4a, b) and ΔG (Fig. 4c) scores. More in detail, we first compared the top-ranked poses for the biogenic VOCs in complex with RBD-ACE2 according to the EADock FullFitness function, which takes into account realistic solvent models (Grosdidier et al. 2007). Therefore, we found that (Table S2, Fig. 4a) the predicted affinities for the four compounds were similar to that found by us for the reference compound (with binding energies being of about -6 kcal/mol in all cases), which was also close to the previously reported score for the same molecule in complex with spike protein (Gowrishankar et al. 2021). In particular, among the four plant compounds, linalool emerged as an interesting potential inhibitor of SARS-CoV-2 infection as, in our simulation, it bound with the highest affinity (showing both the lowest ΔG value and the most favorable FullFitness score) the receptor binding domain of spike protein (Fig. 4), potentially preventing, thus, virus–host ACE2 receptor binding and consequent cellular internalization/release of SARS-CoV-2. Interestingly, isoprene seemed to preferentially

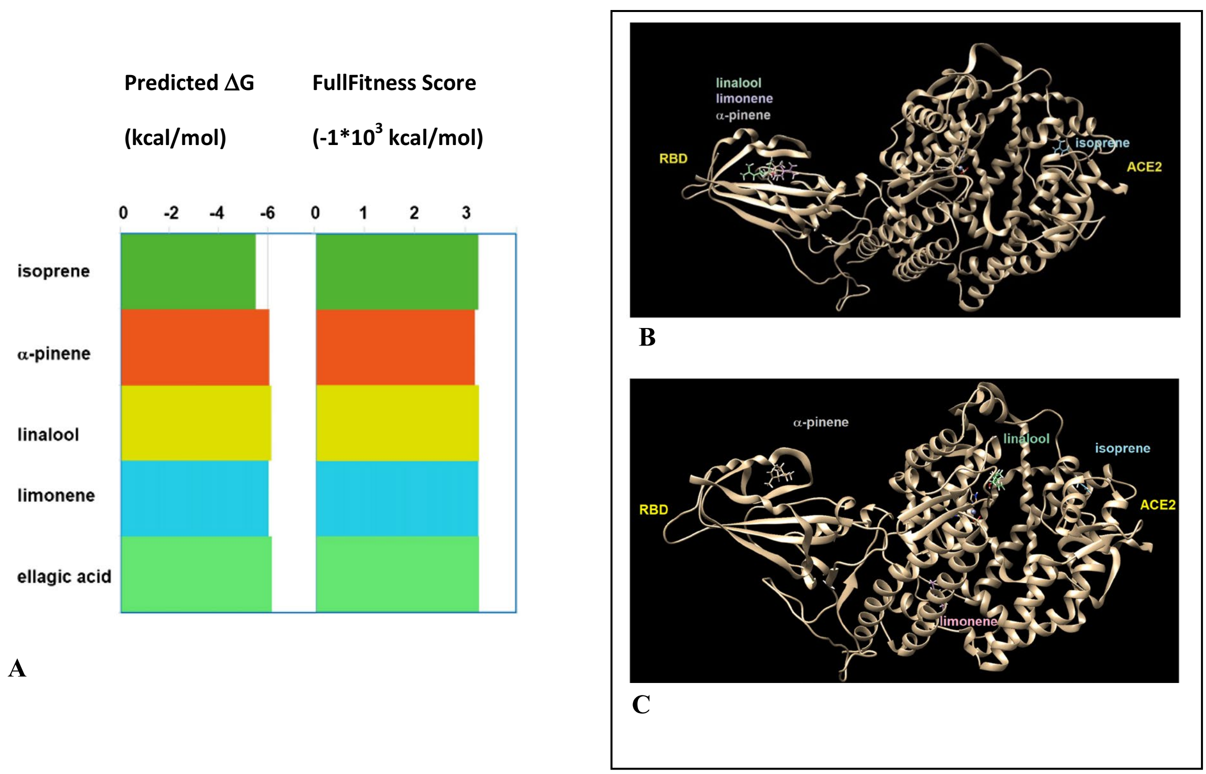

Fig. 4 Molecular docking studies: bar graphs (A) showing predicted ΔG (Gibbs free energy change) and FullFitness scores for the protein–ligand interaction with the four investigated plant volatile organic compounds (VOCs) and the ACE2-RBD (human angiotensin-converting enzyme 2-virus spike receptor binding domain) complex in comparison to the reference compound (ellagic acid). Putative best docking poses for the top-ranked complexes corresponding to the most favorable FullFitness (B) and ΔG (C) scores. Note how plant VOCs and reference ligand are endowed with similar scores, and that according to both ΔG and FullFitness isoprene shows a higher affinity for human receptor ACE2, α-pinene preferentially bind to virus spike receptor binding domain, while linalool and limonene have a comparable tendency to interact with both the protein target domains, with the latter compound being able to bind in the region at the interface between ACE2 and receptor binding domain (C)

bind the human ACE2 portion of the RBD-ACE2 complex (Fig. 4b and c). In fact, according to both complex selections based on ΔG and FullFitness scores, this VOC showed a higher affinity for human receptor angiotensin-converting enzyme 2 than spike, while α-pinene preferentially bound to virus spike receptor binding domain according to both the scoring criteria. On the other hand, linalool and limonene showed a comparable tendency to interact with both the host and virus domains, with the latter VOC being able to bind also the receptor region at the interface between ACE2 and receptor binding domain (Fig. 4c). Remarkably, the anti-infective effect of the Mediterranean plant compounds could be also synergistic, involving, i.e., several VOCs that bind contemporarily ACE2 and/or receptor binding domain in analogy to other studies involving volatile compounds isolated from the Asian evergreen plant *Melaleuca cajuputi* (My et al. 2020). In summary, as shown in Fig. 4, isoprene was predicted by us to bind ACE2 in the ACE2-RBD complex and could thus interfere with the SARS-CoV-2 binding and consequently with the overall infection process by potentially decreasing ACE2 interaction with viral receptor binding domain allosterically. For its part, α-pinene preferentially bound virus receptor binding domain potentially preventing virus recognition of human ACE2. Overall, we hypothesize a synergistic protective effect of Mediterranean plant compounds covering the entire SARS-CoV-2 infection process (corresponding to the interactions with spike receptor binding domain, ACE2 and their interface).

When the highest binding affinity VOCs/ACE2-RBD dockings were examined in detail (Fig. S1), α-pinene showed a certain affinity against residues of the spike receptor binding domain via hydrophobic interaction with 3 L-amino acid residues (phenylalanine 342, leucine 368 and phenylalanine 374), and as well as 6 van der Waals forces. In case of isoprene, we observed hydrophobic interactions with human ACE2 leucine residues 156, 266, 278 and 281, and potential van der Waals interactions with 11 residues (Fig. S1). Moreover, in our prediction limonene formed hydrophobic interactions with leucine 95 and 12 van der Waals forces, while linalool formed hydrophobic interactions with leucine 410 and isoleucine 446, seven van der Waals interactions and two H-bonds, acting as H-bond donor to glutamic acid 406 (1.89 Å) and as an acceptor to serine 409 (2.84 Å), interactions which all explained the stronger interaction of linalool with the ACE2 (Figs. 4c, S1).

Finally, we estimated in silico the vapor pressure values at 25 °C as well some pharmacokinetic properties of the four representative plant volatile organic compounds emitted by Mediterranean trees using the programs UManSysProp and SwissADME (Table S3) and found that all of them are assigned to the volatile class with vapor pressures ranging from 0.34 to 0.72 atm (that corresponds to Log vapor pressures ranging from −4.667 to −0.145, Table S3), with linalool being the less volatile of the four VOCs as we expected for its ability to participate to H-bonds.

Interestingly, for all compounds we predicted useful druglikeness properties, as well their ability to permeate blood–brain barrier (BBB), suggested by SwissADME for all but isoprene. However, when light BBB program was used to estimate BBB permeability, also this 5-carbons (C5) VOC resulted BBB permeable. No pan-assay interference compounds (PAINS) were found within the four examined compounds, excluding thus, that our compounds could be involved in a specific biomolecular processes in human body. Overall, our computational findings and the predicted druggability of the four Mediterranean plant-emitted volatile organic compounds all suggest their importance in realizing medical devices such as nasal sprays based on mixtures of these (and possibly other) plant biogenic VOCs to be used for preventing the SARS-CoV-2 infection. Moreover, clues about their ability to protect human body from the neurological complications of SARS-CoV-2 infection involving BBB (Erickson et al. 2021) emerge from the predicted BBB permeability of the biogenic volatile organic compounds-

Conclusion

We analyzed the impact of COVID-19 in different Italian regions and our findings seem to confirm our hypothesis on the relationship between the severity of the pandemic and certain environmental factors, such as air pollution and scarcity of non-deciduous vegetation. In the last months, COVID-19 had a much greater impact on Mediterranean regions of Italy where in winter/spring 2020 the effects of the pandemic were extremely limited. This demonstrates that SARS-CoV-2 eventually reached all parts of the country and that the still lower impact of the coronavirus observed during fall 2020/winter-spring 2021 in the Mediterranean forested areas when compared to other less green regions cannot be due to factors such as isolation or distance from the first outbreak of COVID-19 in Italy. A mere question of population density or median age could also be excluded by comparing the impacts of COVID-19 in the Aosta Valley and Sardinia and their respective statistical parameters.

Overall, since winter 2020, the lowest COVID-19 impact in Italy in terms of mortality was observed in three Mediterranean regions endowed with high rates of forest area per capita, sustaining the hypothesis that among the other environmental factors, the abundance of evergreen Mediterranean (both spontaneous and cultivated) vegetation could have played a role in the milder outcome of the virus. The Mediterranean vegetation emission of biogenic VOCs, taking place even during the ‘cold’ Mediterranean season, bolsters the human body’s immunity and potentially prevents virus infection when these compounds are inhaled, thus aiding in the protection of Mediterranean populations against SARS-CoV-2. Of course, at southern latitudes, other factors such as a milder climate, lower air pollution, higher average sunlight body exposure and a Mediterranean diet which is rich in foods containing phytochemicals with potential antiviral and virucidal activities could have all contributed in the partial defense observed during the second year of the COVID-19 pandemic.

However, in our opinion, practices utilized through 'green prescriptions'(Ulmer et al. 2016; Hamlin et al. 2016) like 'forest bathing'(Hansen et al. 2017) especially in evergreen forests should be taken into more consideration by governments worldwide and officially prescribed around the world to bolster the immune system and to prevent viral infections. It goes without saying that walking under the canopy of evergreen trees is certainly healthier than staying at home (often adopting unhealthy dietary behaviors (Zhang et al. 2021) and abandoning any physical activities (Pons et al. 2020)) for long periods as has been required by lockdown measures during the most critical phases of the pandemic. In our opinion, medical devices such as nasal sprays, which contain mixtures of plant VOCs, could be ideated and evaluated for their use as immunomodulatory and preventive weapons against the SARS-CoV-2.

Our study ultimately highlights the importance of forest preservation, especially those formed by evergreen species, and suggests that where Mediterranean forests are not present, deciduous plants and their higher levels of VOC emissions in late spring/summer could concur with determining the observed seasonality of COVID-19 (Merow and Urban 2020) and the correlated lower impacts of the coronavirus during these seasons.

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Declarations

Conflict of interest The author declared that there is no conflict of interest.

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