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Screening of Phytoresources from the Romanian Flora with medical applications against Covid - Review

Review Article

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Abstract

Plants are an important means of combating numerous harmful influences on humans (microorganisms, viruses, fungi, etc.) and have always been used to treat various diseases. The most recent pandemic was caused by the coronavirus characterized by a high replication capacity, which led to the improvement of viral fitness. In the context of the Covid pandemic, interest in the use of plants has increased. Great importance has been given to screening plants' potential against Covid (antiviral, anti-inflammatory, immunostimulatory, and antioxidant). According to recent research, many of the plant species used against Covid are of Asian origin. In this review, we aim to discuss the plant species with these medicinal potentials, focusing on Romanian Flora, which is one of the most important European sources of wild medicinal plants. We have listed a total of 50 Phyto-resources from Romanian Flora with different potentials: 26 containing the confirmed anti-covid compounds, and 10 species having all the therapeutic anti-Covid potentials (antiviral, anti-inflammatory, immunostimulant, and antioxidant potentials). *Allium sativum, Matricaria recutita, Solidago virgaurea, Capsella bursa-pastoris, Sambucus nigra, Ocimum basilicum, Origanum vulgare, Malva sylvestris, Chelidonium majus, Plantago lanceolata* are the most important due to their compounds which offer the anti- Covid, anti-inflammatory, immunostimulant, and antioxidant potentials. In the case of these species of interest, it is necessary to introduce them to both conservation and sustainable use programs, through the biotechnological techniques.

Keywords: Biotechnology, Conservation, Immuno-modulatory, Pandemic, Secondary metabolites, Traditional medicine.

Introduction

Throughout human history, plants played important roles in medicine, treating various diseases, and contributing to drug manufacturing (1). World Health Organisation supports and encourages countries to provide traditional remedies, by publishing diverse guidelines concerning medicinal plants (2,3,4).

Natural products showed eloquent roles in the recovery during viral infections (SIDA, Ebola, Influenza, Enterovirus, Zika, Hepatitis B and C, Swine flu, and Bird flu) with little or no harmful effects (5).

Coronavirus Disease 2019 (Covid-19) represents the most recent pandemic that raised new issues regarding infections and also strengthened research on the classical and plant-based treatments of viral infections. Coronaviruses are a diverse group of RNA viruses that infect many different animal species, causing respiratory infections in humans. Starting with SARS-CoV (in 2002) and MERS-CoV (in 2012) highly pathogenic coronaviruses (with zoonotic origin) which are causing fatal respiratory illnesses in humans, coronaviruses have become an important public health problem in the 21 century (6). The genome of the SARS-CoV-2 is similar to other coronaviruses (7). Replication in many hosts leads to mutations across the SARS-CoV-2 genome, the majority being silent, others producing variants with a higher human ACE-2 receptor binding affinity, improving viral fitness. These new variants can present increased infectivity and/or transmissibility, viral replication, pathogenicity and reinfection risk, immune response evasion due to alteration in epitopes recognised by nAbs, and/or decreased T cell immunity (8,9).

Since 2003, during the SARS outbreak, plant-based treatments have proven effective in controlling contagious diseases. Liu et al., 2011 (10) suggested that combining herbal medicines with conventional therapy and applying low doses of drugs such as corticosteroids, may improve the quality of patients' life, reducing the chances of deep lung infiltration. Until now, the most used herbal species against Covid-19 over the world are

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of Asian origin, for instance, *Astragalus mongholicus* Bunge, *Atractylodes lancea* (Thunb.) DC., *Atractylodes macrocephala* Koidz., *Lonicera japonica* Thunb., *Forsythia suspensa* (Thunb.) Vahl. (11), *Althaea officinalis* (L), *Hedera helix* (L), *Commiphora molmol* (Nees), *Glycyrrhiza glabra* L., *Sambucus nigra* (L), *Allium sativum* (L), *Andrographis paniculata* (Bum. F.) Nees, *Echinacea angustifolia* (DC.), *Echinacea purpurea* (L.) Moench, *Eucalyptus globulus* (Labill.) essential oil, *Justicia pectoralis* (Jacq), *Magnolia officinalis* (Rehder & Wilson), *Pelargonium sidoides* (DC.), *Salix* sp, *Zingiber officinale* (Roscoe), *Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk (12). The medicinal plants were screened for antiviral potential capacity. Bhuiyan et al., 2020 (13) found 219 medicinal plants have antiviral compounds from various compounds with different activities. Kim 2021 (14) summarised a list of anti-Covid compounds and extracts. Numerous research studies established a list of confirmed compounds from plants with inhibitory effects on Covid-19 (15, 16,17).

This review combines the published information on medicinal plants with anti-covid potential with a focus on Romanian flora.

Materials and Methods

A systematic literature search was conducted in different databases (Web of Science, PubMed, Scopus, ScienceDirect, ResearchGate) using search terms (e.g. Covid, allopathic treatment, Ayurveda, plant-based treatment, antiviral, antioxidant, immunomodulatory, medicinal plant, aromatic plant, secondary metabolites) to find the relevant articles. The results found were carefully reviewed to select more than 100 articles that were suitable according to our topic. Different databases of Romanian Flora (18,19,20,21) were checked to identify the plant species with potential curative/ preventive effects used in the therapy of viral infections. To verify the status of the selected plant species threatened degree in Europe, the European Environment Agency database was consulted. Databases like the Global Biodiversity Information Facility (22), and Native Plant Trust (23) were checked to identify the areas and habitats of the plant species of interest it.

Literature review

Available Covid-19 treatments

Until now, the recognized treatments for Covid-19 are the allopathic ones (Table 1), which were adapted regarding the severity of the illness or certain risk factors. The clinical presentation of the illness occurs in 2 phases, an early one characterized by SARS-CoV-2 replication (ante or soon after the onset of symptoms), and a second phase characterized by hyperinflammatory status, cytokines release, and disturbance in the coagulation process (24). According to these phases, there are several therapeutic options in use: antiviral medication and antibody-based treatments in the first phase and anti-inflammatory drugs and immunomodulating therapies in the second phase (25).

Table 1. The allopathic therapies used against Covid-19

Therapies	Name	Benefits
Antivirals	Hydroxychloroquine, chloroquine	None for patients hospitalized with severe Covid-19 (26)
	lopinavir/ritonavir, ivermectin, remdesivir, molnupiravir, paxlovid	No significant improvement in symptoms (27)
Immuno-modulatory Agents	Corticosteroids	For patients with severe/critical Covid-19 (28)
	Anakinra (IL-1 receptor antagonist)	Reduced the need for invasive mechanical ventilation and mortality in severe Covid-19 patients (29)
	Tocilizumab (anti-interleukin-6 receptor α receptor monoclonal antibody)	Severe or critical Covid-19 patients
	Sarilumab and Siltuximab (IL-6 receptor antagonists)	Improved survival (30)
Janus kinase (JAK) inhibitors	Baricitinib	Severe /critical illness (31)
	Ruxolitinib	No benefits overall in severe Covid-19 patients (32)
	Tofacitinib	Decrease the respiratory failure/ death risks [33]
SARS-CoV2 vaccine	Messenger RNA (mRNA) vaccines	>90% against the Wuhan strain, at 5-6 months follow-up after the second dose (34)
	Viral vector vaccines	65 - 91% efficacy against the Wuhan strain
	Inactivated and protein subunit vaccines	Novavax 89 - 91.6% efficacy; CoronaVac 55.0 - 82.1% against severe cases [35] BBIBP-CorV vaccine - 94.3% efficacy against symptomatic Covid-19 infection, 60.5% against hospitalizations, 98.6% against death of patients (36)

Antivirals are more effective as they are administered earlier in the disease, preferably chosen from the first days of evolution; the benefit/risk ratio is higher as the patient has a higher risk of severe evolution. It was observed that the supplementation of different treatments with micronutrients and vitamins (vitamins D, and C) improves clinical recovery (37).

Taking into account the virus's versatility, more alternative treatments (ozone therapy - destroys the SARS-Cov2 capsid, being inactivated in the bloodstream; sun UV radiation - germicide; laser therapy - prolifically inactivates the coronavirus) are required (38).

At the same time, there is numerous research concerning plant-based treatments not only for prevention but also for treatment. Patel et al., 2021 (39) underlined that to be an effective therapy in the COVID-19 treatment, plant species should contain secondary metabolites with anti-inflammatory, antioxidant, and antiviral activities. Some of the plant-based therapies against Covid used in the world were summarised in Table 2.

Table 2. Some of the Plant-based therapies against Covid

Herbal mixture	Effects
Lianhuaqingwen (11 medicinal species)	Inhibitory effects and anti-inflammatory potential (40)
Shufeng Jiedu (8 medicinal plants)	Symptoms improvements (41)
Yupingfeng powder (*Astragalus mongholicus* Bunge, *Glycyrrhiza glabra* L., *Saposhnikovia divaricata* Schischk., *Atractylodes lancea* Thunb., *Atractylodes macrocephala* Koidz., *Lonicera japonica* Thunb., *Forsythia suspensa* (Thunb.) Vahl.	Preventive approach (42)
Sambucus javanica subsp. *chinensis* Lindl.	Decreased virus yield, plaque formation, and virus attachment (11)
The mixture of *Berberis integerrima* Mill., *Crataegus laevigata* (Poir.) DC., *Onopordum acanthium* L., *Quercus infectoria* Oliv.	Most active and caused 94% ACE inhibition (43)
Tribulus terrestris L. (cinnamic amides) *Cullen corylifolium* (L.) Medik., *Paulownia tomentosa* (Thunb.) Steud. (flavonoids), *Angelica keiskei* Ito. (chalcones)	Inhibitory effect of SARS-CoV PLpro (11)

Patel et al., 2021 [39] underlined that to be an effective therapy in the COVID-19 treatment, plant species should contain secondary metabolites with anti-inflammatory, antioxidant, and antiviral activities.

Phyto-resources from the Romanian Flora with medical applications against Covid

Romania is characterized by rich vegetation, due to its geographic position, climate, and diverse landscape. In the Romanian Flora are around 3450 vascular plant species (~ 30% of European Flora) (44). Of the total of 756 spontaneous medicinal plants evaluated, 126 species were included in the Red List, and more than 100 plant species are completely forbidden for collection (20). Romania represents one of the most important European sources of wild medicinal plants (45). Checking different databases of Romanian Flora (18, 19, 20, 21) we identified 37 plant species that contain the confirmed anti-Covid compounds, and 10 species having antiviral, anti-inflammatory, antioxidant, and antiviral activities (including anti-covid compounds). These species represent significant sources of secondary metabolites in the fight against covid. Of the total number of secondary metabolites (identified in plants over the world) with confirmed effects against Covid, 16 were found in plant species from Romania (see Table 3). While the compounds such as coumaroyl-tyramine, curcumin, desmethoxyreserpine, epicatechin-gallate, gingerol, oleuropein, lectins, punicalin, gallocatechin gallate, with confirmed inhibitory effects on Covid -19, were not found in plant species from Romania, apparently are found only in plant species from Asian regions.

The identified plant species represent great sources of secondary metabolites with antiviral, antioxidant, immunomodulatory, and anti-inflammatory capacities like polyphenols, flavonoids, vitamins, poly-carbohydrates, proteins, amino acids, and minerals. Table 3 presented some of the characteristic secondary metabolites (without total phenols, flavonoids, saponins, essential oils, vitamins, and alkaloids) that confer to plants the curative/preventive anti-Covid potentials.

Table 3. Romanian medicinal plant species with different therapeutic potentials.

Family	Plant species	Common name	Main compounds	Therapeutic potentials			
				Anti-viral/ Anti Covid19 compounds*	Immuno modulatory	Anti-inflammatory	Anti-oxidant
Anacardiaceae	*Cotinus coggygria* Scop.	Common smokebush	terpenes (46)	+/ Myricetin		+	+
Amaryllidaceae	*Allium sativum* L.	garlic	S-allyl-l-cysteine, diallyl disulfide, diallyl trisulfide, ajoene (47)	+/ Allicin	+	+	+

Apiaceae	*Heracleum mantegazzianum*	Giant hogweed	Angelicin, bergapten, imperatorin, marmezin, osthole, (+)-oxypeucedanin, pangelin, pimpinellin, psoralen, sphondin, umbelliferone, methoxalen (48)	+/-		+	+
	Pimpinella anisum L.	Aniseed	Methylchavicol, carvone, β-caryophyllene, estragole, limonene, anisaldehyde, coumarins, scopoletin, umbelliferone, α-cuparene, α-himachalene, β-bisabolene, p-anisaldehyde (49)	+/-		+	+
Asteraceae	*Achillea millefolium* L.	Common yarrow	Luteolin, apigenin (50)	+/ Quercetin, kaempferol,		+	+
	Arctium lappa L.	Greater burdock	Caffeoylquinic acid derivatives, lignans, caffeic acid, chlorogenic acid, cynarin (51)	+/ Lignan		+	+
	Artemisia absinthium L.	Artemisia	Thujyl alcohol esters, α-thujone, β-thujone, camphene, α-cadinene, guaiazulene (Z)-epoxyocimene, (E)-sabinyl acetate, (Z)-chrysantenyl acetate (52)	+/ Lignan, Quercetin		+	+
	Artemisia annua L.	Artemisia	Monoterpenes, sesquiterpenes, aliphatic compounds, coumarins (53)	+/ Quercetin, Flavonoids		+	+
	Calendula officinalis L.	Pot marigold	Carotenoids, triterpenic alcohols, calendic acid, polycarbohydrates, saturated, etheric oils (54)	+/		+	+
	Centaurea cyanus L.	Corn flower	phenylcarboxylic acids (55)	+/ Kaempferol, Naringenin			+
	Cichorium intybus L.	Common chicory	esculetin, esculin, cichorin, umbelliferone, scopoletin, triterpenoids, sesquiterpenoids, nitrogen-contained compounds, organic acids (56)	-/-	+	+	+
	Helichrysum arenarium L.	dwarf everlast	naringenin (57)	+/ Naringenin			
	Matricaria recutita L.	Chamomile	terpenoids, bisabolol oxides, bisabolone oxide, spathulenol, enyne-dicycloethers, chamazulene (58)	+/ Apigenin-7-glucoside	+	+	+
	Solidago virgaurea L.	Goldenrod	virgaureoside, leiocarposide, vanillic acid, gallic acid, caffeic, chlorogenic, ferulic, synapic, free aglycons, cyanidin derivatives, triterpene, sesquiterpenes (59)	+/ quercetin, kaempferol	+	+	+
	Taraxacum officinale Weber Wigg	Blowball	carotenoids, fatty acids, choline mucilage, pectin, sesquiterpene lactones, taraxasterol, taraxerol, chlorogenic acid (60)	+/ Flavonoids			+
Betulaceae	*Corylus avellana* L.	European hazelnut	3- and 5- caffeoylquinic acid, caffeoyltartaric acid, p-coumaroyltartaric acid, myricetin 3-rhamnoside, quercetin 3-glycoside, quercetin 3-rhamnoside, kaempferol 3-rhamnoside (61)	+/ Catechin, Myricetin			+
Brassicaceae	*Capsella bursa-pastoris* L.	Shepherd's purse	free fatty acids, acetylcholinesterase inhibitors (62)	+/ Quercetin, Hesperidin, Kaempferol	+	+	+
Caprifoliaceae	*Sambucus nigra* L.	Elderberry	chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, isoquercitrin, kaempferol-3-rutinoside, isorhamnetin-3-rutinoside, isorhamnetin-3-glucosid (63)	+/ Quercetin	+	+	+
Elaeagnaceae	*Hippophaë rhamnoides* L.	Sea buckthorn	carotenoids, essential fatty acids (64)	+/ Pedunculagin	+		+
Equisetaceae	*Equisetum arvense* L.	Common horsetail	triterpenoids (65)	+/-		+	+
Gentianaceae	*Centaurium erythraea* Rafn	Common centaury	Kaempferol, Naringenin (66)	+/ Kaempferol, Naringenin			+

Geraniaceae	*Erodium cicutarium* (L.) L'Hér.	Common stork's-bill	Tannins, hydroxycinnamic derivatives (67)	+/-		+	+
	Geranium robertianum L.	Herb Robert	Quercetin, rhamnetin (68)	+/- kaempferol		+	+
Hypericaceae	*Hypericum perforatum* L.	St John's wort	Hyperoside, rutin, hypericin, biapigenin, hyperforin (69)	+/ Myricetin, Quercetin, Kaempferol		+	+
Labiatae	*Thymus vulgaris* L.	Thymus	1,8-cineole, camphor, α-pinene, camphene, thymol (70)	+/-	+	+	
Lamiaceae	*Ajuga genevensis* L. *Ajuga reptans* L.	Upright Common bugle bugle	Polyphenolcarboxylic acids (71)	-/-		+	+
	Lamium album L.	White dead-nettle	Tannins, choline, glycosides, mucilage, iridoids, triterpenes, isoscutellarein derivatives, fatty acids (72)	+/ Scutellarein/ isoscutellarein		+	+
	Ocimum basilicum L.	Great basil	Linalool, 1,8-cineole, eugenol, methyl eugenol, methyl isoeugenol, thymol, methyl cinnamate, citral, camphor (73)	+/ Flavonoids	+	+	+
	Origanum vulgare L.	Oregano	Gentisic, chlorogenic, p-coumaric, rosmarinic acids, syringic, protocatechuic, homovanillic, hydroxybenzoic, caffeic acids, hyperoside, isoquercitrin, rutin, luteolin, apigenin, cirsimartin, diosmetin (74)	+/ Quercetin, Naringenin	+	+	+
	Prunella vulgaris L.	Common self-heal	Rosmarinic acid, ursolic acid, oleanolic acid, caffeic acids, tannins, prunelline (75)	+/	+		+
	Thymus glabrescens Willd.	Thimus	Thymol, γ-terpinene, p-cymene (76)	+/ Apigenin-7-glucoside, Catechin, Naringenin, Luteolin-7-glucoside		+	
Malvaceae	*Althaea officinalis* L.	Marsh mallow	Mucilage, hypolaetin-8-glucoside, caffeic, p-coumaric acid, coumarins, scopoletin, tannins, asparagine (77)	+/ Kaempferol, Quercetin	+	+	
	Althaea rosea Linn.	hollyhocks	3-O-β-D-glucuronopyranoside-8-C-β-D-glucopyranoside, kaempherol-3-O-β-D-rutinoside, kaempherol-4′-O-β-D-glucoside, kaempherol (78)	+/ Quercetin	+		+
	Hibiscus esculentus (L.) Moench	Common mallow	Carotene, folic acid, thiamine, oxalic acid (79)	+/ N-cis-feruloyltyramine			+
	Malva sylvestris L.		Malonate, malate, oxalate, fumarate, citrate, mucilages, pigments, fatty acids, halogens (80)	+/ Myricetin	+	+	+
Nymphaeaceae	*Nymphaea alba* L.	White waterlily	Ellagic acid, gallic acid, esters, aglycones of isokaempferide, apigenin, hydrolyzable tannins (81)	+/ Kaempferol, Quercetin, Naringenin			
Onagraceae	*Epilobium parviflorum* (Schreb) Schreb.	Small flower hairy willowherb	Tannins, steroids, triterpenoids, fatty acids (82)	+/ Myricetin		+	+
Papaveraceae	*Chelidonium majus* L.	Greater celandine	Berberine, chelerythrine, chelidonine, coptisine, sanguinarine, isorhamnetin-3-O-glucoside, chelidonic, malic, citric, succinic, histamine, tyramine, choline, nicotinic acid, lutein, violaxanthin, flavoxanthin, chrysanthemoxanthin (83)	+/ Kaempferol, Quercetin	+	+	+
Plantaginaceae	*Plantago lanceolata* L.	Ribwort plantain	Galacturonic acid, fatty acids, caffeic acid derivatives, iridoid glycosides, terpenoids, glucosinolates, organic acids (84)	+/ Luteolin-7-glucoside	+	+	+
Polygoniaceae	*Rheum palmatum* L.	Rhubarb	anthraquinones, anthrones, stilbenes, butyrophenones, chromones, tannins (85)	+/ Emodin		+	+

Ranunculaceae	*Caltha palustris* L.	Marsh-marigold	Tannins, γ-lactones of protoanemonin and anemonin, bitterness, choline, carotene, berberine (86)	-/-	+	+	
	Nigella arvensis L.	Wild fennel flower	Saponins, terpene (87)	+/ Hesperidin		+	+
Rhamnaceae	*Ziziphus jujuba* Mill.	Chinese jujube	Total phenolics, flavonoids (88)	-/-	+	+	+
Rosaceae	*Crataegus monogyna* Jacq.	Common hawthorn	Chlorogenic acid, epicatechin, hyperoside, rutin, vitexin, procyanidins (89)	+/ Quercetin, Catechin			+
	Potentilla anserina L.	Silverweed	Tannins (90)	+/ Myricetin	+		
	Rosa canina L.	The dog rose	Tannins, organic acids, pectins, carotenoids, fatty acids, carotenoids, tocopherols (91)	-/-	+	+	+
Solanaceae	*Capsicum annuum* L.	Chili pepper	Terpenoids, noncarotenoids, lipoxygenase derivatives, carbonyls, hydroxycinnamic acid, tannins, capsaicin, capsinoids (92)	+/ Luteolin-7-glucoside		+	+
Scrophulariaceae	*Verbascum phlomoides* L.	Orange mullein	Iridoid, phenylethanoid glycosides, neolignan glucosides, spermine alkaloids (93)	+/ Diosmin		+	+
Tiliaceae	*Tilia cordata* Mill.	Small-leaf lime	Arabinogalactans, eugenol, 2-phenylethanol, oligomeric proanthocyanidins, caffeic acid, hydroxylated coumarins (80)	+/ Kaempferol, Quercetin,		+	+

(*confirmed with inhibitory effects on COVID-19 (15, 16, 39).

Allium sativum, Matricaria recutita, and *Rheum palmatum* were recognized as important species with high benefits in medicine and are included in the WHO monographs.

According to Fedoung et al. 2021 (48), the plant species that have been used to manage at least 3 common symptoms of Covid-19 are a potential source of anti-Covid-19 molecules. It is well known that a single plant species may have multiple pharmacological properties. The plant's secondary metabolites could be used to treat symptoms like fever, coughing, etc., or for boosting immunity in Covid-19 patients (95). In this context, these 10 plant species may present a potential for prevention or therapy against viruses including Covid.

Of the multitude of Romanian Flora analyzed, only 29 species meet 3 (different) of the 4 interested potentials (antiviral, anti-inflammatory, immunostimulant, antioxidant), and most of them belong to Asteraceae and Lamiaceae families (Table 3). All 4 interested potentials were found in 10 plant species, 37 plant species contain the confirmed anti-Covid-19 compounds and 10 plant species are the most important containing all 4 potentials and confirmed anti-Covid-19 compounds (see Table 3).

The antiviral compounds were classified into alkaloids (block virus binding growth and reduce the viral titers), polyphenols (inhibit the viral entry), proteins and flavonoids (inhibit viral integration, replication, reverse-transcriptase, and viral protein synthesis), lectins (inhibit viral penetration, reverse-transcriptase), terpenes (inhibit viral replication), polysaccharides (inhibit viral replication and viral binding to cells) (96). There are numerous studies concerning the main compounds of plant species with potential curative effects against Covid (see Table 3).

Plant biotechnology in the pandemic context and future recommendations

In the actual pandemic context, the interest in plant biotechnology has grown. For more than 30 years, plants were used for the production of different pharmaceutical molecules [97]. An increased quantity of secondary metabolites may be obtained in a rapid and eco-friendly way using biotechnology. Plant-based vaccine production has the advantages of low cost, fast production, easy administration, and safety [98]. In this way, target proteins for diagnostic reagents, antibodies, and antiviral proteins for therapeutic use may be produced in molecular farming through plants. An EU consortium is developing plant-based platforms to produce medical, veterinary, and diagnostic products, to deal with different diseases, including Covid-19 [99]. Different biotechnology companies, from Europe and USA, are producing antigens based on a SARS-CoV-2 protein in tobacco plants (97). Also, *Nicotiana benthamiana* (relative to tobacco), plays an important role in order to produce of vaccines in large amounts.

Numerous discoveries related to pharmacology have been made to better management of Earth's biodiversity. Losing biodiversity has negative effects not only on humans but also on science by limiting the discovery of potential treatments for new infection agents. In the context of extensively requires for medicinal plants, the sustainable use of these species should be a priority.

To ensure wild resource sustainability, we have to increase the funding for science, promote scientists' collaboration, and enhance and implement botanical education, as well as the conservation measures required.

According to European Environment Agency, the selected species from Romanian Flora are mentioned in the IUCN list (22), as the least concern (most of them), not evaluated (8 species), and invasive species (4 species) at the European level. Due to their IUCN categories, these species have not been classified as priority species for conservation. Because of its various habitat types (arable land, fields, gardens, industrial, man-made/disturbed habitats, market gardens, parks, roadside, urban peripheries, and waste deposits), the selected species may be subject to anthropogenic impact (23).

There is no data at the European level concerning conservation programs for selected plants. Different conservation methodologies should be applied even if the plant species of interest are not endangered. To guide conservation activities, good knowledge about the distribution and biological/ecological characteristics must be known (99). Numerous international policies protect biodiversity from uncontrolled exploitation (100). Sometimes, protecting biodiversity may also discourage research to discover new metabolites. In this context, scientists, governments, and stakeholders must establish agreements to ensure the sustainable use of vegetal resources through plant protection. The Nagoya Protocol emphasizes access and benefit-sharing, considering the value and origin of the specimens collected (101).

There are numerous recommendations for medicinal plant conservation (102, 103). Wild nurseries and natural reserves represent two modalities for conserving plant species *in situ*, in their natural habitats. *Ex-situ* conservation is realized through botanic gardens and seed banks, which assure future replanting and also material for biotechnology research. Cultivation practice through good agricultural practices is also part of conservation strategies already applied (104) improving the active compounds yields, ensuring production stability and recovery in the wild (due to reducing the harvest from the wild), and decreasing the prices of secondary metabolites production (105). *Ex-situ* conservation through *in vitro* techniques was wildly applied to the conservation of medicinal plants (106).

After more than 2 years of the pandemic, and a lot of research concerning the effect of different secondary metabolites (on the virus, on the immune system) there are still lots of aspects to be cleared. Natural plant compounds are essential for the existence of humans. There are countries that encourage the use of traditional medicine in the prevention of Covid (107).

Conclusions and perspectives

We revised the Romanian Flora based on a literature screening for the possibility of discovering plant species that have a curative/preventive potential against Covid-19. The literature search revealed that 37 species of Romanian flora have secondary metabolites with proven effects on Covid-19, 10 of them having antiviral, anti-inflammatory, immunostimulant, and antioxidant potential. *Allium sativum, Matricaria recutita, Solidago virgaurea, Capsella bursa-pastoris, Sambucus nigra, Ocimum basilicum, Origanum vulgare, Malva sylvestris, Chelidonium majus, Plantago lanceolata* are the most important due to their compounds which offer the anti- Covid, anti-inflammatory, immunostimulant, and antioxidant potentials. Further studies on the therapeutic potential of plants, alone or in combination with antiviral therapy, as well as on the effective dosage and toxicity of the different plant extracts commonly used are needed.

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