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The role of medicinal plants in the treatment of Coronavirus infections

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Abstract

The coronavirus family consists of numerous species that cause respiratory and gastrointestinal infections in vertebrates, but some members such as SARS, MERS, and SARS-CoV-2 are particularly dangerous to humans. So far, SARS-CoV-2 is confirmed in 636.440.663 patients worldwide, and it is responsible for 6.606.624 deaths. Plants possess a number of chemical constituents, which act as inhibitors of viral proteins and can be used in the treatment of viral diseases, with a lower rate of virus resistance. The retrospective investigation covered a period of 27 years, from 1995 to 2022 and it is implemented through the analysis of results from previously reported studies focused on alternative anti-coronavirus agents. The total of 73 plant species from 46 families, with reported anti-coronavirus activity, was noted. Considering the number of species with anti-coronavirus effects, the most prevalent family was *Fabaceae* with 9.59%. Many bioactive compounds were secondary metabolites, and the vast majority was isolated from leaves. The anti-coronavirus activity of plant products was recorded against six coronaviruses: SARS-CoV, SARS-CoV-2, MERS-CoV, BCV, HCoV-OC43, and HCoV-NL63. Among the mechanisms of antiviral action, the inhibition of 3-chymotrypsin-like protease, 3Clpro was frequently described. This study illustrated the high potential of plants and their products in terms of anti-coronaviral compounds. Since viruses represent molecular pathogens, with high mutations range as well as resistance to synthetic antiviral drugs, a novel investigation should be oriented towards the isolation and characterization of efficient antiviral agents of natural origin.

Keywords: coronaviruses, SARS-CoV-2, medicinal plants, herbal medicine.

1. Introduction

Coronaviridae (*Nidovirales*) is a large family of viruses that could be divided into two subfamilies: *Coronavirinae* and *Torovirinae* [1]. Subfamily *Coronavirinae* contains two genera restricted to mammals and causing respiratory illnesses (*Alphacoronavirus* and *Betacoronavirus*), while *Gammacoronavirus* and *Deltacoronavirus* occur in both birds and mammals [2]. *Torovirinae* includes genera *Torovirus* and *Bafinivirus*, isolated from humans, cattle, pigs, sheep, goats, and horses [3]. Coronaviruses are single-stranded positive-sense RNA viruses with a genome of around 30 kb [4]. Some members of the *Coronaviridae* family are particularly dangerous to humans since they cause severe respiratory disease and also have pandemic potential. Such members are SARS-CoV (SARS-associated coronavirus) the causative agent of the severe acute respiratory syndrome, MERS-CoV (Middle East Respiratory Syndrome coronavirus), and novel coronavirus SARS-CoV-2 responsible for the ongoing pandemic of coronavirus disease (COVID-19). This pandemic originated in Wuhan (China) in 2019 and so far, led to 6.606.624 cumulative death cases worldwide [5].

Antiviral drugs are a specific class of medicines, used for the treatment of viral infections. Since the viruses use the host's cell for replication, the design of a safe and effective antiviral drug is challenging [6]. Natural compounds with a broad spectrum of antiviral activity are involved in the treatment of SARS, MERS, and other non-coronaviruses, due to their ability to inhibit multiple steps in the viral infective and replication cycle. Events like the COVID-19 outbreak increase the usage of medicinal plants and their products in the prevention and treatment of viral infections [7]. The main goal of this study was to examine the features and importance of phytotherapy in the prevention and treatment of infections caused by coronaviruses.

2. Material and Methods

2.1. Literature search

In this retrospective analysis, the results from previously reported scientific studies were used to achieve the stated goal. Relevant databases such as Web of Science, Scopus, PubMed, ScienceDirect (Elsevier), etc were used for searching natural compounds and medicinal plants with pharmacological activity against coronaviruses. To carry out the search, keywords such as coronavirus; COVID-19; medicinal plants; bioactive compounds; natural antimicrobials; spike protein; 3Clpro; PLpro; RNA-dependent RNA polymerase; Angiotensin-Converting-Enzyme (ACE) inhibitors; were used. The investigation of trends in the use of medicinal plants in the treatment of coronavirus infections covered a period of 27 years, from 1995 to 2022. This article represents an overview of the current knowledge about the anti-coronavirus properties of plants, herbal preparations, and individual compounds. There are many similar papers regarding the antiviral properties of medicinal plants against SARS-CoV-2 in particular, but this research refers to all members of *Coronaviridae* that are in some manner inhibited by plant products.

3. Results

Through the retrospective analysis of scientific studies published in relevant journals and other sources, a total of 73 plant species with recorded and confirmed anti-coronavirus activity were identified. The listed plant species by systematic affiliation include a total of 46 families.

3.1. Taxonomic designation

According to the number of species with anti-coronavirus activity, the most prevalent family was Fabaceae with a share of 9.59% (7 species), followed by Lamiaceae with 5.48% (4 species), Cupressaceae, Lauraceae, Solanaceae, Apiaceae, Scrophulariaceae, and Amaryllidaceae with 4.11% (3 species), as well as Taxaceae, Betulaceae, Polygonaceae, Meliaceae, Adoxaceae, and Asteraceae with 2.74% (2 species). The rest of the detected families were included in the final score with one species with anti-coronavirus properties (1.37%): Lessoniaceae, Cibotiaceae, Polypodiaceae, Brassicaceae, Resedaceae, Fagaceae, Moraceae, Menispermaceae, Rosaceae, Cannabaceae, Urticaceae, Vitaceae, Saururaceae, Ranunculaceae, Lythraceae, Myricaceae, Celastraceae, Hypericaceae, Anacardiaceae, Sapindaceae, Rutaceae, Rubiaceae, Zygophyllaceae, Acanthaceae, Gentianaceae, Celastraceae, Rutaceae, Linaceae, Oleaceae, Loranthaceae, Theaceae, Zingiberaceae (Figure 1.).

The vast majority of detected plants with anti-coronavirus properties were angiosperms (Magnoliophytina, Angiospermae), while the gymnosperms (=Coniferophytina, Gymnospermae) were less common. From the angiosperms, dicotyledonous plants were represented with 97%, and monocotyledons with 3%. In terms of life forms, the percentage of herbaceous plants was 56%, and woody plants 40%, of which 72% were deciduous and 28% were evergreen.In addition to higher plants (Cormophytes) *sensu stricto*, the list also included two plant species from the family Polypodiaceae (=Pteridophyta, ferns), and one species from the family Lessoniaceae (=Phaeophyceae, brown algae).

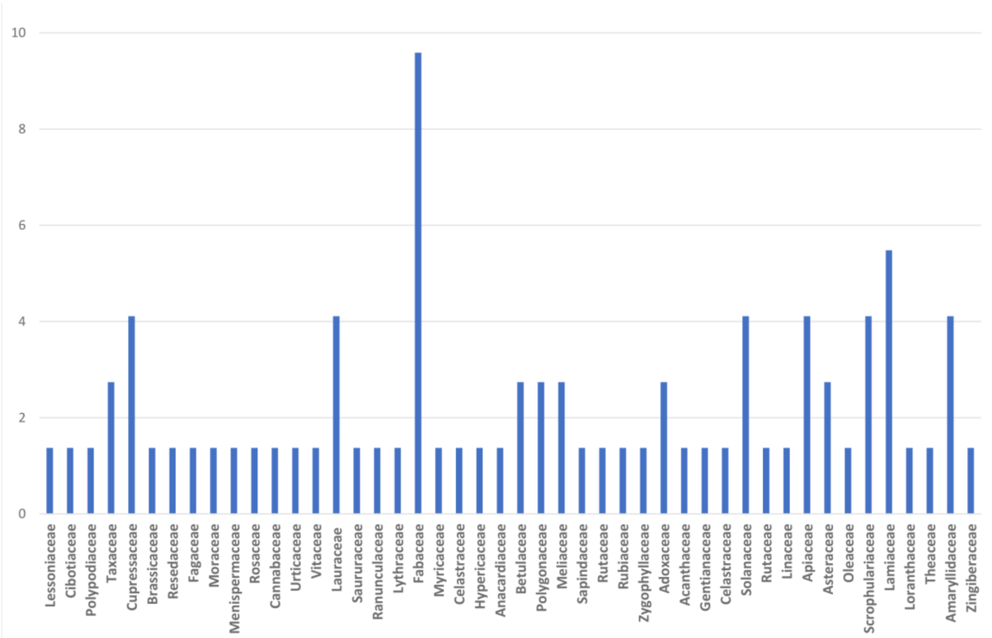

Figure 1. Systematic affiliation of detected plant species with anti-coronavirus activity

3.2. Bioactive compounds and mechanisms of antiviral activity

The largest number of bioactive substances with anti-coronavirus activity from the investigated plants were isolated from the leaves (25%), followed by the bark (18%), root and the whole plant (14%), fruit (12%), seed (10%), stem and flower (3%), and rhizome (1%) (Figure 2.).

According to the previous identifications, compounds responsible for the anti-coronavirus activity were chlorogenic acid, savinine, betulinic acid, luteolin, agglutinins, glycyrrhizin, myricetin, celastrol, pristimerin, tigenone, emodin, quercetin, herbacetin, lectins, glycosides, and lycorine. In addition to these, mangiferin, isomangiferin, astragalin, trifolin, homoharringtonine, amentoflavone, hinokinine, hydroxy-deoxycryptojaponol, thujopsene, sinigrin, hesperetin, papyriflavonol A, cepharanthine cannabidiol, resveratrol, procyanidin A2, procyanidin B1, cinnamtannin B1, artecanin were recorded in a smaller extent. In addition to the above, punicalagin, ellagitannin, anthraquinones, psoralidin, hypericin, pseudohypericin, tetra-O-galloyl-β-D-glucose (TGG), leptodactylone, emetine, pectolinarin, rhoifolin, caffeic acid, gallic acid, tryptanthrin, secoiridoid, limonene, linalool, xanthoangelol E, saikosaponins, artemisinin, oleouropein, tomentin E, verbascoside, menthol, pulegone, cryptotanshinone, scutellarin, 1,8-cineole, tannic acid, 3-isotheaflavin-3-gallate, allyl disulfide, allyl trisulfide, mycophenolate, and curcumin were related to coronavirus inhibition. The main groups of chemical constituents of plants that are related to anti-coronavirus inhibition are presented in (Figure 3.).

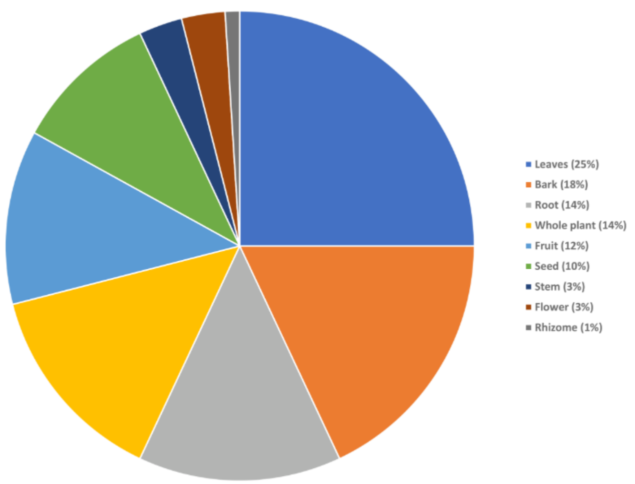

Figure 2. Origin of the reported anti-coronavirus compounds

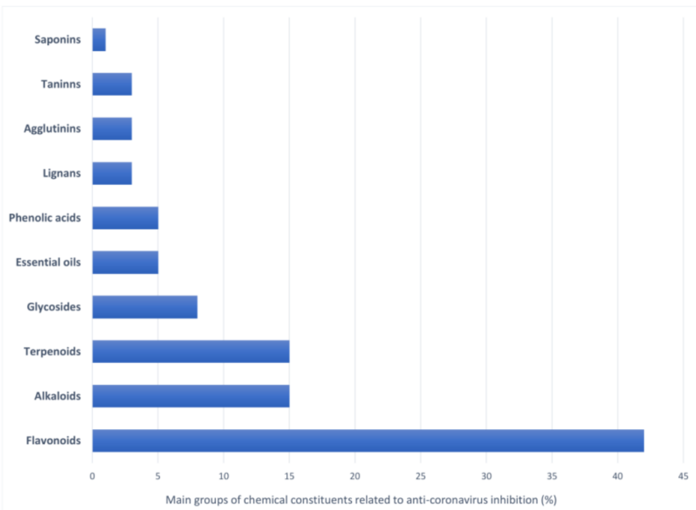

Figure 3. Groups of the chemical constituents involved in coronavirus inhibition

In total, it has been recorded that plant species had anti-coronavirus activity against six coronaviruses: SARS-CoV, SARS-CoV-2, MERS-CoV, BCV (Bovine coronavirus), HCoV-OC43 (Human coronavirus OC43), HCoV-NL63 (Human coronavirus Netherland 63). Among the mechanisms of action of plant-derived compounds, the most frequently recorded was the inhibition of 3-chymotrypsin-like protease or 3Clpro, followed by the inhibition of viral replication, inhibition of ACE2, inhibition of Plpro, NSP13, and TRP genes expression. Types of the main mechanisms of viral inhibition achieved by the medicinal plant compounds are presented in (Figure 4.).

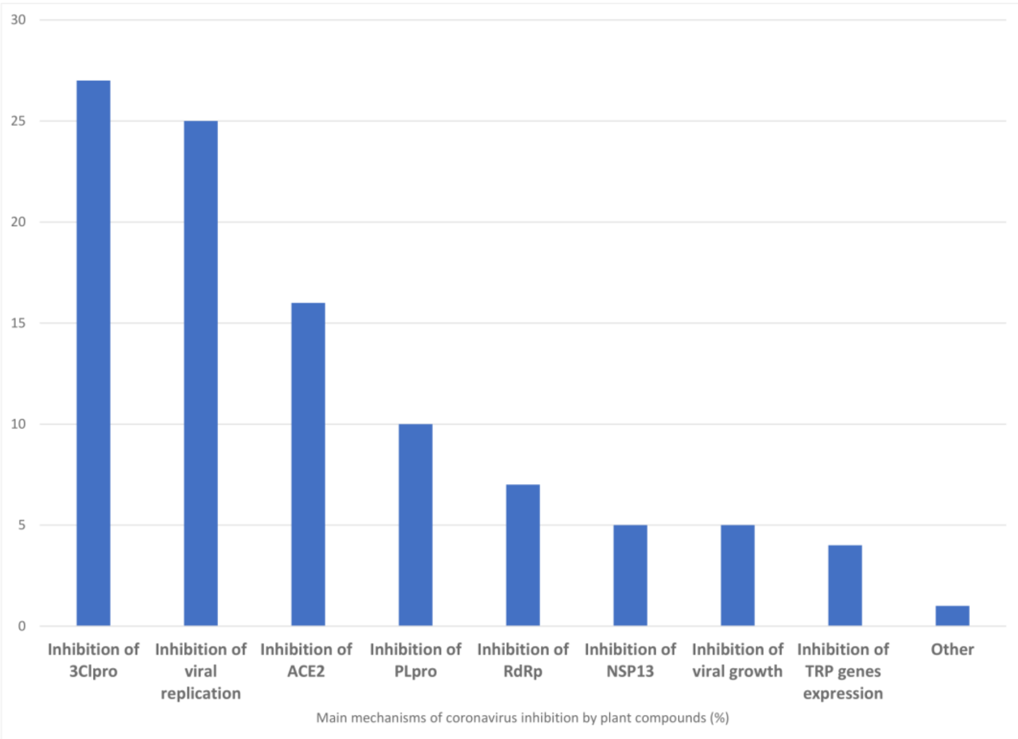

Figure 4. The main mechanisms of activity of anti-coronavirus compounds from plants

Results of this investigation, including the taxonomic affiliation, bioactive compound/s with anti-coronavirus activity (if known), and described mechanism of antiviral activity are presented in (Table 1.).

Table 1. The list of plant species with proven anti-coronavirus activity

Plant species/genus	Family	Part used	Bioactive compound	Targeted coronavirus	Mechanism of action	Reference
***Ecklonia cava* Kjellman**	Lessoniaceae	Whole plant	Dieckol	SARS-CoV	Dose-dependent inhibition of 3Clpro	[8]
***Cibotium barometz* (L.) J.Sm.**	Cibotiaceae	Rhizome	Alcoholic extract	SARS-CoV	Inhibition of replication	[9]
***Pyrrosia lingua* (Thunb.) Farw**	Polypodiaceae	Leaf	Chlorogenic acid, mangiferin, isomangiferin, astragalin, trifolin	SARS-CoV	Inhibition of RdRp	[10]
***Cephalotoxus fortuei* Hook**	Taxaceae	Leaf	Homoharringtonine	SARS-CoV-2	Inhibition of replication	[11]
***Torreya nucifera* (L.) Siebold & Zucc.**	Taxaceae	Leaf	Amentoflavone	SARS-CoV	Dose-dependent inhibition of 3Clpro	[12]
***Chamaecyparis taiwanensis* Masam. & Suzuki**	Cupressaceae	Leaf	Savinine, hinokinin, betulinic acid	SARS-CoV	Inhibition of 3Clpro	[13]
***Cryptomeria japonica* (L.f.) D.Don**	Cupressaceae	Bark	Hydroxy-deoxycryptojaponol	SARS-CoV	Inhibition of viral growth	[13]
***Thuja orientalis* L.**	Cupressaceae	Bark	Thujopsene	SARS-CoV	Inhibition of viral growth	[14]
***Isatis indigotica* Fort.**	Brassicaceae	Root	Sinigrin, hesperetin	SARS-CoV	Inhibition of 3Clpro and NSP13 helicase	[15]
***Reseda luteola* L.**	Resedaceae	Whole plant	Luteolin	SARS-CoV	Inhibition of viral entry into the cell by the binding with S protein	[16]
***Quercus infectoria* G. Olivier**	Fagaceae	Bark	Aqueous/Alcoholic extract	SARS-CoV	Inhibition of ACE receptors	[17]
***Broussonetia papyrifera* (L.) Vent.**	Moraceae	Bark	Papyriflavonol A	SARS-CoV MERS-CoV	Inhibition of PLpro	[18]
***Stephania cepharantha* Hayata**	Menispermaceae	Whole plant	Cepharantine	SARS-CoV SARS-CoV-2	Inhibition of replication	[19], [20]
***Rosa nutkana* Presl.**	Rosaceae	Root	Extract	BCV	Unknown	[21]
***Cannabis sativa* L.**	Cannabaceae	Leaf	Cannabidiol	SARS-CoV MERS-CoV SARS-CoV-2	Inhibition of replication	[22], [23]
***Urtica dioica* L.**	Urticaceae	Leaf	*Urtica dioica* aglutinin (UDA)	SARS-CoV	Inhibition of viral entry into the cell by the binding to glycoproteins	[24]
***Vitis vinifera* L.**	Vitaceae	Fruit	Resveratrol	MERS-CoV	Reduction of the nucleocapsid (N) protein expression	[15]

***Cinnamomum* sp.**	Lauraceae	Stem	Procyanidin A2, B1, cinnamtannin B1	SARS-CoV	Inhibition of endocytosis	[25]
***Laurus nobilis* L.**	Lauraceae	Leaf	Artecanin	SARS-CoV MERS-CoV SARS-CoV-2	Inhibition of 3Clpro	[14], [26]
***Lindera aggregata* (Sims) Kosterm**	Lauraceae	Root	Ethanolic extract	SARS-CoV SARS-CoV-2	Inhibition of RdRp; Inhibition of replication	[10], [27]
***Houttuynia cordata* Thunb**	Saururaceae	Whole plant	Extract	SARS-CoV	Inhibition of 3Clpro and RdRp	[28]
***Nigella sativa* L.**	Ranunculaceae	Seed	Thymoquinone	SARS-CoV	Inhibition of SARS-CoV replication and TRP genes expression	[29]
***Punica granatum* L.**	Lythraceae	Fruit	punicalagin, ellagitannin	SARS-CoV SARS-CoV-2	Inhibition of ACE receptor activity	[30]
***Cassia tora* L.**	Fabaceae	Seed	Anthraquinone	SARS-CoV	Inhibition of SARS-CoV replication	[9]
***Clitoria ternatea* L.**	Fabaceae	Leaf	Flavonol glycosides	SARS-CoV SARS-CoV-2	Inhibition of metalloproteinase (ADAM17)	[31], [32],
***Cullen corylifolium* (L.) Medik.**	Fabaceae	Seed	Psoralidin	SARS-CoV	Dose-dependent inhibition of PLpro activity	[33]
***Glycyrrhiza glabra* L.**	Fabaceae	Root	glycyrrhizin	SARS-CoV SARS-CoV-2	Inhibition of replication	[34]
***Glycyrrhiza uralensis* L.**	Fabaceae	Root	glycyrrhizin	SARS-CoV SARS-CoV-2	Blocking of SARS-CoV S protein and ACE2	[35], [36]
***Psoralea corylifolia* Linn.**	Fabaceae	Seed	Ethanolic extract	SARS-CoV	Dose-dependent inhibition of PLpro activity	[33]
***Pterocarpus santalinus* L.**	Fabaceae	Bark	Savinine	SARS-CoV	Inhibition of 3Clpro activity	[13]
***Myrica faya* Ait.**	Myricaceae	Bark	Myricetin	SARS-CoV	Inhibition of nsP13 helicase	[37]
***Tripterygium regelii* Sprague & Takeda**	Celastraceae	Bark	Celastrol, pristimerin, tigenone	SARS-CoV	Inhibition of 3Clpro activity	[38]
***Hypericum perforatum* L.**	Hypericaceae	Flower	hypericin, pseudohypericin	SARS-CoV-2	Blocking of the S protein and ACE2	[39]
***Rhus chinensis* Mill.**	Anacardiaceae	Leaf	tetra-O-galloyl-β-D-glucose (TGG)	SARS-CoV	Blocking of the S protein and ACE2	[40]
***Alnus japonica* (Thunb.) Steub.**	Betulaceae	Bark	Hirsutenone	SARS-CoV	Dose-dependent inhibition of PLpro	[41]
***Betula pubescens* Ehrh.**	Betulaceae	Bark	Betulinic acid	SARS-CoV	Inhibition of 3Clpro	[13]
***Rheum* sp.**	Polygonaceae	Whole plant	Emodin	SARS-CoV	Blocking of the S protein and ACE2	[42]
Polygonum sp.	Polygonaceae	Whole plant	Emodin	SARS-CoV	Blocking of the S protein and ACE2	[42]
***Aglaia perviridis* Hiem**	Meliaceae	Whole plant	Myricetin	SARS-CoV	Inhibition of SARS-CoV helicase	[37]

***Cedrella sinensis* Juss.**	Meliaceae	Leaf	Quercetin	SARS-CoV	Inhibition of replication	[43]
***Litchi chinensis* Sonn.**	Sapindaceae	Fruit	Extract	MERS-CoV	Inhibition of 3Clpro	[44]
***Boennighausenia sessilicarpa* H.Lév.**	Rutaceae	Bark	Leptodactylone	SARS-CoV	Protection of infected cells	[45]
***Carapichea ipecacuanha* (Brot.) L.Andersson**	Rubiaceae	Root	Emetine	HCoV-OC43 MERS-CoV HCoV-NL63	Inhibition of replication	[46]
***Tribulus terrestris* L.**	Zygophyllaceae	Fruit	Herbacetin, Pectolinarin, Rhoifolin	SARS-CoV SARS-CoV-2	Inhibition of 3Clpro and replication	[47], [48], [49]
***Sambucus javanica subsp. chinensis* (Lindl.) Fukuoka**	Adoxaceae	Stem	Caffeic acid, chlorogenic acid, gallic acid	SARS-CoV	Inhibition of viral cytopathogenesis and viral plaque	[50]
***Sambucus nigra* L.**	Adoxaceae	Fruit	Agglutinins, Lectins	SARS-CoV-2	Blocking of the S protein and ACE2	[51]
***Strobilanthes cusia* Nees (Knutze)**	Acanthaceae	Leaf	Tryptanthrin	HCoV-NL63	Inhibition of replication	[52]
***Gentiana scabra* Bunge**	Gentianaceae	Root	Secoiridoids	SARS-CoV	Inhibition of replication	[9]
***Tripterygium regelii* Sprague & Takeda**	Celastraceae	Bark	Celastrol, pristimerin	SARS-CoV	Dose-dependent inhibition of 3Clpro	[38]
***Capsicum annuum* L.**	Solanaceae	Fruit	Glucosydes	SARS-CoV MERS-CoV SARS-CoV-2	Inhibition of the Mpro activity	[53]
***Hyoscyamus niger* L.**	Solanaceae	Seed	Hyosciamin	SARS-CoV-2	Inhibition of the Ca^{2+} channels	[54]
***Nicotiana benthamiana* Domin.**	Solanaceae	Leaf	Lectins	SARS-CoV	Inhibition of the viral growth	[55]
***Citrus sinensis* (L.) Osbeck**	Rutaceae	Bark	Limonene, linalool	SARS-CoV	Inhibition of replication and TRP genes expression	[29]
***Linum usitatissimum* L.**	Linaceae	Seed	Herbacetin	MERS-CoV	Inhibition of 3Clpro	[44]
***Angelica keiskei* (Miq.) Koidz.**	Apiaceae	Leaf	Xanthoangelol E	SARS-CoV	Dose-dependent inhibition of PLpro and 3Clpro	[18]
***Bupleurum marginatum* Wall. ex DC**	Apiaceae	Root	Saikosaponins	SARS-CoV	Inhibition of replication	[56]
***Coriandrum sativum* L.**	Apiaceae	Seed	Flavonol-glycosides	SARS-CoV-2	Blocking of the S protein and ACE2	[57], [58]
***Anthemis hyalina* DC.**	Asteraceae	Flower	Ethanolic extract	SARS-CoV	Inhibition of replication and TRP genes expression	[29]
***Artemisia annua* L.**	Asteraceae	Leaf	Artemisinin	SARS-CoV SARS-CoV-2	Inhibition of the RdRp	[59]

***Olea europaea* L.**	Oleaceae	Fruit	Oleuropein	SARS-CoV MERS-CoV SARS-CoV-2	Inhibition of the Mpro activity	[53]
***Paulownia tomentosa* (Thunb.) Steud**	Scrophulariaceae	Fruit	Tomentin E	SARS-CoV	Dose-dependent inhibition of PLpro	[60]
***Verbascum thapsus* L.**	Scrophulariaceae	Leaf	Verbascoside	BCV	Uknown	[61]
Veronica linariifolia	Scrophulariaceae	Whole plant	Luteolin	SARS-CoV	Inhibition of the viral growth	[40]
***Mentha longıfolia* L.**	Lamiaceae	Whole plant	Menthol, pulegone	MERS-CoV SARS-CoV-2	Inhibition of the Mpro activity	[53]
***Salvia miltiorrhiza* Bunge**	Lamiaceae	Root	Ryptotanshinone	SARS-CoV	Inhibition of PLpro and 3Clpro	[8]
***Scutellaria baicalensis* Georg**	Lamiaceae	Whole plant	Scutellarin	SARS-CoV	Inhibition of the helicase activity	[37]
***Vitex trifolia* L.**	Lamiaceae	Leaf	1,8-cineol	SARS-CoV SARS-CoV-2	Reduction in the concentration of the cytokine	[62]
***Taxillus chinensis* DC.**	Loranthaceae	Leaf	Quercetin	SARS-CoV	Inhibition of replication	[63]
***Camellia sinensis* (L.) Knutze**	Theaceae	Leaf	Tannic acid, 3-isotheaflavin-3-gallate	SARS-CoV	Inhibition of 3Clpro	[64]
***Allium sativum* L.**	Amaryllidaceae	Bulb	Allicin	SARS-CoV SARS-CoV-2	Inhibition of ACE2	[65]
***Clivia miniata* (Lindl.) Verschaff**	Amaryllidaceae	Fruit	Lycorine	HCoV-OC43 MERS-CoV HCoV-NL63	Inhibition of replication	[46]
***Lycoris radiata* Bulb.**	Amaryllidaceae	Bark	Lycorine	SARS-CoV	Inhibition of the RdRp	[10]
***Curcuma longa* L.**	Zingiberaceae	Flower	Curcumin	SARS-CoV	Inhibition of 3Clpro	[13]

4. Discussion

According to recent meta-analyses [66]around 30 plants are noted for their *in vitro* activity against different coronaviruses, including pandemic species MERS and SARS-CoV. *In vivo* studies are conducted in a smaller amount, and in those cases, the activity of *Allium sativum* L. (Amaryllidaceae), *Epimedium koreanum* Nakai (Berberidaceae), and *Houttuynia cordata* Thunb. (Saururaceae) is noted against IBV (avian coronavirus) and PEDV (porcine epidemic diarrhea virus).

The first step in the viral infectious cycle is viral attachment and penetration into the host cell. This is a very popular target for the development of antiviral drugs. Herbal compounds tetra-O-galloyl-β-d-glucose (from *Rhus chinensis* Mill., Anacardiaceae) and luteolin (from *Veronica linariifolia* Pall. ex Link, Plantaginaceae) are known for their ability to interfere with the viral cell fusion process [67]. Inhibition of the viral attachment can also be achieved by glycyrrhizin isolated from *Glycyrrhiza glabra* L. (Fabaceae) [68]. Furthermore, emodin, an anthraquinone glycoside significantly obstructed the S protein and ACE2 interaction. This specific compound is isolated from *Rheum officinale* Baill. and *Polygonum multiflorum* Thunb. (Polygonaceae). Extracts of *Sambucus formosana* Nakai (Viburnaceae) possess caffeic acid that demonstrated potential anti-coronavirus activity through viral entry inhibition [69].*Artemisia annua* L. (Asteraceae) is a well-known medicinal plant, and recent investigations suggest its anti-coronavirus activity through the interaction of aurantiamide acetate and SARS cathepsin L [70]. Another mechanism of the viral entry is the endocytosis route, and in that terms butanol fraction of *Cinnamomum verum* J. Presl (Lauraceae) is noted for inhibition of the clathrin-mediated endocytosis pathway [71].

Viral enzymes are very important targets in the understanding of the interference of the viral life cycle through the inhibitory agents. 3Clpro is also called the main protease (Mpro) and plays a crucial role in viral replication [72]. This enzyme is considered a potential drug target for coronaviruses since it is essential in processing the polyproteins that are translated from viral RNA [73], [74]. Furthermore, a possible target is viral RNA-dependent RNA polymerase (RdRp). This is a viral enzyme with no cell homologs, so safer and selective viral inhibitors could have improved potency and fewer off-target effects against host proteins [75]. Helicase NSP13 is a 67 kDa non-structural protein from helicase superfamily 1B.

It is essential for coronavirus replication, where catalytically active as an NTPase and RNA helicase, NSP13 binds to RdRp polymerase to stimulate its backtracking. It is also involved in the proper folding and replication of viral RNA [76]. Besides its role in viral replication, this protein is identified as a target for anti-virals because of its high sequence conservation [77]. The ACE2 receptor (angiotensin-converting enzyme homolog) is very common within the human body, but coronavirus surface proteins possess a great affinity to this receptor it is inevitably involved in the viral attachment to the host cells. Direct binding of natural compounds to ACE2 receptors with high affinity limits further binding of coronaviruses with the extracellular domain of ACE2 [78]. Some of the noted natural compounds were targeting the viral papain-like protease (PLpro). The PLpro is an essential coronavirus enzyme, required for processing the viral polyproteins to generate a functional replicase complex and enable viral spread [79]. Some plant compounds are acting as viral inhibitors at the level of TRP gene expression. Transient receptor potential (TRP) channels are cation

channels with high permeability to Ca^{2+}, and they are involved in the life cycle of coronaviruses [80]. It is proven that medicinal plant extracts significantly change the expression of many TRP genes [29].
Besides the already mentioned plants in this survey, several plants such as *Sanguisorba officinalis* L. (Rosaceae), *Stephania tetrandra* S. Moore (Menispermaceae), and *Strobilanthes cusia* (Nees) Kuntze (Acanthaceae) exhibit activity towards RNA and protein synthesis of the coronavirus [81]. Active compounds are most probably bis-benzylisoquinoline alkaloids, tryptanthrin, and indigodole B [82]. The reduction of the intracellular viral RNA concentrations is caused by the extracts of *Sophora flavescens* Aiton (Fabaceae), *Acanthopanax gracilistylus* W.W.Sm. (Araliaceae), and *Tortilis japonica* (Houtt.) (Apiaceae) [81]. Since RdRp plays a vital role in the virus life cycle, several polymerase inhibitors are implemented in that course. Many plant species identified in this study use that target to exhibit its anti-coronavirus properties. The results of this investigation could be accompanied by recent *in silico* docking analyses that investigate the inhibitory potential of plant compounds against viral proteases 3Clpro and Plpro, which play a prominent role in the replication of coronavirus [82].
Plant compounds could also be involved in the mechanism of the viral release, where an herbal agent that suppressed the ion-channel protein could be anticipated to prevent the viral spread to other cells [84]. There is also the possibility of boosting the host immunity as a strategy to fight against the viral infection. In that regard, several herbal products are investigated [85]. Less common mechanisms of coronavirus inhibition by plant compounds include the reduction of the N (nucleocapsid) protein expression, inhibition of endocytosis, changes in cytoplasticity, and in the function of proteolytic enzyme matrix metalloproteinase-9 (MMP-9).

5. Conclusions

This investigation highlighted the prolonged and excessive need for efficient antiviral agents of natural origin. Viruses are molecular pathogens and achieving their inhibition while keeping the cell functions intact is challenging. Natural compounds have bioactive properties and could be used in the treatment of various infections with a lower toxicity rate. Furthermore, while synthetic antiviral drugs have precise composition, plant products can vary in their chemical profile almost on daily basis, which is a solid ground for avoiding viral resistance. Plant products are also considered more available and less expensive in comparison to synthetic drugs. Although some coronaviruses are frequent in the human population and could be treated easily, the events associated with the ongoing pandemic of SARS-CoV-2 suggest that medicinal plants represent the excessive source of anti-coronavirus substances. The efficiency of the inhibition of major viral targets by these compounds is promising. Future investigations should be oriented towards the isolation and characterization of individual antiviral compounds of natural origin, which would allow the utilization of natural drugs on a higher global scale. It is necessary that medicinal plants and their products undergo clinical trials that would validate their health benefits and identify potential side effects.

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