Potential Treatments for Viral Diseases

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The COVID-19 pandemic, as well as the more general global increase in viral diseases, has led researchers to look to the plant kingdom as a potential source for antiviral compounds. Since ancient times, herbal medicines have been extensively applied in the treatment and prevention of various infectious diseases in different traditional systems. The purpose of this review is to highlight the potential antiviral activity of plant compounds as effective and reliable agents against viral infections, especially by viruses from the coronavirus group.

Keywords: bioactive compounds ; coronavirus ; hairy roots ; herbal medicines ; molecular farming ; plant extracts ; respiratory diseases

1. Introduction

Bronchitis is a respiratory disease caused by bacterial infections, viral infections, or irritant particles [1]. In response to infection, the bronchial tubes become inflamed and swollen, which may eventually result in acute respiratory arrest. Nowadays, viral pneumonia is diagnosed through analyzing a sample of bronchoalveolar lavage fluid using PCR, cell cultures, and whole-genome sequencing [2]. The virus was isolated from infected individuals and recognized as genus beta-coronavirus, placing it alongside other viruses causing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [3].

The treatment of this disease is a great challenge due to several reasons, including the rapid emergence of mutant strains, the consequent high rate of virus adaptation, and the development of resistance to antiviral medicines. Another factor is that of unwanted side effects and the high cost of synthetic antiviral drugs. The standard approach for viral infections comprises antiviral medicines that do not cause damage to the human host but can help shorten viral infection, inhibit virus expansion, and help in reducing/blocking complications [1]. The potency of marine natural products has been confirmed to target SARS-CoV-2 main protease (Mpro) [4].

Medicinal plants have been identified as reliable resource against several diseases for millennia. More than 70% of the global population still depends on herbal medicines due to their relatively low cost and better compatibility with the human body compared to synthetic drugs [5]. During the pandemic period, studies were performed using databases of scientific literature to screen and identify the potential of herbal plants to act as anti-coronavirus medication [6]. It has been reported that water and ethanol plant extracts contain biologically active substances with antiviral activity [7].

A wide range of compounds identified in several plant species have demonstrated antiviral activities, including alkaloids, flavonoids, triterpenes, anthraquinones, and lignans. Interestingly, plant selection based on ethnomedical concerns provides a higher hit rate than screening plants or general synthetic products [8]. Some known pharmacophore structures of bioactive substances may be useful in the creation of new anti-Covid-19 drugs. In addition, plants have also been introduced as a safe and reliable bioreactor for the production of recombinant virus proteins that can be used in vaccine development [9], e.g., nuclear transformed tomatoes and tobacco-expressing antigens have been reported to induce immunogenic responses against SARS-CoV [10].

The main objective of the current review is to provide the complete overview of the ethnomedicinal uses of herbs employed to treat respiratory diseases. We address questions regarding the potential of plant-derived compounds in inhibiting virus propagation, thus providing relief for viral-induced pathogenesis. We also discuss how biotechnology may help solve the challenge of rapidly obtaining pure antiviral compounds. Furthermore, this review discusses the current state of the art regarding the possible antiviral activities of herbal medicine and makes an effort to tackle the gaps in scientific knowledge that may lead to the advancement of innovative treatments for the welfare of people and against the spread of viral diseases, especially SAR-CoV.

2. Replication Inhibitors of SARS-CoV

Previous investigations have demonstrated that the development of proteases is an ideal goal to be tackled for the inhibition of CoV replication. Though the protease activity disruption causes various diseases, host proteases are considered reliable therapeutic targets. For several different viruses, protease activity represents a vital factor in replication; thus, proteases are frequently targeted as protein candidates during antiviral therapeutics studies [11]. Lopinavir and nelfinavir are in the category of medications named protease inhibitors with a high level of cytotoxicity recommended for the treatment of cells infected with MERS, SARS, and HIV [12].

3. Evidence Supporting the Antiviral Efficacy of Medicinal Plants

The use of therapeutic plants against viral infection can be traced back to the dawn of civilization; however, BOOTS Pure Drug Co., Ltd., Nottingham (England) made the first systematic effort to screen plants against influenza [13]. Later on, the inhibitory effect of medicinal plants on the replication of viruses was studied on severe acute respiratory syndrome (SARS) virus, emerging viral infections linked with poxvirus, hepatitis B virus (HBV), HIV, and herpes simplex virus type 2 (HSV-2) [14][15][16][17][18][19] It has been demonstrated that molecular mechanisms linked to the antiviral effects of medicinal plant extracts vary among various types of viruses. Thus far, some investigations have discovered immunostimulatory properties of medicinal plant extracts possessing antiviral activity [20].

4. Plant-Derived Immunomodulators

The phagocyte–microbe interactions in the immune system comprise a defense reaction that, under more harmful circumstances, may take part in the advancement of various immune and non-immune chronic inflammatory diseases. Agents that express a capacity to modulate and normalize pathophysiological processes are named immunomodulators [21]. Most of the well-known immunostimulants and immunosuppressants used in clinical practice are cytotoxic drugs, which can have severe side effects. Therefore, plant-derived compounds and extracts have been studied regarding their immunomodulatory potential in humans due to their lower cytotoxicity and high bioavailability [22][23].

Some plant-derived compounds, e.g., curcumin, genistein, fisetin, quercetin, resveratrol, epigallocatechin-3-gallate, andrographolide, and colchicine, have immunomodulatory effects [24][25][26][27][28][29][30]. These compounds can downregulate the production of proinflammatory cytokines induced by some viroidal agents [26]. Andrographolide and other natural, immunomodulators can enhance the activity of cytotoxic T cells, phagocytosis, natural killer (NK) cells, and antibody dependent cell-mediated cytotoxicity [26]. The use of quercetin in combination with highly active compounds such as psoralen, baccatin III, embelin, and menisdaurin increased its anti-hepatitis B activity up to 10% [31].

At the same time, analyses of other medicinal plant extracts with antiviral properties have shown thatGymnema sylvestre[25],Stephania tetrandraS [32][33][34], andVitex trifoliaextracts [35] possess immunomodulating activity. [36] found immunomodulation potential and antiviral activities against acute common cold in leaf extracts of Thuja occidentalis. The anti-SARS and immunomodulatory activity of water extracts of Houttuynia cordatahave been reported via the stimulation of lymphocyte proliferation together with enhancing the proportion of CD4+ and CD8+ T cells [37] (**Table 1**).

Table 1. The mode of action against viruses and methods of active compound extraction from medicinal plants.

Plant Species and Plant Part	Active Compounds						Extract	Model Organism	Mode of Action/Activity	Ref
	Terpenes Terpenoids	Flavonoids Flavones	Alkaloids	Coumarins	Tannins					
Mentha piperita (whole plant) *Lamiaceae*	α-pinene β-pinene β-caryophyllene L-Limonene Menthol	Eriocitrin Hesperidin Kaempferol-7-O-rutinoside Luteolin and its derivatives	n/a	Trans-resveratrol	n/a		Ethanol	Vero cell cultures	High antiviral activity	[38] [39] [40]
Thymus vulgaris (whole plant) *Lamiaceae*	Thymol p-cymene γ-Terpinene Linalool	Rutin Quercetin	n/a	n/a	n/a		Ethanol	Vero cell cultures	High antiviral activity and antioxidant effects	[38] [41] [42]

References

1. Amber, R.; Adnan, M.; Tariq, A.; Mussarat, S. A review on antiviral activity of the Himalayan medicinal plants traditionally used to treat bronchitis and related symptoms. J. Pharm. Pharmacol. 2017, 69, 109–122.
2. Peeri, N.C.; Shrestha, N.; Rahman, S.; Zaki, R.; Tan, Z.; Bibi, S.; Baghbanzadeh, M.; Aghamohammadi, N.; Zhang, W.; Haque, U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: What lessons have we learned? Int. J. Epidemiol. 2020, 49, 717–726.
3. Li, J.; Liu, W. Puzzle of highly pathogenic human coronaviruses (2019-nCoV). Protein Cell 2020, 11, 235–238.
4. Khan, M.T.; Ali, A.; Wang, Q.; Irfan, M.; Khan, A.; Zeb, M.T.; Zhang, Y.J.; Chinnasamy, S.; Wei, D.Q. Marine natural compounds as potents inhibitors against the main protease of SARS-CoV-2—A molecular dynamic study. J. Biomol. Struct. Dyn. 2020, 1–11.
5. Wang, X.; Liu, Z. Prevention and treatment of viral respiratory infections by traditional Chinese herbs. Chin. Med. J. 2014, 127, 1344–1350.
6. Remali, J.; Aizat, W.M. A Review on Plant Bioactive Compounds and Their Modes of Action Against Coronavirus Infection. Front. Pharmacol. 2021, 11, 589044.
7. Chojnacka, K.; Witek-Krowiak, A.; Skrzypczak, D.; Mikula, K.; Młynarz, P. Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus. J. Funct. Foods 2020, 73, 104146.
8. Siddiqui, M.H.; Al-Amri, S.; Al-Whaibi, M.H.; Hussain, Z.; Ali, H.M.; El-Zaidy, M.E. A mini-review of anti-hepatitis B virus activity of medicinal plants. Biotechnol. Biotechnol. Equip. 2016, 31, 9–15.
9. Pogrebnyak, N.; Golovkin, M.; Andrianov, V.; Spitsin, S.; Smirnov, Y.; Egolf, R.; Koprowski, H. Severe acute respiratory syndrome (SARS) S protein production in plants: Development of recombinant vaccine. Proc. Natl. Acad. Sci. USA 2005, 102, 9062–9067.
10. Li, H.-Y.; Ramalingam, S.; Chye, M.-L. Accumulation of recombinant SARS-CoV spike protein in plant cytosol and chloroplasts indicate potential for development of plant-derived oral vaccines. Exp. Biol. Med. 2006, 231, 1346–1352.
11. Chang, K.-O.; Kim, Y.; Lovell, S.; Rathnayake, A.D.; Groutas, W.C. Antiviral Drug Discovery: Norovirus Proteases and Development of Inhibitors. Viruses 2019, 11, 197.

12. Li, J.-Y.; You, Z.; Wang, Q.; Zhou, Z.-J.; Qiu, Y.; Luo, R.; Ge, X.-Y. The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. Microbes Infect. 2020, 22, 80–85.

13. Chantrill, B.H.; Coulthard, C.E.; Dickinson, L.; Inkley, G.W.; Morris, W.; Pyle, A.H. The Action of Plant Extracts on a Bacteriophage of Pseudomonas pyocyanea and on Influenza A Virus. J. Gen. Microbiol. 1952, 6, 74–84.

14. Debiaggi, M.; Pagani, L.; Cereda, P.M.; Landini, P.; Romero, E. Antiviral activity of Chamaecyparis lawsoniana extract: Study with herpes simplex virus type 2. Microbiology 1988, 11, 55–61.

15. Vermani, K.; Garg, S. Herbal medicines for sexually transmitted diseases and AIDS. J. Ethnopharmacol. 2002, 80, 49–66.

16. Asres, K.; Bucar, F. Anti-HIV activity against immunodeficiency virus type 1 (HIV-I) and type II (HIV-II) of compounds isolated from the stem bark of Combretum molle. Ethiop. Med. J. 2005, 43, 15–20.

17. Kotwal, G.J.; Kaczmarek, J.N.; Leivers, S.; Ghebremariam, Y.T.; Kulkarni, A.P.; Bauer, G.; De Beer, C.; Preiser, W.; Mohamed, A.R. Anti-HIV, Anti-Poxvirus, and Anti-SARS Activity of a Nontoxic, Acidic Plant Extract from the Trifolium Species Secomet-V/anti-Vac Suggests That It Contains a Novel Broad-Spectrum Antiviral. Ann. N. Y. Acad. Sci. 2005, 1056, 293–302.

18. Kwon, D.H.; Kwon, H.Y.; Kim, H.J.; Chang, E.J.; Kim, M.B.; Yoon, S.K.; Song, E.Y.; Yoon, D.Y.; Lee, Y.H.; Choi, I.S.; et al. Inhibition of hepatitis B virus by an aqueous extract of Agrimonia eupatoria L. Phytotherapy Res. 2005, 19, 355–358.

19. Huang, K.-L.; Lai, Y.-K.; Lin, C.-C.; Chang, J.-M. Inhibition of hepatitis B virus production byBoehmeria nivearoot extract in HepG2 2.2.15 cells. World J. Gastroenterol. 2006, 12, 5721–5725.

20. Webster, D.; Taschereau, P.; Lee, T.D.; Jurgens, T. Immunostimulant properties of Heracleum maximum Bartr. J. Ethnopharmacol. 2006, 106, 360–363.

21. Puri, A.; Saxena, R.P.; Saxena, K.; Srivastava, V.; Tandon, J. Immunostimulant activity of Nyctanthes arbor-tristis L. J. Ethnopharmacol. 1994, 42, 31–37.

22. Ejentan, I.; Eahmad, W.; Ebukhari, S.N.A. Plant-derived immunomodulators: An insight on their preclinical evaluation and clinical trials. Front. Plant Sci. 2015, 6, 655.

23. Mohammadi, S.; Jafari, B.; Asgharian, P.; Martorell, M.; Sharifi-Rad, J. Medicinal plants used in the treatment of Malaria: A key emphasis to Artemisia, Cinchona, Cryptolepis and Tabebuia genera. Phytother. Res. 2020, 34, 1556–1569.

24. Yadav, V.S.; Mishra, K.P.; Singh, D.P.; Mehrotra, S.; Singh, V.K. Immunomodulatory Effects of Curcumin. Immunopharmacol. Immunotoxicol. 2005, 27, 485–497.

25. Fürst, R.; Zündorf, I. Plant-Derived Anti-Inflammatory Compounds: Hopes and Disappointments regarding the Translation of Preclinical Knowledge into Clinical Progress. Mediat. Inflamm. 2014, 2014, 146832.

26. Ložienė, K.; Švedienė, J.; Paškevičius, A.; Raudonienė, V.; Sytar, O.; Kosyan, A. Influence of plant origin natural α-pinene with different enantiomeric composition on bacteria, yeasts and fungi. Fitoterapia 2018, 127, 20–24.

27. Lecher, J.C.; Diep, N.; Krug, P.W.; Hilliard, J.K. Genistein Has Antiviral Activity against Herpes B Virus and Acts Synergistically with Antiviral Treatments to Reduce Effective Dose. Viruses 2019, 11, 499.

28. Malaguarnera, L. Influence of Resveratrol on the Immune Response. Nutrients 2019, 11, 946.

29. Gupta, S.; Mishra, K.P.; Ganju, L. Broad-spectrum antiviral properties of andrographolide. Arch. Virol. 2017, 162, 611–623.

30. Perricone, C.; Triggianese, P.; Bartoloni, E.; Cafaro, G.; Bonifacio, A.F.; Bursi, R.; Perricone, R.; Gerli, R. The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. J. Autoimmun. 2020, 111, 102468.

31. Parvez, M.K.; Rehman, T.; Alam, P.; Al-Dosari, M.S.; Alqasoumi, S.I.; Alajmi, M.F. Plant-derived antiviral drugs as novel hepatitis B virus inhibitors: Cell culture and molecular docking study. Saudi Pharm. J. 2019, 27, 389–400.

32. Khan, F.; Sarker, M.R.; Ming, L.C.; Mohamed, I.N.; Zhao, C.; Sheikh, B.Y.; Tsong, H.F.; Rashid, M.A. Comprehensive Review on Phytochemicals, Pharmacological and Clinical Potentials of Gymnema sylvestre. Front. Pharmacol. 2019, 10, 1223.

33. Liu, T.; Liu, X.; Li, W. Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. Oncotarget 2016, 7, 40800–40815.

34. Kim, E.; Kwak, J. Antiviral phenolic compounds from the whole plants of Zostera marina against influenza A virus. Planta Medica 2015, 81, PW_06.

35. Vimalanathan, S.; Ignacimuthu, S.; Hudson, J.B. Medicinal plants of Tamil Nadu (Southern India) are a rich source of antiviral activities. Pharm. Biol. 2009, 47, 422–429.

Plant Species and Plant Part	Active Compounds: Terpenes Terpenoids	Flavonoids Flavones	Alkaloids	Stilbenes	Coumarins	Extract	Model Organism	Mode of Action/Activity	Ref
Desmodium canadense (whole plant) *Fabaceae*	Sandosaponin B and its derivatives Soyasaponin I Soyasaponin I...	Homoorientin Orientin 2-Videnin Vitexin Isovitexin Rutin Desmodin Homoadonivernite	Indole-3-alkylamine phenylethylamine alkaloids, pyrrolidine alkaloids	n/a	n/a	Ethanol	Vero cell cultures	High antiviral activity	[38] [43] [44] [45] [46]
Camellia japonica (whole plant, flowers) *Theaceae*	Oleanane triterpenes 3β,18β-dihydroxy-28-norolean-12-en-16-one 18β-hydroxy-28-norolean-12-ene-3,16-dione	Quercetin Kaempferol Apigenin	Do not produce purine alkaloids	n/a	n/a	Ethanol	Vero cells (African green monkey kidney cell line; ATCC CCR-81)	High antiviral activity on PEDV corona virus Inhibitory effects on key gene and protein synthesis during PEDV replication	[47] [48] [49] [50] [51] [52]
Saposhnikovia divaricata (whole plant) *Apiaceae*	n/a	n/a	n/a	n/a	cis-3′-Isovaleryl-4′-acetylkhellactone Praeruptorin F Praeruptorin B (−)-cis-khellactone	Ethanol	Vero cells (African green monkey kidney cell line; ATCC CCR-81)	High antiviral activity on PEDV corona virus	[48]
Quercus ilex L. (Leaves) *Fagaceae*		kaempferol glycosides (juglanin, kaempferol-3-O-α-L-arabinofuranoside, and afzelin, kaempferol-3-*O*-α-L-rhamnoside	n/a	n/a	n/a	DMSO	*Xenopus oocytes*	Inhibits 3a channel protein of coronavirus	[49] [50]
Bupleurum sp. (whole plant) *Apiaceae*	Triterpenoid saponins Saikosaponins 2″-O-Acetylsaikosaponins Prosaikogenins Bupleurosides Etc.	Quercetin Isorhamnetin Narcissin Rutin Eugenin Saikochrome A	n/a	n/a	n/a	DMSO	Human fetal lung fibroblasts (MRC-5; ATCC CCL-171)	Saikosaponins attenuate viral attachment and penetration	[53] [54]
Houttuynia cordata (whole plant) (*Saururaceae*)	Cycloart-25-ene-3b,24-diol	Quercetin 7-rhamnoside Hyperin Quercetin Afzelin Rutin	Arisolactams Piperolactam A Caldensin	n/a	n/a	Water	BALB/c mice	Decreases the viral SARS-3CL^{pro} activity Stops viral RNA polymerase activity (RdRp) Increases the secretion of interleukin (IL)-2 and (IL)-10	[55] [56]
Isatis tinctoria (Roots extracts) *Brasicaceae*	n/a	Hesperetin Quercetin Isoorientin Isovitexin	Indigo Indirubin Indican	Sinigrin	n/a	Water	Vero cells	Cleavage of the activity of SARS-3CL^{pro} enzyme decreased	[57] [58]
Lycoris radiata (Bulbs) *Amaryllidaceae*	β-Myrcene A-terpineol Eucalyptol β-cyclocitral	n/a	Lycorine Amaryllidaceae alkaloids Lycoramines	n/a		Ethanol	Vero E6 cells	Exhibits anti-SARS-CoV activity	[59] [60] [61] [62]

Plant Species and Plant Part	Diterpenoids Triterpenoids Terpenoids	Flavonoids Flavones	Alkaloids	Coumarins Stilbenes	Extract	Model Organism	Mode of Action/Activity	Ref
Litchi chinensis (seeds) *Sapindaceae*	3-Oxotrirucalla-7,24-dien-21-oic acid	Herbacetin Rhoifolin Pectolinarin Quercetin Epigallocatechin gallate Gallocatechin gallate Litchitannins Kaemferol derivatives Cyanidin-3-O-rutinoside Cinnamtannin	n/a	n/a	Water	On model with SARS-CoV $3CL^{pro}$	Inhibits SARS-$3CL^{pro}$ activity	[63] [64] [65] [66]
Stephania tetrandra S. Moore (Roots) *Menispermaceae*	n/a	n/a	Tetrandrine, Fangchinoline, Cepharanthine	n/a	DMSO	Human cell line MRC-5 cells	Inhibits the expression of HCoV-OC43 spike and nucleocapsid protein. Immunomodulation/	[31] [67]
Scutellaria baicalensis (Roots) *Lamiaceae*	Oroxylin A	Scutellarein Baicalin Wogonin Wogonoside	n/a	n/a	n/a	Model with SARS-CoV helicase, and nsP13	Inhibits nsP13 by targeting its ATPase activity	[68] [69]
Allium sativum (Bulbs) *Alliaceae*	Nerolidol Phytol Sitosterol α-pinene Terpinolene Limonene 1,8-cineole γ-terpinene	Catechin Epicatechin	*Allicin* Ajoene Allin Diallyl disulfide Diallyl trisulfide	n/a	Aquaporin	Chicken embryos	Inhibitory effects on avian coronavirus	[70] [71] [72] [73]
Artemisia sp. *Artemisia absentium* (whole plants) *Asteraceae*	Absinthin Artemisin Scopoletin Vanillic acid	Glycosides of quercetin Quercetin	*Artemarin* Artamaridin Artamaridinin, Artamarinin	n/a	Water	Delayed brain tumor cells	Reduces coronavirus replication	[74] [75]
Juniperus communis (Fruits) *Cupressaceae*	Sugiol α-pinene β-pinene	Rutin Scutellarein Quercetin-3-O-rhamnoside Quercitrin	n/a	n/a	Dimethylether	n/a	Protein-molecular docking with network pharmacology analysis	Inhibits the replication, $3CL^{pro}$	[76] [77]
Ecklonia cava (whole plant) *Lessoniaceae*	n/a	Quercetin	n/a	n/a	n/a	n/a	Protein-molecular docking with network pharmacology analysis	PL^{pro} and $3CL^{pro}$	[78]

Plant sources of polyphenolic compounds with anti-protease activity.

The mode of action against viruses and methods of active compound extraction from medicinal plants.

Lectins are a special type of natural proteins (split into seven different classes of evolutionarily- and structurally-related proteins) found in higher plants, that bind to the sugar moieties of a wide range of glycoproteins [76]. Plant lectins can inhibit virus replication by preventing the adsorption of host cells [77][78][79][80][81][82][83][84][85]. Furthermore, the antiviral effect of agglutinins specific for N-acetylglucosamine and mannose on HIV has been reported. The inhibitory effect of these plant lectins has been shown in vitro on infection with influenza A virus, respiratory syncytial virus, and cytomegalovirus [84][85][86].

During the digestion of food, quercetin and its conjugated metabolites can be converted into a range of metabolites (phenolic acids) by enteric enzymes and bacteria in intestinal mucosal epithelial cells (IMECs) [87]. Additionally, several studies have shown the protective function of this flavonol against inflammation in human umbilical vein endothelial cells (HUVECs), as well as mediation via the downregulation of vascular cell adhesion molecule 1 (VCAM-1) and CD80 expression [88][89]. Quercetin considerably induces the production of derived interferon (IFN) and T helper type 1 (Th-1),

36. Naser, B.; Bodinet, C.; Tegtmeier, M.; Lindequist, U. Thuja occidentalis(Arbor vitae): A Review of its Pharmaceutical, Pharmacological and Clinical Properties. Evid. Based Complement. Altern. Med. 2005, 2, 69–78.

37. Lin, L.-C.; Kuo, Y.-C.; Chou, C.-J. Anti-Herpes Simplex Virus Type-1 Flavonoids and a New Flavanone from the Root of Limonium sinense. Planta Medica 2000, 66, 333–336.

38. Lelešius, R.; Karpovaitė, A.; Mickienė, R.; Drevinskas, T.; Tiso, N.; Ragažinskienė, O.; Kubilienė, L.; Maruška, A.; Satkauskas, S. In vitro antiviral activity of fifteen plant extracts against avian infectious bronchitis virus. BMC Vet. Res. 2019, 15, 178.

39. Dolzhenko, Y.; Bertea, C.M.; Occhipinti, A.; Bossi, S.; Maffei, M. UV-B modulates the interplay between terpenoids and flavonoids in peppermint (Mentha piperita L.). J. Photochem. Photobiol. B Biol. 2010, 100, 67–75.

40. Fatih, B.; Madani, K.; Chibane, M.; Duez, P.; Brahmi, F.; Khodir, M.; Mohamed, C.; Pierre, D. Chemical Composition and Biological Activities of Mentha Species. In Aromatic and Medicinal Plants—Back to Nature; IntechOpen: London, UK, 2017.

41. Fraga, A.; Godoy, R. Chemical composition of Thymus vulgaris L. (Thyme) essential oil from the Rio de Janeiro state. Braz. J. Serb. Chem. Soc. 2008, 73, 307–310.

42. Gedikoğlu, A.; Sökmen, M.; Çivit, A. Evaluation of Thymus vulgaris and Thymbra spicata essential oils and plant extracts for chemical composition, antioxidant, and antimicrobial properties. Food Sci. Nutr. 2019, 7, 1704–1714.

43. Puodziuniene, G.; Kairyte, V.; Janulis, V.; Razukas, A.; Barsteigiene, Z.; Ragažinskienė, O. Quantitative hplc estimation of flavonoids in snowy tick trefoil (Desmodium canadense) herbs. Pharm. Chem. J. 2011, 45, 88–90.

44. Babyuk, V.S.V.; Vasenkova, L.N.; Chernobrovaya, N.V.; Komissarenko, N.F. Flavonoids of Desmodium canadense and their analgesic effect. Khim. Farm. Zh. 1987, 21, 63–67.

45. Taylor, W.G.; Sutherland, D.H.; Pickards, K.W. Soyasaponins and Related Glycosides of Desmodium canadense and Desmodium illinoense. Open Nat. Prod. J. 2009, 2, 59–67.

46. Ma, X.; Zheng, C.; Hu, C.; Rahman, K.; Qin, L. The genus Desmodium (Fabaceae)-traditional uses in Chinese medicine, phytochemistry and pharmacology. J. Ethnopharmacol. 2011, 138, 314–332.

47. Yang, J.-L.; Ha, T.-K.-Q.; Dhodary, B.; Pyo, E.; Nguyen-Ngoc, H.; Cho, H.; Kim, E.; Oh, W.K. Oleanane Triterpenes from the Flowers ofCamellia japonicaInhibit Porcine Epidemic Diarrhea Virus (PEDV) Replication. J. Med. Chem. 2015, 58, 1268–1280.

48. Yang, J.-L.; Ha, T.K.Q.; Oh, W.K. Discovery of inhibitory materials against PEDV corona virus from medicinal plants. Jpn. J. Vet. Res. 2016, 64, S53–S63.

49. Azuma, C.M.; Dos Santos, F.C.S.; Lago, J.H.G. Flavonoids and fatty acids of Camellia japonica leaves extract. Rev. Bras. Farm. 2011, 21, 1159–1162.

50. Itokawa, H.; Nakajima, H.; Ikuta, A.; Iitaka, Y. Two triterpenes from the flowers of Camellia japonica. Phytochemistry 1981, 20, 2539–2542.

51. Kato, M.; Ashihara, H. Biosynthesis and Catabolism of Purine Alkaloids in Camellia Plants. Nat. Prod. Commun. 2008, 3, 1934578 0800300907.

52. Karioti, A.; Bilia, A.R.; Skaltsa, H. Quercus ilex L.: A rich source of polyacylated flavonoid glucosides. Food Chem. 2010, 123, 131–142.

53. Cheng, P.-W.; Huang, L.-T.; Chiang, L.-C.; Lin, C.-C. Antiviral effects of saikosaponins on human coronavirus 229e in vitro. Clin. Exp. Pharmacol. Physiol. 2006, 33, 612–616.

54. Yang, F.; Dong, X.; Yin, X.; Wang, W.; You, L.; Ni, J. Radix Bupleuri: A Review of Traditional Uses, Botany, Phytochemistry, Pharmacology, and Toxicology. BioMed. Res. Int. 2017, 2017, 7597596.

55. Lau, K.M.; Lee, K.M.; Koon, C.M.; Cheung, C.S.; Lau, C.P.; Ho, H.M.; Lee, M.Y.; Au, S.W.; Cheng, C.H.; Lau, C.B.; et al. Immunomodulatory and anti-SARS activities of Houttuynia cordata. J. Ethnopharmacol. 2008, 118, 79–85.

56. Hemalatha, S.; Kumar, M.; Prasad, S. A current update on the phytopharmacological aspects of Houttuynia cordata Thunb. Pharmacogn. Rev. 2014, 8, 22–35.

57. Lin, C.-W.; Tsai, F.-J.; Tsai, C.-H.; Lai, C.-C.; Wan, L.; Ho, T.-Y.; Hsieh, C.-C.; Chao, P.-D.L. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antivir. Res. 2005, 68, 36–42.

58. Speranza, J.; Miceli, N.; Taviano, M.F.; Ragusa, S.; Kwiecień, I.; Szopa, A.; Ekiert, H. Isatis tinctoria L. (Woad): A Review of its Botany, Ethnobotanical Uses, Phytochemistry, Biological Activities, and Biotechnological Studies. Plants 2020, 9, 298.

59. Li, Y.; Chen, C.; Zhang, H.; Guo, H.; Wang, H.; Wang, L.; Zhang, X.; Hua, S.; Yu, J.; Xiao, P.G.; et al. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antivir. Res. 2005, 67, 18–23.

60. Wang, L.; Zhang, X.-Q.; Yin, Z.-Q.; Wang, Y.; Ye, W.-C. Two New Amaryllidaceae Alkaloids from the Bulbs of Lycoris radiata. Chem. Pharm. Bull. 2009, 57, 610–611.

61. Tian, Y.; Zhang, C.; Guo, M. Comparative Analysis of Amaryllidaceae Alkaloids from Three Lycoris Species. Molecules 2015, 20, 21854–21869.

62. Shi, T.; Hou, C.; Shi, M.; Shen, M.; Wang, X.; Wang, L. Exploration of Floral Volatile Organic Compounds in Six Typical Lycoris Species by GC-MS. Plants 2019, 8, 422.

63. Gong, S.J.; Su, X.J.; Yu, H.P.; Li, J.; Qin, Y.J.; Xu, Q.; Luo, W.S. A study on anti-SARS-CoV 3CL protein of flavonoids from litchi chinensis sonn core. Chin. Pharmacol. 2008, 24, 699–700.

64. Jo, S.; Kim, S.; Shin, D.H.; Kim, M.-S. Inhibition of SARS-CoV 3CL protease by flavonoids. J. Enzym. Inhib. Med. Chem. 2020, 35, 145–151.

65. Nimmanpipug, P.; Lee, V.S.; Wolschann, P.; Hannongbua, S. Litchi chinensis-derived terpenoid as anti-HIV-1 protease agent: Structural design from molecular dynamics simulations. Mol. Simul. 2009, 35, 673–680.

66. Ibrahim, S.R.; Mohamed, G.A. Litchi chinensis: Medicinal uses, phytochemistry, and pharmacology. J. Ethnopharmacol. 2015, 174, 492–513.

67. Kim, D.E.; Min, J.S.; Jang, M.S.; Lee, J.Y.; Shin, Y.S.; Park, C.M.; Song, J.H.; Kim, H.R.; Kim, S.; Jin, Y.-H.; et al. Natural Bis-Benzylisoquinoline Alkaloids-Tetrandrine, Fangchinoline, and Cepharanthine, Inhibit Human Coronavirus OC43 Infection of MRC-5 Human Lung Cells. Biomolecules 2019, 9, 696.

68. Yu, M.-S.; Lee, J.; Lee, J.M.; Kim, Y.; Chin, Y.-W.; Jee, J.-G.; Keum, Y.-S.; Jeong, Y.-J. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg. Med. Chem. Lett. 2012, 22, 4049–4054.

69. Zhao, T.; Tang, H.; Xie, L.; Zheng, Y.; Ma, Z.; Sun, Q.; Li, X. Scutellaria baicalensis Georgi. (Lamiaceae): A review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. J. Pharm. Pharmacol. 2019, 71, 1353–1369.

70. Shojaii, T.M.; Langeroudi, A.G.; Karimi, V.; Barin, A.; Sadri, N. The effect of Allium sativum (Garlic) extract on infectious bronchitis virus in specific pathogen free embryonic egg. Avicenna J. Phytomed. 2016, 6, 458.

71. Weber, N.D.; Andersen, D.O.; North, J.A.; Murray, B.K.; Lawson, L.D.; Hughes, B.G. In VitroVirucidal Effects of Allium sativum (Garlic) Extract and Compounds. Planta Med. 1992, 58, 417–423.

72. Szychowski, K.A.; Binduga, U.E.; Rybczyńska-Tkaczyk, K.; Leja, M.L.; Gmiński, J. Cytotoxic effects of two extracts from garlic (Allium sativum L.) cultivars on the human squamous carcinoma cell line SCC-15. Saudi J. Biol. Sci. 2018, 25, 1703–1712.

73. Pontin, M.; Bottini, R.; Burba, J.L.; Piccoli, P. Allium sativum produces terpenes with fungistatic properties in response to infection with Sclerotium cepivorum. Phytochemistry 2015, 115, 152–160.

74. Ekiert, H.; Klin, P.; Pajor, J.; Szopa, A. Influence of Elicitation on Production of Active Ingredients and Biological Activity of In Vitro Cultures of Artemisia annua L. Against Antibiotic-Susceptible and-Resistant Strains of Salmonella typhimurium. Yakhak Hoeji 2007, 51, 355–360.

75. Nigam, M.; Atanassova, M.; Mishra, A.P.; Pezzani, R.; Devkota, H.P.; Plygun, S.; Salehi, B.; Setzer, W.N.; Sharifi-Rad, J. Bioactive Compounds and Health Benefits of Artemisia Species. Nat. Prod. Commun. 2019, 14, 19850354.

76. Li, W.; Moore, M.J.; Vasilieva, N.; Sui, J.; Wong, S.K.; Berne, M.A.; Somasundaran, M.; Sullivan, J.L.; Luzuriaga, K.; Greenough, T.C.; et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003, 426, 450–454.

77. Bais, S.; Gill, N.S.; Rana, N.; Shandil, S. A Phytopharmacological Review on a Medicinal Plant: Juniperus communis. Int. Sch. Res. Not. 2014, 2014, 634723.

78. Park, J.Y.; Kim, J.H.; Kwon, J.M.; Kwon, H.J.; Jeong, H.J.; Kim, Y.M. Dieckol, a SARS-CoV 3CL inhibitor, isolated from the edible brown algae Ecklonia cava. Phytochemistry 2013, 20, 2539–2542.

79. Van Damme, E.J.M.; Peumans, W.J.; Barre, A.; Rougé, P. Plant Lectins: A Composite of Several Distinct Families of Structurally and Evolutionary Related Proteins with Diverse Biological Roles. Crit. Rev. Plant Sci. 1998, 17, 575–692.

80. Müller, W.E.; Renneisen, K.; Kreuter, M.H.; Schröder, H.C.; Winkler, I. The D-mannose-specific lectin from Gerardia savaglia blocks binding of human immunodeficiency virus type I to H9 cells and human lymphocytes in vitro. J. Acquir. Immune Defic. Syndr. 1988, 1, 453–458.

81. Hammar, L.; Eriksson, S.; Morein, B. Human Immunodeficiency Virus Glycoproteins: Lectin Binding Properties. AIDS Res. Hum. Retrovir. 1989, 5, 495–506.

82. Hansen, J.-E.S.; Nielsen, C.; Heegaard, P.; Mathiesen, L.R.; Nielsen, J.O.; Nielsen, C. Correlation between carbohydrate structures on the envelope glycoprotein gp120 of.HIV-1 and HIV-2 and syncytium inhibition with lectins. AIDS 1989, 3, 635–642.
83. Matsui, T.; Kobayashi, S.; Yoshida, O.; Ishii, S.-I.; Abe, Y.; Yamamoto, N. Effects of succinylated concanavalin A on infectivity and syncytial formation of human immunodeficiency virus. Med. Microbiol. Immunol. 1990, 179, 225–235.
84. Balzarini, J.; Schols, D.; Neyts, J.; Van Damme, E.; Peumans, W.; De Clercq, E. Alpha-(1-3)- and alpha-(1-6)-D-mannose-specific plant lectins are markedly inhibitory to human immunodeficiency virus and cytomegalovirus infections in vitro. Antimicrob. Agents Chemother. 1991, 35, 410–416.
85. Balzarini, J.; Neyts, J.; Schols, D.; Hosoya, M.; Van Damme, E.; Peumans, W.; De Clercq, E. The mannose-specific plant lectins from Cymbidium hybrid and Epipactis helleborine and the (N-acetylglucosamine)n-specific plant lectin from Urtica dioica are potent and selective inhibitors of human immunodeficiency virus and cytomegalovirus replication in vitro. Antivir. Res. 1992, 18, 191–207.
86. Balzarini, J.; Hatse, S.; Vermeire, K.; Princen, K.; Aquaro, S.; Perno, C.-F.; De Clercq, E.; Egberink, H.; Mooter, G.V.; Peumans, W.; et al. Mannose-Specific Plant Lectins from the Amaryllidaceae Family Qualify as Efficient Microbicides for Prevention of Human Immunodeficiency Virus Infection. Antimicrob. Agents Chemother. 2004, 48, 3858–3870.
87. Krokhin, O.; Li, Y.; Andonov, A.; Feldmann, H.; Flick, R.; Jones, S.; Stroeher, U.; Bastien, N.; Dasuri, K.V.N.; Cheng, K.; et al. Mass Spectrometric Characterization of Proteins from the SARS Virus. Mol. Cell. Proteom. 2003, 2, 346–356.
88. Haslberger, A.; Jacob, U.; Hippe, B.; Karlic, H. Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review. Funct. Foods Heal. Dis. 2020, 10, 195.
89. Coppé, J.-P.; Desprez, P.-Y.; Krtolica, A.; Campisi, J. The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression. Annu. Rev. Pathol. Mech. Dis. 2010, 5, 99–118.
90. Thaler, R.; Maurizi, A.; Roschger, P.; Sturmlechner, I.; Khani, F.; Spitzer, S.; Rumpler, M.; Zwerina, J.; Karlic, H.; Dudakovic, A.; et al. Anabolic and Antiresorptive Modulation of Bone Homeostasis by the Epigenetic Modulator Sulforaphane, a Naturally Occurring Isothiocyanate. J. Biol. Chem. 2016, 291, 6754–6771.
91. Olesin, E.; Nayar, R.; Saikumar-Lakshmi, P.; Berg, L.J. The Transcription Factor Runx2 Is Required for Long-Term Persistence of Antiviral CD8+ Memory T Cells. ImmunoHorizons 2018, 2, 251–261.
92. Müller, L.; Meyer, M.; Bauer, R.N.; Zhou, H.; Zhang, H.; Jones, S.; Robinette, C.; Noah, T.L.; Jaspers, I. Effect of Broccoli Sprouts and Live Attenuated Influenza Virus on Peripheral Blood Natural Killer Cells: A Randomized, Double-Blind Study. PLoS ONE 2016, 11, e0147742.
93. Marinella, M.A. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. Int. J. Clin. Pract. 2020, 74, e13535.
94. Medina-Bolivar, F.; Condori, J.; Rimando, A.M.; Hubstenberger, J.; Shelton, K.; O'Keefe, S.F.; Bennett, S.; Dolan, M.C. Production and secretion of resveratrol in hairy root cultures of peanut. Phytochemistry 2007, 68, 1992–2003.
95. Sowndhararajan, K.; Deepa, P.; Kim, M.; Park, S.J.; Kim, S. Neuroprotective and Cognitive Enhancement Potentials of Baicalin: A Review. Brain Sci. 2018, 8, 104.
96. Yonesi, M.; Rezazadeh, A. Plants as a prospective source of natural anti-viral compounds and oral vaccines against COVID-19 coronavirus. Preprints 2020.
97. Chen, Z.; Ye, S.-Y.; Yang, Y.; Li, Z.-Y. A review on charred traditional Chinese herbs: Carbonization to yield a haemostatic effect. Pharm. Biol. 2019, 57, 498–506.
98. Shah, S.L.; Wahid, F.; Khan, N.; Farooq, U.; Shah, A.J.; Tareen, S.; Ahmad, F.; Khan, T. Inhibitory Effects ofGlycyrrhiza glabraand Its Major Constituent Glycyrrhizin on Inflammation-Associated Corneal Neovascularization. Evid. Based Complement. Altern. Med. 2018, 2018, 8438101.
99. Pilcher, H. Liquorice may tackle SARS. Nature 2003.
100. Chen, H.; Du, Q. Potential natural compounds for preventing SARS-CoV-2 (2019-nCoV) infection. Preprints 2020.
101. Dubey, K.; Dubey, R. Computation screening of narcissoside a glycosyloxyflavone for potential novel coronavirus 2019 (COVID-19) inhibitor. Biomed. J. 2020, 43, 363–367.
102. Praditya, D.; Kirchhoff, L.; Brüning, J.; Rachmawati, H.; Steinmann, J.; Steinmann, E. Anti-infective Properties of the Golden Spice Curcumin. Front. Microbiol. 2019, 10, 912.
103. Rein, M.J.; Renouf, M.; Cruz-Hernandez, C.; Actis-Goretta, L.; Thakkar, S.K.; Da Silva Pinto, M. Bioavailability of bioactive food compounds: A challenging journey to bioefficacy. Br. J. Clin. Pharmacol. 2013, 75, 588–602.
104. Bansal, T.; Awasthi, A.; Jaggi, M.; Khar, R.K.; Talegaonkar, S. Pre-clinical evidence for altered absorption and biliary excretion of irinotecan (CPT-11) in combination with quercetin: Possible contribution of P-glycoprotein. Life Sci. 2008,

83, 250–259.

105. Shoba, G.; Joy, D.; Joseph, T.; Majeed, M.; Rajendran, R.; Srinivas, P.S.S.R. Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. Planta Med. 1998, 64, 353–356.