**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 65847

**Manuscript Type:** REVIEW

**Evaluation of botanicals as potential COVID-19 symptoms terminator**

Caliskan UK *et al*. Botanicals as potential COVID-19 symptoms terminator

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**Received:** March 16, 2021

**Revised:** May 1, 2021

**Accepted:** September 14, 2021

**Published online:**

**Abstract**

Information about the coronavirus disease 2019 (COVID-19) pandemic is still evolving since its appearance in December 2019 and has affected the whole world. Particularly, a search for an effective and safe treatment for COVID-19 continues. Botanical mixtures contain secondary metabolites (such as flavonoids, phenolics, alkaloids, essential oils *etc.*) with many therapeutic effects. In this study, the use of herbal treatments against COVID-19 was evaluated. Medical synthetic drugs focus mainly on respiratory symptoms, however herbal therapy with plant extracts may be useful to relieve overall symptoms of COVID-19 due to the variety of bioactive ingredients. Since COVID-19 is a virus that affects the respiratory tract, the antiviral effects of botanicals/plants against respiratory viruses have been examined through clinical studies. Data about COVID-19 patients revealed that the virus not only affects the respiratory system but different organs including the gastrointestinal (GI) system. As GI symptoms seriously affect quality of life, herbal options that might eliminate these problems were also evaluated. Finally, computer modeling studies of plants and their active compounds on COVID-19 were included. In summary, herbal therapies were identified as potential options for both antiviral effects and control of COVID-19 symptoms. Further data will be needed to enlighten all aspects of COVID-19 pathogenesis, before determining the effects of plants on severe acute respiratory syndrome coronavirus 2.

**Key Words:** COVID-19; Herbal therapies; Plant; SARS-CoV-2; Antiviral; Symptom

Caliskan UK, Karakus MM. Evaluation of botanicals as potential COVID-19 symptoms terminator. *World J Gastroenterol* 2021; In press

**Core Tip:** To stop the coronavirus disease 2019 (COVID-19) pandemic, extensive search is ongoing to develop effective and safe drugs against severe acute respiratory syndrome coronavirus 2. COVID-19 in a major way affects the respiratory system, but many patients also have gastrointestinal (GI) symptoms. Plants have beneficial effects on various systems with their varied array of metabolites. In our study, the potential effects of herbal treatments against COVID-19 were examined. Their antiviral effects, their effects on the respiratory system, GI system, and other COVID-19 symptoms were investigated.

**INTRODUCTION**

New coronavirus disease 2019 (COVID-19), which emerged in Wuhan in December 2019, spread rapidly and affected the whole world. The emergence, epidemiology, origin and evolution of COVID-19 has been extensively studied by Sun *et al*[1].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to carry out viral replication in the human host mainly through three main proteins and enzymes: 3-chymotrypsin-like protease (3CLpro), angiotensin-converting enzyme-2 (ACE2) and spike protein (TMPRSS2)[2,3]. ACE2 receptors are found in the body not only in the lungs but also in tissues such as the endothelium, heart, kidney and intestine[2]. This distribution makes many organs a target of COVID-19. The significance of ACE2, which is found in intestinal tissues, especially for amino acid uptake from foods, has been emphasized and it has been suggested that the intestine may be an important entry site for SARS-CoV-2[2-4] Azithromycin, chloroquine, lopinavir, remdesivir, ritonavir are options used in treatment and whose effects are evaluated[5]. Effective and safe drugs and vaccines are sought all over the world to prevent novel coronavirus. Minerals, herbs, herbal products, probiotics and vitamins are the main natural resources, whose effectiveness and also the usability of herbal medicines in COVID-19 were investigated and benefit, risk assessments were evaluated[6-8]. Truly, since the beginning of the COVID-19, herbal medicines have been used in China. A study has shown that 90% of the 214 patients were treated with the traditional herbal medicine, moreover, it is reported that some of them prevented COVID-19 infection in healthy individuals and enhanced the health state of patients with mild or severe symptoms[9,10]. Health scientists from the Zhongnan Hospital of Wuhan University included the use of traditional medicines in the guidelines for the treatment and prevention of COVID-19. The experts recommended using medicinal plants for the prevention of COVID-19, additionally, the use of different herbal mixtures were recommended according to the disease-stage[11].

Herbs and herbal products provide generous sources of primary and mostly secondary metabolites, which are valuable compounds (phenolics, flavonoids, tannins, alkaloids, essential oils, *etc.*) for prophylactic and chronical therapeutic purposes. Some of these metabolites in herbs and herbal mixtures have high chemical variety than the synthetics in stopping viral proliferations, and having antiviral activities[12]. Thus, botanicals can both show antiviral effects and relieve the symptoms of COVID-19 thanks to the different substance groups, which demonstrate different biological effects that will not be possible to achieve with a single synthetic drug. Based on this understanding, in this review, we offer all the potential interventions for COVID-19 infection according to previous and recently found antiviral effects of herbals. Considering the major transmission routes of COVID-19, where mostly ACE2 receptors found and the symptoms, the plants have been handled especially with their effects on the mostly respiratory and also gastrointestinal (GI) systems. Although ACE2, is typically expressed in epithelial cells of the airways, various GI symptoms in COVID-19 might be explained by the high expression of ACE2 in the digestive tract. Additionally, liver tests abnormalities, active viral replication in GI tract and patients’ manifestations with GI symptoms (abdominal pain, diarrhea, nausea, vomiting) and possible fecal-oral transmission reveal the GI involvement in COVID-19[13].

Recent findings demonstrated that early blocking of COVID-19 with ACE2 inhibitors was one of the mechanisms used by novel drugs[14], on the other hand diabetes mellitus and hypertension enhanced the risk of COVID-19 infection, in spite of using ACE2 inhibitors[15-17]. Furthermore, unpredicted ACE2 upregulation by ACE2 inhibitors, ibuprofen and angiotensin II type-I receptor blockers lead to need of identifying/using alternative ACE2 blockers[18]. Consequently, botanicals or natural products might be alternatively and selectively might block the ACE2 receptors without inhibiting the enzyme activity in order to treat and/or prevent COVID-19 spread in humans without increasing ACE2 expression in patients and therefore increased risk for COVID-19[19].

Clinical human studies showing the effect of plants on respiratory infections are presented as a table. Based on the pharmacological properties of plants, their practicality on COVID-19 symptoms have been evaluated. In the last part of the article, plants that inhibit ACE receptors, the research studies and their active compounds on COVID-19 also included and it is aimed to examine the plants from a broad perspective.

**ANTIVIRAL EFFECTS OF HERBAL THERAPIES**

Most of the respiratory diseases (approximately 80%) are caused by viral agents[20]. Viral respiratory diseases are responsible for high mortality and morbidity, especially in disadvantaged and sensitive elderlies and immunocompromised individuals[21,22]. The main respiratory viruses are adenovirus, coronavirus, influenza virus, respiratory syncytial virus and rhinovirus[20]. Plants with antiviral effects and studies showing the effects of these on respiratory viruses are given in Table 1. Human clinical studies showing the effects of plants on respiratory tract infections are presented in Table 2.

**EFFECTS OF HERBAL TREATMENT ON COVID-19 SYMPTOMS**

Cough and fever are common symptoms in patients with COVID-19, including fatigue, shortness of breath, headache, muscle pain, sore throat, sputum, hemoptysis, diarrhea, dyspnea, rhinorrhea, chest pain, nausea, and vomiting[23]. COVID-19 symptoms in children are similar to those in adults and are relatively mild[24].

Although, the current synthetic drugs focus on mainly respiratory symptoms, herbal therapy can be used to relieve overall symptoms of COVID-19 with their bioactive ingredients[25]. The meta-analysis study, which included randomized controlled trial studies, found significant effects of the combination of western medicine and herbal therapies. Combined treatment has been effective in cough, fever, dry and sore throat, fatigue and overall GI symptoms. The combined therapy significantly improved the disappearance rate of cough and sputum production[26]. In another meta-analysis, it was found that the addition of Chinese herbal medicine for standard care improved the symptoms and signs of COVID-19 as well as decreased levels of C-reactive protein[27]. The effects of plants that can alleviate the symptoms of COVID-19 are summarized in Table 3. In addition, plants regarded as ACE inhibitors are shown in Table 4.

**THE EFFECTS OF HERBS AND THEIR ACTIVE COMPOUNDS ON COVID-19**

In recent years, artificial intelligence has often been used to discover natural products as medicine[28,29]. After the outbreak of COVID-19, computer models were used to investigate the effect of many plants and their components on SARS-CoV-2. Khaerunnisa *et al*[30], determined the COVID-19 Main Protease (Mpro) inhibitor effects of medicinal plant components in a molecular docking study. They suggested apigenin-7-glucoside, curcumin, catechin, demethoxycurcumin, epicatechin-gallate, luteolin-7-glucoside, and oleuropein, as potential inhibitors of COVID-19 Mpro. In a similar molecular docking study using sixty-seven molecules of natural origin, crocin, digitoxigenin and b-eudesmol were proposed as inhibitors against coronavirus[31]. Another study was carried out using one hundred seventy-one essential oil components. The study determined the best docking ligands for the SARS-CoV target proteins were (E)--farnesene, (E,E)--farnesene and (E,E)-farnesol, thereby suggesting essential oil components may act synergistically with other antiviral agents, or they may provide some relief of COVID-19 symptoms[32]. Computer modeling studies and clinical studies against SARS-CoV-2 in some prominent plants/products and their metabolites are given below.

***Curcuma longa***

Utomo and Meiyanto[33] revealed the potential of several compounds of *Curcuma longa* against SARS-CoV-2 by binding to three protein receptors (*RBD-S*, *PD-ACE2*, *SARS-CoV-2 protease*). They showed that *Curcuma* sp*.* compounds can bind to target receptors, thus, have potential inhibitory effects on SARS-CoV-2 infectivity.Rajagopal *et al*[34] showed in their *in silico* docking study that *Curcuma longa* components could be effective against COVID-19 by inhibiting the SARS-CoV-2 Mpro enzyme. Morever, cyclocurcumin and curcumin possess significant binding at the active site of SARS-CoV-2 Mpro when compared to hydroxychloroquine and nelfinavir. When compared to remdesivir, cyclocurcumin is significantly more active [Glide score: Cyclocurcumin (−6.77); remdesivir (−6.38); curcumin (−6.13); nelfinavir (−5.93); hydroxychloroquine (− 5.47)].In a similar study, diacetylcurcuminin was more effective on COVID-19 (Mpro) than nelfinavir[35]. Another study suggested the use of curcumin with hydroxychloroquine to destabilize the SARS-CoV2 receptor proteins[36]. Gonzalez-Paz *et al*[37] showed that curcumin strongly binds to 3CL-protease of COVID-19 Curcumin caused enzyme folding and structural changes in viral protease. Moreover, curcumin bound more strongly to the enzyme than chloroquine.

***Eucalyptus globulus***

Sharma[38] suggested that eucalyptus essential oil active compounds are potential inhibitors of COVID-19 Mpro. They conducted a molecular docking study to evaluate the effect of eucalyptol (1.8 cineol), which is a component of eucalyptus essential oil, on Mpro. They showed that eucalyptol/Mpro complexes produce hydrophobic interactions, strong ionic interactions, hydrogen bond interactions, and eucalyptol may be a potential inhibitor of COVID-19 Mpro. Similarly, M pro/3CL pro/eucalyptol complexes have been shown to form hydrophobic interactions[39]. In another study, Sharma and Kaur[40] suggested jensenone, the component of eucalyptus essential oil, as a potential COVID-19 Mpro inhibitor. In a molecular docking study of 12 active ingredients of eucalyptus essential oil, all of these ingredients were found to bind effectively to the COVID-19 S-protein. Especially the toruatone component was effectively bound and the Spike (S) protein/Toruatone complexes formed hydrogen and hydrophobic interactions[41]. Muhammad *et al*[42], in a study of the molecular insertion of eucalyptus active ingredients into Mpro, showed that the α-gurjune of eucalyptus, aromadene and allo-aromadene components have strong binding energy.

***Glycyrrhiza glabra***

Sinha *et al*[43] conducted molecular docking simulation studies of two antiviral drugs (lopinavir and ribavirin) and 20 compounds of *Glycyrrhiza glabra*. Two protein targets from COVID-19 have been identified: Non-structural protein-15 endoribonuclease and spike glycoprotein. Glycyrrhizic acid prevented the virus from entering the host cell, due to its bulky structure. Gliasperin A showed high affinity to Nsp15 endoribonuclease and inhibited its activity. The authors suggested that glycyrrhizic acid disrupts the connection of the virus with the ACE2 receptor at the input level, and Gliasperin A inhibits the replication process of the virus after it enters the host cell. Another study showed that glycyrrhizin can be highly bound to Mpro[44].

***Scutellaria baicalensis***

Liu *et al*[45] investigated the *in vitro* effect of *Scutellaria baicalensis* and its components on COVID-19. Baicalein (its main ingredient) and the ethanol extract of the plant inhibited the 3CLpro activity and replication of COVID-19. The ethanol extract also inhibited viral entry. Udrea *et al*[46] suggested the benefit *Scutellaria baicalensis* flavones (especially baicalein) against respiratory damage caused by COVID-19. Flavones bound to 3CLpro. strongly bound to wogonin flavone, nitric oxide synthase and cyclooxygenase 2. In addition, norwogonin and baicalein arachidonate modulated 15-lipoxygenase and lysine-specific demethylase 4D analogue.

***Thymus vulgaris***

In a randomized clinical study conducted on patients suffering from COVID-19, it was found that *Thymus vulgaris* strengthens the immune system and can be used to reduce COVID-19 symptoms. In the study, 83 COVID-19 patients were randomly divided into the control group and the group receiving thyme (TRG). TRG was given as thyme essential oil three times a day for seven days. A questionnaire asking about symptoms such as fever, cough, fatigue, and loss of appetite was completed before and at the end of treatment to determine the effect of thyme on symptoms. Thyme essential oil significantly reduced the severity of symptoms such as fever, cough, shortness of breath, dizziness, muscle pain, anorexia, weakness and lethargy and fatigue. Additionally, thyme increased lymphocyte count and calcium while decreasing blood urea nitrogen and neutrophil count[47].Carvacrol, a component of thyme, has been shown to inhibit Mpro by *in silico* study. It can be a potential inhibitor of controlling viral replication[48].

***Withania somnifera***

*W. somnifera* components withanolides have potential antiviral properties on COVID-19[49]. Patel *et al*[50]demonstrated that *W. somnifera*'s Withanoside VI components have positive interactions at the binding site of protein targets of SARS-CoV-2. Withanonereduced the electrostatic interaction between ACE2 and receptor binding domain[51]. Withaferin A, which is found in the *W. somnifera* plant, has been shown to interact with Mpro and Glucose regulated protein 78 (GRP78) receptor[52].

**CONCLUSION**

In this study, the concept of “being effective against COVID-19” for herbal treatments was discussed from the angles of antiviral effect and control of symptoms, specifically related to GI system

***Antiviral effects on COVID-19***

Since COVID-19 is a virus that mainly affects the respiratory tract, the antiviral effects of medicinal plants against respiratory viruses have been examined firstly. The structure similarities of SARS-CoV-2 have been found with SARS-CoV and Middle East respiratory syndrome coronavirus. Therefore, it can be suggested that plants and their compounds affecting these viruses may also be potential treatment options for COVID-19. Here firstly, clinical studies supporting antiviral effects of 22 plant on respiratory viruses has been reviewed which determined that glycyrrhizic acid derivatives obtained from *Glycyrrhiza* sp, *Nigella sativa*, *Scutellaria baicalensis* and *Torreya nucifera* have anti-COVID-19 effects. Plants such as *Allium sativum*, *Glycyrrhiza glabra*, *Melaleuca* sp, *Withania somnifera* have been shown to bind to ACE2 receptors that are imperative for COVID-19 replication. Focusing on these plants might be a logical way to go for herbal treatment against COVID-19.

This review also showed the antiviral effects of essential oils obtained from plants have the potential to affect COVID-19. The treatment involves using inhaled steam supplemented by essential oils possessing natural antimicrobial properties, oropharyngeal sanitization, as well as they are remedies for symptomatic relief. Inhalation of antimicrobial essential oils may help attenuate the virus in the nasal cavity, nasopharynx, oropharynx, and laryngopharynx. Antiseptic mouthwashes and gargles can also help to sanitize the oral cavity and oropharynx, whereas antiseptic lozenges can help to sanitize the oro- and laryngopharynx as well. The steam will carry the tiny particles of the antimicrobial constituents from these essential oils into the respiratory tract and is likely to improve the efficacy of the steam treatment. The steam supplemented by antimicrobial volatile oils may help to provide a local antimicrobial effect within the airways.

There are computer model studies showing that some botanicals and active ingredients are effective in COVID-19. *Allium sativum*, *Curcuma longa*, *Eucalyptus globulus*, *Glycyrrhiza glabra*, *Melaleuca* sp, *Thymus vulgaris*, *Withania somnifera* is among these plants. These studies with commonly found plants will guide future studies to develop effective supplements or drugs for COVID-19.

***Symptomatic treatment of COVID-19***

Since the symptoms of COVID-19 seriously affect the quality of life, herbal options to eliminate them were also evaluated in this review. Previously, herbs such as garlic, echinacea and ginseng were found to reduce the symptoms of cold in healthy individuals. Plants with their pharmacological effects are natural options for eliminating the symptoms of COVID-19. Based on the effects described in Table 3, *Allium sativum*, *Curcuma longa*, *Scutellaria baicalensis* and *Zingiber officinale* are easily found as prominent plants to eliminate the GI symptoms of COVID-19. For example, ginger can eliminate the negative effects of COVID-19 on the GI system with its antiemetic and hepatic protective properties. A clinical study was conducted with thyme essential oil on COVID-19. Thyme essential oil was found to significantly reduce COVID-19 symptoms. This revealed an option that thyme and essential oil have potential effects for consideration in treatment of COVID-19. Studies on more essential oils of eucalyptus reveal more effects of eucalyptus on respiratory system symptoms. *Eucalyptus globulus*, *Hedera helix*, *Pelargonium sidoides*, *Sambucus nigra*, *Thymus vulgaris* can be recommended for relief of respiratory symptoms. ACE2 receptors are found in tissues other than the lung, such as the intestine. Based on this fact, we concluded that the use of herbs binding to ACE2 receptors can eliminate the side effects that may occur in variety of organs including GI tract. As shown in Table 4 these plants are *Ammoides verticillate*, *Allium sativum*, *Apium graveolens*, *Camellia sinensis*, *Citrus aurantium*, *Erigeron breviscapus*, *Glycine max*, *Glycyrrhiza glabra*, *Hibiscus sabdariffa*, *Linum usitatissimum*, *Melaleuca* sp., *Nicotiana benthamiana*, *Withania somnifera*.

Based on these studies, herbal treatments offer several potential treatments of COVID-19. Plants may be an option for the treatment of COVID-19 and its symptoms, as well as protection from COVID-19. Even though these data point to good outcomes there is always the possibility of interaction between drugs used and these herbs. For instance, herbs such as ginger with antithrombotic effects can be beneficial on COVID-19 symptoms, but one might be cautious about escalated risk of bleeding when it is used together with antithrombotic or anticoagulant drugs. Therefore, it is extremely important to avoid the indiscriminate use of plants.

For a plant to be used as a medicine, its effect must be supported by clinical studies. COVID-19 is just emerging, and more research are needed for its treatment. Yet, herbal therapies are potential options for both antiviral effects and the control of COVID-19 symptoms. Since plants with multiple pharmacological effects can affect many systems (respiratory, GI, and nervous), herbs might be more effective against COVID-19 than synthetic drugs. But first, all aspects of SARS-CoV-2 need to be examined. Then, the effects of plants on this virus should be determined by further studies.

***The strengths and weaknesses of this review***

Unlike other studies, in this report, the effect of plants on COVID-19 was evaluated in several ways. Preclinical studies, clinical studies and silico studies are included in this review. Moreover, the efficacy on COVID-19 symptoms has been addressed by including different systems. On the other hand, the focus is on the respiratory and GI systems. The effects, not only of botanicals but also active metabolites of have been studied.

The biggest limitation of this study is the lack of sufficient studies on the efficacy of botanicals. Since botanical studies are generally preclinical studies, results may vary due to conducting and including clinical studies. In clinical studies showing the effects of the plants in Table 2 on respiratory tract infections, the results were generally obtained with questionnaire studies. Placebo effects and breadth of study may be effective in positive results.

**REFERENCES**

1 **Sun J**, He WT, Wang L, Lai A, Ji X, Zhai X, Li G, Suchard MA, Tian J, Zhou J, Veit M, Su S. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. *Trends Mol Med* 2020; **26**: 483-495 [PMID: 32359479 DOI: 10.1016/j.molmed.2020.02.008]

2 **Zhang H**, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Med* 2020; **46**: 586-590 [PMID: 32125455 DOI: 10.1007/s00134-020-05985-9]

3 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

4 **Hashimoto T**, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477-481 [PMID: 22837003 DOI: 10.1038/nature11228]

5 **Felsenstein S**, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. *Clin Immunol* 2020; **215**: 108448 [PMID: 32353634 DOI: 10.1016/j.clim.2020.108448]

6 **Singh R**, Shaik L, Mehra I, Kashyap R, Surani S. Novel and Controversial Therapies in COVID-19. *Open Respir Med J* 2020; **14**: 79-86 [PMID: 33717367 DOI: 10.2174/1874306402014010079]

7 **Silveira D**, Prieto-Garcia JM, Boylan F, Estrada O, Fonseca-Bazzo YM, Jamal CM, Magalhães PO, Pereira EO, Tomczyk M, Heinrich M. COVID-19: Is There Evidence for the Use of Herbal Medicines as Adjuvant Symptomatic Therapy? *Front Pharmacol* 2020; **11**: 581840 [PMID: 33071794 DOI: 10.3389/fphar.2020.581840]

8 **Panyod S**, Ho CT, Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective. *J Tradit Complement Med* 2020; **10**: 420-427 [PMID: 32691006 DOI: 10.1016/j.jtcme.2020.05.004]

9 **DU HZ**, Hou XY, Miao YH, Huang BS, Liu DH. Traditional Chinese Medicine: an effective treatment for 2019 novel coronavirus pneumonia (NCP). *Chin J Nat Med* 2020; **18**: 206-210 [PMID: 32245590 DOI: 10.1016/S1875-5364(20)30022-4]

10 **Xu K**, Cai H, Shen Y, Ni Q, Chen Y, Hu S, Li J, Wang H, Yu L, Huang H, Qiu Y, Wei G, Fang Q, Zhou J, Sheng J, Liang T, Li L. [Management of corona virus disease-19 (COVID-19): the Zhejiang experience]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020; **49**: 147-157 [PMID: 32096367 DOI: 10.3785/j.issn.1008-9292.2020.02.02]

11 **Jin YH**, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH; , for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020; **7**: 4 [PMID: 32029004 DOI: 10.1186/s40779-020-0233-6]

12 **Naithani R,** Mehta RG, Shukla D, Chandersekera SN, Moriarty RM. Antiviral activity of phytochemicals: A current perspective. In Dietary Components and Immune Function. Totowa, NJ, Humana Press, 2010: 421-468

13 **Vespa E**, Pugliese N, Colapietro F, Aghemo A. Stay (GI) Healthy: COVID-19 and Gastrointestinal Manifestations. *Tech Innov Gastrointest Endosc* 2021; **23**: 179-189 [PMID: 33521703 DOI: 10.1016/j.tige.2021.01.006]

14 **Adedeji AO**, Severson W, Jonsson C, Singh K, Weiss SR, Sarafianos SG. Novel inhibitors of severe acute respiratory syndrome coronavirus entry that act by three distinct mechanisms. *J Virol* 2013; **87**: 8017-8028 [PMID: 23678171 DOI: 10.1128/JVI.00998-13]

15 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

16 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

17 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]

18 **Fang L**, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; **8**: e21 [PMID: 32171062 DOI: 10.1016/S2213-2600(20)30116-8]

19 **Benarba B**, Pandiella A. Medicinal Plants as Sources of Active Molecules Against COVID-19. *Front Pharmacol* 2020; **11**: 1189 [PMID: 32848790 DOI: 10.3389/fphar.2020.01189]

20 **Mahony JB**, Petrich A, Smieja M. Molecular diagnosis of respiratory virus infections. *Crit Rev Clin Lab Sci* 2011; **48**: 217-249 [PMID: 22185616 DOI: 10.3109/10408363.2011.640976]

21 **Talbot HK**, Falsey AR. The diagnosis of viral respiratory disease in older adults. *Clin Infect Dis* 2010; **50**: 747-751 [PMID: 20121411 DOI: 10.1086/650486]

22 **Englund J**, Feuchtinger T, Ljungman P. Viral infections in immunocompromised patients. *Biol Blood Marrow Transplant* 2011; **17**: S2-S5 [PMID: 21195305 DOI: 10.1016/j.bbmt.2010.11.008]

23 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

24 **Xia W**, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol* 2020; **55**: 1169-1174 [PMID: 32134205 DOI: 10.1002/ppul.24718]

25 **Geier MR**, Geier DA. Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality. *Med Hypotheses* 2020; **140**: 109760 [PMID: 32344310 DOI: 10.1016/j.mehy.2020.109760]

26 **Ang L**, Song E, Lee HW, Lee MS. Herbal Medicine for the Treatment of Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med* 2020; **9** [PMID: 32456123 DOI: 10.3390/jcm9051583]

27 **Fan AY**, Gu S, Alemi SF; Research Group for Evidence-based Chinese Medicine. Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis. *J Integr Med* 2020; **18**: 385-394 [PMID: 32792254 DOI: 10.1016/j.joim.2020.07.008]

28 **Chen Y**, de Bruyn Kops C, Kirchmair J. Data Resources for the Computer-Guided Discovery of Bioactive Natural Products. *J Chem Inf Model* 2017; **57**: 2099-2111 [PMID: 28853576 DOI: 10.1021/acs.jcim.7b00341]

29 **Yang YJ**, Bang CS. Application of artificial intelligence in gastroenterology. *World J Gastroenterol* 2019; **25**: 1666-1683 [PMID: 31011253 DOI: 10.3748/wjg.v25.i14.1666]

30 **Khaerunnisa S,** Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. 2020 Preprint. Available from: 20944 [DOI: 10.20944/preprints202003.0226.v1]

31 **Aanouz I**, Belhassan A, El-Khatabi K, Lakhlifi T, El-Ldrissi M, Bouachrine M. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. *J Biomol Struct Dyn* 2021; **39**: 2971-2979 [PMID: 32306860 DOI: 10.1080/07391102.2020.1758790]

32 **Silva JKRD**, Figueiredo PLB, Byler KG, Setzer WN. Essential Oils as Antiviral Agents. Potential of Essential Oils to Treat SARS-CoV-2 Infection: An *In-Silico* Investigation. *Int J Mol Sci* 2020; **21** [PMID: 32408699 DOI: 10.3390/ijms21103426]

33 **Utomo RY,** Meiyanto E. Revealing the potency of citrus and galangal constituents to halt SARS-CoV-2 infection. 2020 Preprint. Available from: 2020030214 [DOI: 10.20944/preprints202003.0214.v1]

34 **Rajagopal K**, Varakumar P, Baliwada A, Byran G. Activity of phytochemical constituents of *Curcuma longa* (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19): an in silico approach. *Futur J Pharm Sci* 2020; **6**: 104 [PMID: 33215042 DOI: 10.1186/s43094-020-00126-x]

35 **Adem S,** Eyupoglu V, Sarfraz I, Rasul A, Ali M. Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: An in silico strategy unveils a hope against corona. 2020 Preprint. Available from: 2020030333 [DOI: 10.20944/preprints202003.0333.v1]

36 **Srivastava A,** Singh D. Destabilizing the structural integrity of SARS-CoV2 receptor proteins by curcumin along with hydroxychloroquine: An in silico approach for a combination therapy. 2020 Preprint. Available from: chemrxiv:12090438 [DOI: 10.26434/chemrxiv.12090438]

37 **Gonzalez-Paz LA,** Lossada CA, Moncayo LS, Romero F, Paz JL, Vera-Villalobos J, Pérez AE, San-Blas E, Alvarado YJ. Theoretical molecular docking study of the structural disruption of the viral 3CL-protease of COVID19 induced by binding of capsaicin, piperine and curcumin part 1: A comparative study with chloroquine and hydrochloroquine two antimalaric drugs. 2020 Preprint. Available from: rs-21206 [DOI: 10.21203/rs.3.rs-21206/v1]

38 **Sharma AD.** Eucalyptol (1, 8 cineole) from eucalyptus essential oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies. 2020 Preprint. Available from: 2020030455

39 **Sharma AD,** Inderjeet KAUR. Molecular docking and pharmacokinetic screening of eucalyptol (1, 8 cineole) from eucalyptus essential oil against SARS-CoV-2. *Not Sci Biol* 2020; **12:** 536-545 [DOI: 10.15835/nsb12210711]

40 **Sharma AD,** Kaur I. Molecular docking studies on jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection. 2020 Preprint. Available from: arXiv:2004.00217

41 **Sharma AD,** Kaur I. Eucalyptus essential oil bioactive molecules from against SARS-CoV-2 spike protein: Insights from computational studies. 2021 Preprint. Available from: rs-140069 [DOI: 10.21203/rs.3.rs-140069/v1]

42 **Muhammad IA,** Muangchoo K, Muhammad A, Ajingi YUS, Muhammad IY, Umar ID, Muhammad AB. A computational study to ıdentify potential inhibitors of SARS-CoV-2 main protease (Mpro) from Eucalyptus active compounds. *Computation* 2020; **8:** 79 [DOI: 10.3390/computation8030079]

43 **Sinha SK**, Prasad SK, Islam MA, Gurav SS, Patil RB, AlFaris NA, Aldayel TS, AlKehayez NM, Wabaidur SM, Shakya A. Identification of bioactive compounds from *Glycyrrhiza glabra* as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: a pharmacoinformatics study. *J Biomol Struct Dyn* 2021; **39**: 4686-4700 [PMID: 32552462 DOI: 10.1080/07391102.2020.1779132]

44 **Narkhede RR**, Pise AV, Cheke RS, Shinde SD. Recognition of Natural Products as Potential Inhibitors of COVID-19 Main Protease (Mpro): In-Silico Evidences. *Nat Prod Bioprospect* 2020; **10**: 297-306 [PMID: 32557405 DOI: 10.1007/s13659-020-00253-1]

45 **Liu H**, Ye F, Sun Q, Liang H, Li C, Li S, Lu R, Huang B, Tan W, Lai L. *Scutellaria baicalensis* extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease *in vitro*. *J Enzyme Inhib Med Chem* 2021; **36**: 497-503 [PMID: 33491508 DOI: 10.1080/14756366.2021.1873977]

46 **Udrea AM,** Mernea M, Buiu C, Avram S. *Scutellaria baicalensis* flavones as potent drugs against acute respiratory injury during SARS-CoV-2 infection: Structural biology approaches. *Processes* 2020; **8:** 1468 [DOI: 10.3390/pr8111468]

47 **Sardari S,** Mobaiend A, Ghassemifard L, Kamali K, Khavasi N. Therapeutic effect of thyme (*Thymus vulgaris*) essential oil on patients with COVID19: A randomized clinical trial. *J Adv Med* 2021; **29:** 83-91 [DOI: 10.30699/jambs.29.133.83]

48 **Kumar A**, Choudhir G, Shukla SK, Sharma M, Tyagi P, Bhushan A, Rathore M. Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches. *J Biomol Struct Dyn* 2021; **39**: 3760-3770 [PMID: 32448034 DOI: 10.1080/07391102.2020.1772112]

49 **Dhawan M,** Parmar M, Sharun K, Tiwari R, Bilal M, Dhama K. Medicinal and therapeutic potential of withanolides from *Withania somnifera* against COVID-19. *J Appl Pharm Sci* 2021; **11:** 6-13 [DOI: 10.7324/JAPS.2021.110402]

50 **Patel CN,** Goswami D, Jaiswal DG, Parmar RM, Solanki HA, Pandya HA. Pinpointing the potential hits for hindering interaction of SARS-CoV-2 S-protein with ACE2 from the pool of antiviral phytochemicals utilizing molecular docking and molecular dynamics (MD) simulations. *J Mol Graph Model* 2021; **105:** 107874 [PMID: 33647752 DOI: 10.1016/j.jmgm.2021.107874]

51 **Balkrishna A,** Pokhrel S, Singh J, Varshney A. Withanone from *Withania somnifera* may inhibit novel coronavirus (COVID-19) entry by disrupting interactions between viral S-protein receptor binding domain and host ACE2 receptor. 2020 Preprint. Available from: rs-17806 [DOI: 10.21203/rs.3.rs-17806/v1]

52 **Sudeep HV,** Gouthamchandra K, Shyamprasad K. Molecular docking analysis of Withaferin A from *Withania somnifera* with the Glucose regulated protein 78 (GRP78) receptor and the SARS-CoV-2 main protease. *Bioinformation* 2020; **16:** 411-417 [PMID: 32831523 DOI: 10.6026/97320630016411]

53 **Rasool A**, Khan MU, Ali MA, Anjum AA, Ahmed I, Aslam A, Mustafa G, Masood S, Ali MA, Nawaz M. Anti-avian influenza virus H9N2 activity of aqueous extracts of *Zingiber officinalis* (Ginger) and *Allium sativum* (Garlic) in chick embryos. *Pak J Pharm Sci* 2017; **30**: 1341-1344 [PMID: 29039335]

54 **Mohajer Shojai T**, Ghalyanchi Langeroudi A, 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**: 458-267 [PMID: 27516987]

55 **Chavan RD**, Shinde P, Girkar K, Madage R, Chowdhary A. Assessment of Anti-Influenza Activity and Hemagglutination Inhibition of *Plumbago indica* and *Allium sativum* Extracts. *Pharmacognosy Res* 2016; **8**: 105-111 [PMID: 27034600 DOI: 10.4103/0974-8490.172562]

56 **Choi HJ**. Chemical Constituents of Essential Oils Possessing Anti-Influenza A/WS/33 Virus Activity. *Osong Public Health Res Perspect* 2018; **9**: 348-353 [PMID: 30584499 DOI: 10.24171/j.phrp.2018.9.6.09]

57 **Mehrbod P,** Aini I, Amini E, Eslami M, Torabi A, Bande F, Kheiri MT. Assessment of direct immunofluorescence assay in detection of antiviral effect of garlic extract on influenza virus. *Afr J Microbiol Res* 2013; **7:** 2608-2612 [DOI: 10.5897/ajmr12.2329]

58 **Chen CH,** Chou TW, Cheng LH, Ho CW. *In vitro* anti-adenoviral activity of five *Allium* plants. *Taiwan Huaxuegongchengshi Xuehui Xuebao* 2011; **42:** 228-232 [DOI: 10.1016/j.jtice.2010.07.011]

59 **Borges-Argáez R**, Chan-Balan R, Cetina-Montejo L, Ayora-Talavera G, Sansores-Peraza P, Gómez-Carballo J, Cáceres-Farfán M. *In vitro* evaluation of anthraquinones from *Aloe vera* (*Aloe barbadensis* Miller) roots and several derivatives against strains of influenza virus. *Ind Crops Prod* 2019; **132**: 468-475 [PMID: 32288269 DOI: 10.1016/j.indcrop.2019.02.056]

60 **Li SW**, Yang TC, Lai CC, Huang SH, Liao JM, Wan L, Lin YJ, Lin CW. Antiviral activity of aloe-emodin against influenza A virus via galectin-3 up-regulation. *Eur J Pharmacol* 2014; **738**: 125-132 [PMID: 24877694 DOI: 10.1016/j.ejphar.2014.05.028]

61 **Zhang P**, Liu X, Liu H, Wang W, Liu X, Li X, Wu X. *Astragalus* polysaccharides inhibit avian infectious bronchitis virus infection by regulating viral replication. *Microb Pathog* 2018; **114**: 124-128 [PMID: 29170045 DOI: 10.1016/j.micpath.2017.11.026]

62 **Kallon S**, Li X, Ji J, Chen C, Xi Q, Chang S, Xue C, Ma J, Xie Q, Zhang Y. *Astragalus* polysaccharide enhances immunity and inhibits H9N2 avian influenza virus *in vitro* and *in vivo*. *J Anim Sci Biotechnol* 2013; **4**: 22 [PMID: 23786718 DOI: 10.1186/2049-1891-4-22]

63 **Weber JM**, Ruzindana-Umunyana A, Imbeault L, Sircar S. Inhibition of adenovirus infection and adenain by green tea catechins. *Antiviral Res* 2003; **58**: 167-173 [PMID: 12742577 DOI: 10.1016/s0166-3542(02)00212-7]

64 **Kuzuhara T**, Iwai Y, Takahashi H, Hatakeyama D, Echigo N. Green tea catechins inhibit the endonuclease activity of influenza A virus RNA polymerase. *PLoS Curr* 2009; **1**: RRN1052 [PMID: 20025206 DOI: 10.1371/currents.rrn1052]

65 **Liu J,** Yang Z, Wang S, Liu L, Chen G, Wang L. Exploring the molecular basis of H5N1 hemagglutinin binding with catechins in green tea: A flexible docking and molecular dynamics study. *J Theor Comput Chem* 2012; **11:** 111-125 [DOI: 10.1142/s0219633612500071]

66 **Yang ZF**, Bai LP, Huang WB, Li XZ, Zhao SS, Zhong NS, Jiang ZH. Comparison of in vitro antiviral activity of tea polyphenols against influenza A and B viruses and structure-activity relationship analysis. *Fitoterapia* 2014; **93**: 47-53 [PMID: 24370660 DOI: 10.1016/j.fitote.2013.12.011]

67 **Chen TY**, Chen DY, Wen HW, Ou JL, Chiou SS, Chen JM, Wong ML, Hsu WL. Inhibition of enveloped viruses infectivity by curcumin. *PLoS One* 2013; **8**: e62482 [PMID: 23658730 DOI: 10.1371/journal.pone.0062482]

68 **Dai J**, Gu L, Su Y, Wang Q, Zhao Y, Chen X, Deng H, Li W, Wang G, Li K. Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-κB pathways. *Int Immunopharmacol* 2018; **54**: 177-187 [PMID: 29153953 DOI: 10.1016/j.intimp.2017.11.009]

69 **Chen DY,** Shien JH, Tiley L, Chiou SS, Wang SY, Chang TJ, Lee YJ, Chan KW, Hsu WL. Curcumin inhibits influenza virus infection and haemagglutination activity. *Food Chem* 2010; **119:** 1346-1351 [DOI: 10.1016/j.foodchem.2009.09.011]

70 **Obata K**, Kojima T, Masaki T, Okabayashi T, Yokota S, Hirakawa S, Nomura K, Takasawa A, Murata M, Tanaka S, Fuchimoto J, Fujii N, Tsutsumi H, Himi T, Sawada N. Curcumin prevents replication of respiratory syncytial virus and the epithelial responses to it in human nasal epithelial cells. *PLoS One* 2013; **8**: e70225 [PMID: 24058438 DOI: 10.1371/journal.pone.0070225]

71 **Vimalanathan S,** Schoop R, Hudson J. High-potency anti-influenza therapy by a combination of *Echinacea purpurea* fresh herb and root tinctures. *J App Pharmac Sci* 2013; **3:** 001-005 [DOI: 10.1055/s-0033-1352301]

72 **Pleschka S**, Stein M, Schoop R, Hudson JB. Anti-viral properties and mode of action of standardized *Echinacea purpurea* extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV). *Virol J* 2009; **6**: 197 [PMID: 19912623 DOI: 10.1186/1743-422X-6-197]

73 **Hudson J,** Vimalanathan S. Echinacea—A source of potent antivirals for respiratory virus infections. *Pharmaceuticals* 2011; **4:** 1019-1031 [DOI: 10.3390/ph4071019]

74 **Vimalanathan S,** Hudson J. Anti-influenza virus activity of essential oils and vapors. *Am J Essent Oil* 2014; **2:** 47-53 [DOI: 10.7324/japs.2012.2734]

75 **Haruyama T**, Nagata K. Anti-influenza virus activity of *Ginkgo biloba* leaf extracts. *J Nat Med* 2013; **67**: 636-642 [PMID: 23179317 DOI: 10.1007/s11418-012-0725-0]

76 **Feng Yeh C**, Wang KC, Chiang LC, Shieh DE, Yen MH, San Chang J. Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *J Ethnopharmacol* 2013; **148**: 466-473 [PMID: 23643542 DOI: 10.1016/j.jep.2013.04.040]

77 **Hoever G**, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, Doerr HW, Cinatl J Jr. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. *J Med Chem* 2005; **48**: 1256-1259 [PMID: 15715493 DOI: 10.1021/jm0493008]

78 **Dao TT**, Nguyen PH, Lee HS, Kim E, Park J, Lim SI, Oh WK. Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from *Glycyrrhiza inflata*. *Bioorg Med Chem Lett* 2011; **21**: 294-298 [PMID: 21123068 DOI: 10.1016/j.bmcl.2010.11.016]

79 **Wolkerstorfer A**, Kurz H, Bachhofner N, Szolar OH. Glycyrrhizin inhibits influenza A virus uptake into the cell. *Antiviral Res* 2009; **83**: 171-178 [PMID: 19416738 DOI: 10.1016/j.antiviral.2009.04.012]

80 **Michaelis M**, Geiler J, Naczk P, Sithisarn P, Ogbomo H, Altenbrandt B, Leutz A, Doerr HW, Cinatl J Jr. Glycyrrhizin inhibits highly pathogenic H5N1 influenza A virus-induced pro-inflammatory cytokine and chemokine expression in human macrophages. *Med Microbiol Immunol* 2010; **199**: 291-297 [PMID: 20386921 DOI: 10.1007/s00430-010-0155-0]

81 **Del Valle Mendoza J**, Pumarola T, Gonzales LA, Del Valle LJ. Antiviral activity of maca (*Lepidium meyenii*) against human influenza virus. *Asian Pac J Trop Med* 2014; **7S1**: S415-S420 [PMID: 25312160 DOI: 10.1016/S1995-7645(14)60268-6]

82 **Garozzo A**, Timpanaro R, Stivala A, Bisignano G, Castro A. Activity of *Melaleuca alternifolia* (tea tree) oil on Influenza virus A/PR/8: Study on the mechanism of action. *Antiviral Res* 2011; **89**: 83-88 [PMID: 21095205 DOI: 10.1016/j.antiviral.2010.11.010]

83 **Usachev EV,** Pyankov OV, Usacheva OV, Agranovski IE. Antiviral activity of tea tree and eucalyptus oil aerosol and vapour. *J Aerosol Sci* 2013; **59:** 22-30 [DOI: 10.1016/j.jaerosci.2013.01.004]

84 **Pyankov OV,** Usachev EV, Pyankova O, Agranovski IE. Inactivation of airborne influenza virus by tea tree and eucalyptus oils. *Aerosol Sci Technol* 2012; **46:** 1295-1302 [DOI: 10.1080/02786826.2012.708948]

85 **Pourghanbari G**, Nili H, Moattari A, Mohammadi A, Iraji A. Antiviral activity of the oseltamivir and *Melissa officinalis* L. essential oil against avian influenza A virus (H9N2). *Virusdisease* 2016; **27**: 170-178 [PMID: 27366768 DOI: 10.1007/s13337-016-0321-0]

86 **Lelešius R**, Karpovaitė A, Mickienė R, Drevinskas T, Tiso N, Ragažinskienė O, Kubilienė L, Maruška A, Šalomskas A. *In vitro* antiviral activity of fifteen plant extracts against avian infectious bronchitis virus. *BMC Vet Res* 2019; **15**: 178 [PMID: 31142304 DOI: 10.1186/s12917-019-1925-6]

87 **Li Y**, Liu Y, Ma A, Bao Y, Wang M, Sun Z. *In vitro* antiviral, anti-inflammatory, and antioxidant activities of the ethanol extract of *Mentha piperita* L. *Food Sci Biotechnol* 2017; **26**: 1675-1683 [PMID: 30263705 DOI: 10.1007/s10068-017-0217-9]

88 **Dorra N,** El-Berrawy M, Sallam S, Mahmoud R. Evaluation of antiviral and antioxidant activity of selected herbal extracts. *Public Health* 2019; **49:** 36-40 [DOI: 10.21608/jhiph.2019.29464]

89 **Umar S,** Munir MT, Subhan S, Azam T, Nisa Q, Khan MI, Umar W, Rehman Z, Saqib AS, Shah MA. Protective and antiviral activities of *Nigella sativa* against avian influenza (H9N2) in Turkeys. *J Saudi Soc Agric Sci* 2016; **10** [DOI: 10.1016/j.jssas.2016.09.004]

90 **Ulasli M**, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M, Igci YZ, Cakmak EA, Arslan A. The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Mol Biol Rep* 2014; **41**: 1703-1711 [PMID: 24413991 DOI: 10.1007/s11033-014-3019-7]

91 **Lee JS**, Ko EJ, Hwang HS, Lee YN, Kwon YM, Kim MC, Kang SM. Antiviral activity of ginseng extract against respiratory syncytial virus infection. *Int J Mol Med* 2014; **34**: 183-190 [PMID: 24756136 DOI: 10.3892/ijmm.2014.1750]

92 **Lee JS**, Cho MK, Hwang HS, Ko EJ, Lee YN, Kwon YM, Kim MC, Kim KH, Lee YT, Jung YJ, Kang SM. Ginseng diminishes lung disease in mice immunized with formalin-inactivated respiratory syncytial virus after challenge by modulating host immune responses. *J Interferon Cytokine Res* 2014; **34**: 902-914 [PMID: 25051168 DOI: 10.1089/jir.2013.0093]

93 **Yin SY**, Kim HJ, Kim HJ. A comparative study of the effects of whole red ginseng extract and polysaccharide and saponin fractions on influenza A (H1N1) virus infection. *Biol Pharm Bull* 2013; **36**: 1002-1007 [PMID: 23727921 DOI: 10.1248/bpb.b13-00123]

94 **Yoo DG**, Kim MC, Park MK, Song JM, Quan FS, Park KM, Cho YK, Kang SM. Protective effect of Korean red ginseng extract on the infections by H1N1 and H3N2 influenza viruses in mice. *J Med Food* 2012; **15**: 855-862 [PMID: 22856395 DOI: 10.1089/jmf.2012.0017]

95 **Roth M**, Fang L, Stolz D, Tamm M. *Pelargonium sidoides* radix extract EPs 7630 reduces rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells. *PLoS One* 2019; **14**: e0210702 [PMID: 30707726 DOI: 10.1371/journal.pone.0210702]

96 **Michaelis M**, Doerr HW, Cinatl J Jr. Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses. *Phytomedicine* 2011; **18**: 384-386 [PMID: 21036571 DOI: 10.1016/j.phymed.2010.09.008]

97 **Theisen LL**, Muller CP. EPs® 7630 (Umckaloabo®), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity *in vitro* and *in vivo*. *Antiviral Res* 2012; **94**: 147-156 [PMID: 22475498 DOI: 10.1016/j.antiviral.2012.03.006]

98 **Chen C**, Zuckerman DM, Brantley S, Sharpe M, Childress K, Hoiczyk E, Pendleton AR. *Sambucus nigra* extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res* 2014; **10**: 24 [PMID: 24433341 DOI: 10.1186/1746-6148-10-24]

99 **Krawitz C**, Mraheil MA, Stein M, Imirzalioglu C, Domann E, Pleschka S, Hain T. Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses. *BMC Complement Altern Med* 2011; **11**: 16 [PMID: 21352539 DOI: 10.1186/1472-6882-11-16]

100 **Kinoshita E**, Hayashi K, Katayama H, Hayashi T, Obata A. Anti-influenza virus effects of elderberry juice and its fractions. *Biosci Biotechnol Biochem* 2012; **76**: 1633-1638 [PMID: 22972323 DOI: 10.1271/bbb.120112]

101 **Roschek B Jr**, Fink RC, McMichael MD, Li D, Alberte RS. Elderberry flavonoids bind to and prevent H1N1 infection in vitro. *Phytochemistry* 2009; **70**: 1255-1261 [PMID: 19682714 DOI: 10.1016/j.phytochem.2009.06.003]

102 **Ji S**, Li R, Wang Q, Miao WJ, Li ZW, Si LL, Qiao X, Yu SW, Zhou DM, Ye M. Anti-H1N1 virus, cytotoxic and Nrf2 activation activities of chemical constituents from *Scutellaria baicalensis*. *J Ethnopharmacol* 2015; **176**: 475-484 [PMID: 26578185 DOI: 10.1016/j.jep.2015.11.018]

103 **Chen F**, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, Cheng VC, Tsui WH, Hung IF, Lee TS, Guan Y, Peiris JS, Yuen KY. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* 2004; **31**: 69-75 [PMID: 15288617 DOI: 10.1016/j.jcv.2004.03.003]

104 **Ryu YB**, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, Nguyen TT, Park SJ, Chang JS, Park KH, Rho MC, Lee WS. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. *Bioorg Med Chem* 2010; **18**: 7940-7947 [PMID: 20934345 DOI: 10.1016/j.bmc.2010.09.035]

105 **Cai Z**, Zhang G, Tang B, Liu Y, Fu X, Zhang X. Promising Anti-influenza Properties of Active Constituent of *Withania somnifera* Ayurvedic Herb in Targeting Neuraminidase of H1N1 Influenza: Computational Study. *Cell Biochem Biophys* 2015; **72**: 727-739 [PMID: 25627548 DOI: 10.1007/s12013-015-0524-9]

106 **Chang JS**, Wang KC, Yeh CF, Shieh DE, Chiang LC. Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *J Ethnopharmacol* 2013; **145**: 146-151 [PMID: 23123794 DOI: 10.1016/j.jep.2012.10.043]

107 **Nantz MP**, Rowe CA, Muller CE, Creasy RA, Stanilka JM, Percival SS. Supplementation with aged garlic extract improves both NK and γδ-T cell function and reduces the severity of cold and flu symptoms: A randomized, double-blind, placebo-controlled nutrition intervention. *Clin Nutr* 2012; **31**: 337-344 [PMID: 22280901 DOI: 10.1016/j.clnu.2011.11.019]

108 **Barrett B**, Brown R, Rakel D, Mundt M, Bone K, Barlow S, Ewers T. Echinacea for treating the common cold: A randomized trial. *Ann Intern Med* 2010; **153**: 769-777 [PMID: 21173411 DOI: 10.7326/0003-4819-153-12-201012210-00003]

109 **Jawad M**, Schoop R, Suter A, Klein P, Eccles R. Safety and Efficacy Profile of *Echinacea purpurea* to Prevent Common Cold Episodes: A Randomized, Double-Blind, Placebo-Controlled Trial. *Evid Based Complement Alternat Med* 2012; **2012**: 841315 [PMID: 23024696 DOI: 10.1155/2012/841315]

110 **Tiralongo E**, Lea RA, Wee SS, Hanna MM, Griffiths LR. Randomised, double blind, placebo-controlled trial of echinacea supplementation in air travellers. *Evid Based Complement Alternat Med* 2012; **2012**: 417267 [PMID: 22229040 DOI: 10.1155/2012/417267]

111 **Matsumoto K**, Yamada H, Takuma N, Niino H, Sagesaka YM. Effects of green tea catechins and theanine on preventing influenza infection among healthcare workers: A randomized controlled trial. *BMC Complement Altern Med* 2011; **11**: 15 [PMID: 21338496 DOI: 10.1186/1472-6882-11-15]

112 **Fazio S**, Pouso J, Dolinsky D, Fernandez A, Hernandez M, Clavier G, Hecker M. Tolerance, safety and efficacy of *Hedera helix* extract in inflammatory bronchial diseases under clinical practice conditions: A prospective, open, multicentre postmarketing study in 9657 patients. *Phytomedicine* 2009; **16**: 17-24 [PMID: 16860549 DOI: 10.1016/j.phymed.2006.05.003]

113 **Schmidt M**, Thomsen M, Schmidt U. Suitability of ivy extract for the treatment of paediatric cough. *Phytother Res* 2012; **26**: 1942-1947 [PMID: 22532491 DOI: 10.1002/ptr.4671]

114 **Zeil S**, Schwanebeck U, Vogelberg C. Tolerance and effect of an add-on treatment with a cough medicine containing ivy leaves dry extract on lung function in children with bronchial asthma. *Phytomedicine* 2014; **21**: 1216-1220 [PMID: 24916707 DOI: 10.1016/j.phymed.2014.05.006]

115 **Ha KC**, Kim MG, Oh MR, Choi EK, Back HI, Kim SY, Park EO, Kwon DY, Yang HJ, Kim MJ, Kang HJ, Lee JH, Choi KM, Chae SW, Lee CS. A placebo-controlled trial of Korean red ginseng extract for preventing influenza-like illness in healthy adults. *BMC Complement Altern Med* 2012; **12**: 10 [PMID: 22314101 DOI: 10.1186/1472-6882-12-10]

116 **Hwang JH**, Park SH, Choi EK, Jung SJ, Pyo MK, Chae SW. A randomized, double-blind, placebo-controlled pilot study to assess the effects of protopanaxadiol saponin-enriched ginseng extract and pectinase-processed ginseng extract on the prevention of acute respiratory illness in healthy people. *J Ginseng Res* 2020; **44**: 697-703 [PMID: 32913399 DOI: 10.1016/j.jgr.2019.01.002]

117 **High KP**, Case D, Hurd D, Powell B, Lesser G, Falsey AR, Siegel R, Metzner-Sadurski J, Krauss JC, Chinnasami B, Sanders G, Rousey S, Shaw EG. A randomized, controlled trial of *Panax quinquefolius* extract (CVT-E002) to reduce respiratory infection in patients with chronic lymphocytic leukemia. *J Support Oncol* 2012; **10**: 195-201 [PMID: 22266154 DOI: 10.1016/j.suponc.2011.10.005]

118 **Wu L**, Zhang AL, Di YM, Shergis JL, Chen Y, Guo X, Wen Z, Thien F, Worsnop C, Lin L, Xue CC. *Panax ginseng* therapy for chronic obstructive pulmonary disease: A clinical trial protocol and pilot study. *Chin Med* 2014; **9**: 20 [PMID: 25161696 DOI: 10.1186/1749-8546-9-20]

119 **Xue CC**, Shergis JL, Zhang AL, Worsnop C, Fong H, Story D, Da Costa C, Thien FC. *Panax ginseng* C.A Meyer root extract for moderate chronic obstructive pulmonary disease (COPD): Study protocol for a randomised controlled trial. *Trials* 2011; **12**: 164 [PMID: 21718484 DOI: 10.1186/1745-6215-12-164]

120 **Matthys H**, Funk P. *Pelargonium sidoides* preparation EPs 7630 in COPD: Health-related quality-of-life and other patient-reported outcomes in adults receiving add-on therapy. *Curr Med Res Opin* 2018; **34**: 1245-1251 [PMID: 29231073 DOI: 10.1080/03007995.2017.1416344]

121 **Kamin W**, Ilyenko LI, Malek FA, Kieser M. Treatment of acute bronchitis with EPs 7630: Randomized, controlled trial in children and adolescents. *Pediatr Int* 2012; **54**: 219-226 [PMID: 22360575 DOI: 10.1111/j.1442-200X.2012.03598.x]

122 **Patiroglu T**, Tunc A, Eke Gungor H, Unal E. The efficacy of *Pelargonium sidoides* in the treatment of upper respiratory tract infections in children with transient hypogammaglobulinemia of infancy. *Phytomedicine* 2012; **19**: 958-961 [PMID: 22809962 DOI: 10.1016/j.phymed.2012.06.004]

123 **Tahan F**, Yaman M. Can the *Pelargonium sidoides* root extract EPs® 7630 prevent asthma attacks during viral infections of the upper respiratory tract in children? *Phytomedicine* 2013; **20**: 148-150 [PMID: 23142309 DOI: 10.1016/j.phymed.2012.09.022]

124 **Berezhnoi VV,** Heger M, Lehmacher W, Seifert G. Clinical efficacy and safety of liquid *Pelargonium sidoides* preparation (EPs 7630) in children with acute non-streptococcal tonsillopharyngitis. *J Compr Ped* 2016; **7** [DOI: 10.17795/compreped-42158]

125 **Riley DS**, Lizogub VG, Zimmermann A, Funk P, Lehmacher W. Efficacy and Tolerability of High-dose *Pelargonium* Extract in Patients with the Common Cold. *Altern Ther Health Med* 2018; **24**: 16-26 [PMID: 29055287]

126 **Kong FK.** Pilot clinical study on a proprietary elderberry extract: Efficacy in addressing influenza symptoms. *J Pharmacokinet Pharmacodyn* 2009; **5:** 32-43 [DOI: 10.1007/s10928-014-9365-1]

127 **Tiralongo E**, Wee SS, Lea RA. Elderberry Supplementation Reduces Cold Duration and Symptoms in Air-Travellers: A Randomized, Double-Blind Placebo-Controlled Clinical Trial. *Nutrients* 2016; **8**: 182 [PMID: 27023596 DOI: 10.3390/nu8040182]

128 **Dehghani S**, Alipoor E, Salimzadeh A, Yaseri M, Hosseini M, Feinle-Bisset C, Hosseinzadeh-Attar MJ. The effect of a garlic supplement on the pro-inflammatory adipocytokines, resistin and tumor necrosis factor-alpha, and on pain severity, in overweight or obese women with knee osteoarthritis. *Phytomedicine* 2018; **48**: 70-75 [PMID: 30195882 DOI: 10.1016/j.phymed.2018.04.060]

129 **Arreola R**, Quintero-Fabián S, López-Roa RI, Flores-Gutiérrez EO, Reyes-Grajeda JP, Carrera-Quintanar L, Ortuño-Sahagún D. Immunomodulation and anti-inflammatory effects of garlic compounds. *J Immunol Res* 2015; **2015**: 401630 [PMID: 25961060 DOI: 10.1155/2015/401630]

130 **Hiyasat B**, Sabha D, Grotzinger K, Kempfert J, Rauwald JW, Mohr FW, Dhein S. Antiplatelet activity of *Allium ursinum* and *Allium sativum*. *Pharmacology* 2009; **83**: 197-204 [PMID: 19174616 DOI: 10.1159/000196811]

131 **Sultana MR**, Bagul PK, Katare PB, Anwar Mohammed S, Padiya R, Banerjee SK. Garlic activates SIRT-3 to prevent cardiac oxidative stress and mitochondrial dysfunction in diabetes. *Life Sci* 2016; **164**: 42-51 [PMID: 27590611 DOI: 10.1016/j.lfs.2016.08.030]

132 **Aprioku JS,** Amah-Tariah FS. Garlic (*Allium sativum* L.) protects hepatic and renal toxicity of alloxan in rats. *Br J Pharm Res* 2017; 1-7 [DOI: 10.9734/JPRI/2017/34909]

133 **Chen YA**, Tsai JC, Cheng KC, Liu KF, Chang CK, Hsieh CW. Extracts of black garlic exhibits gastrointestinal motility effect. *Food Res Int* 2018; **107**: 102-109 [PMID: 29580467 DOI: 10.1016/j.foodres.2018.02.003]

134 **Seckiner I**, Bayrak O, Can M, Mungan AG, Mungan NA. Garlic supplemented diet attenuates gentamicin nephrotoxicity ın rats. *Int Braz J Urol* 2014; **40**: 562-567 [PMID: 25251961 DOI: 10.1590/S1677-5538.IBJU.2014.04.17]

135 **Henrotin Y**, Donneau AF, de Vlam K, Wittoek R, Luyten F. Responses to "Bio-optimized *Curcuma longa* extract is efficient on knee osteoarthritis pain: A double-blind multicenter randomized placebo controlled three-arm study": authors' reply. *Arthritis Res Ther* 2020; **22**: 23 [PMID: 32046787 DOI: 10.1186/s13075-020-2109-2]

136 **Eke-Okoro UJ**, Raffa RB, Pergolizzi JV Jr, Breve F, Taylor R Jr; NEMA Research Group. Curcumin in turmeric: Basic and clinical evidence for a potential role in analgesia. *J Clin Pharm Ther* 2018; **43**: 460-466 [PMID: 29722036 DOI: 10.1111/jcpt.12703]

137 **Liu Z**, Huang P, Law S, Tian H, Leung W, Xu C. Preventive Effect of Curcumin Against Chemotherapy-Induced Side-Effects. *Front Pharmacol* 2018; **9**: 1374 [PMID: 30538634 DOI: 10.3389/fphar.2018.01374]

138 **Huang WC**, Chiu WC, Chuang HL, Tang DW, Lee ZM, Wei L, Chen FA, Huang CC. Effect of curcumin supplementation on physiological fatigue and physical performance in mice. *Nutrients* 2015; **7**: 905-921 [PMID: 25647661 DOI: 10.3390/nu7020905]

139 **Shimizu K**, Funamoto M, Sunagawa Y, Shimizu S, Katanasaka Y, Miyazaki Y, Wada H, Hasegawa K, Morimoto T. Anti-inflammatory Action of Curcumin and Its Use in the Treatment of Lifestyle-related Diseases. *Eur Cardiol* 2019; **14**: 117-122 [PMID: 31360234 DOI: 10.15420/ecr.2019.17.2]

140 **Gouda MM**, Bhandary YP. Acute Lung Injury: IL-17A-Mediated Inflammatory Pathway and Its Regulation by Curcumin. *Inflammation* 2019; **42**: 1160-1169 [PMID: 31011925 DOI: 10.1007/s10753-019-01010-4]

141 **Haider S**, Naqvi F, Tabassum S, Saleem S, Batool Z, Sadir S, Rasheed S, Saleem D, Nawaz A, Ahmad S. Preventive effects of curcumin against drug- and starvation-induced gastric erosions in rats. *Sci Pharm* 2013; **81**: 549-558 [PMID: 23833720 DOI: 10.3797/scipharm.1207-17]

142 **Ram A**, Das M, Ghosh B. Curcumin attenuates allergen-induced airway hyperresponsiveness in sensitized guinea pigs. *Biol Pharm Bull* 2003; **26**: 1021-1024 [PMID: 12843631 DOI: 10.1248/bpb.26.1021]

143 **Dulbecco P**, Savarino V. Therapeutic potential of curcumin in digestive diseases. *World J Gastroenterol* 2013; **19**: 9256-9270 [PMID: 24409053 DOI: 10.3748/wjg.v19.i48.9256]

144 **Nosalova G**, Fleskova D, Jurecek L, Sadlonova V, Ray B. Herbal polysaccharides and cough reflex. *Respir Physiol Neurobiol* 2013; **187**: 47-51 [PMID: 23597834 DOI: 10.1016/j.resp.2013.03.015]

145 **Kuang Y**, Li B, Fan J, Qiao X, Ye M. Antitussive and expectorant activities of licorice and its major compounds. *Bioorg Med Chem* 2018; **26**: 278-284 [PMID: 29224994 DOI: 10.1016/j.bmc.2017.11.046]

146 **Kao TC**, Shyu MH, Yen GC. Glycyrrhizic acid and 18beta-glycyrrhetinic acid inhibit inflammation via PI3K/Akt/GSK3beta signaling and glucocorticoid receptor activation. *J Agric Food Chem* 2010; **58**: 8623-8629 [PMID: 20681651 DOI: 10.1021/jf101841r]

147 **Shi Q**, Hou Y, Yang Y, Bai G. Protective effects of glycyrrhizin against β₂-adrenergic receptor agonist-induced receptor internalization and cell apoptosis. *Biol Pharm Bull* 2011; **34**: 609-617 [PMID: 21532146 DOI: 10.1248/bpb.34.609]

148 **Rushmi ZT**, Akter N, Mow RJ, Afroz M, Kazi M, de Matas M, Rahman M, Shariare MH. The impact of formulation attributes and process parameters on black seed oil loaded liposomes and their performance in animal models of analgesia. *Saudi Pharm J* 2017; **25**: 404-412 [PMID: 28344496 DOI: 10.1016/j.jsps.2016.09.011]

149 **Muralidharan-Chari V**, Kim J, Abuawad A, Naeem M, Cui H, Mousa SA. Thymoquinone Modulates Blood Coagulation in Vitro via Its Effects on Inflammatory and Coagulation Pathways. *Int J Mol Sci* 2016; **17**: 474 [PMID: 27043539 DOI: 10.3390/ijms17040474]

150 **Ansari MA,** Ansari NA, Junejo SA. Montelukast vs *Nigella sativa* for management of seasonal allergic rhinitis: A single blind comparative clinical trial. *Pak J Med Sci* 2010; **26:** 249-254 [DOI: 10.1046/j.1365-2222.2002.01422.x]

151 **Alsamarai AM**, Abdulsatar M, Ahmed Alobaidi AH. Evaluation of topical black seed oil in the treatment of allergic rhinitis. *Antiinflamm Antiallergy Agents Med Chem* 2014; **13**: 75-82 [PMID: 23855426 DOI: 10.2174/18715230113129990014]

152 **Majdalawieh AF**, Fayyad MW. Immunomodulatory and anti-inflammatory action of *Nigella sativa* and thymoquinone: A comprehensive review. *Int Immunopharmacol* 2015; **28**: 295-304 [PMID: 26117430 DOI: 10.1016/j.intimp.2015.06.023]

153 **Mahdavi R**, Namazi N, Alizadeh M, Farajnia S. *Nigella sativa* oil with a calorie-restricted diet can improve biomarkers of systemic inflammation in obese women: A randomized double-blind, placebo-controlled clinical trial. *J Clin Lipidol* 2016; **10**: 1203-1211 [PMID: 27678438 DOI: 10.1016/j.jacl.2015.11.019]

154 **Boskabady MH**, Mohsenpoor N, Takaloo L. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomedicine* 2010; **17**: 707-713 [PMID: 20149611 DOI: 10.1016/j.phymed.2010.01.002]

155 **Salem AM**, Bamosa AO, Qutub HO, Gupta RK, Badar A, Elnour A, Afzal MN. Effect of *Nigella sativa* supplementation on lung function and inflammatory mediatorsin partly controlled asthma: a randomized controlled trial. *Ann Saudi Med* 2017; **37**: 64-71 [PMID: 28151459 DOI: 10.5144/0256-4947.2017.64]

156 **Ratan ZA**, Youn SH, Kwak YS, Han CK, Haidere MF, Kim JK, Min H, Jung YJ, Hosseinzadeh H, Hyun SH, Cho JY. Adaptogenic effects of *Panax ginseng* on modulation of immune functions. *J Ginseng Res* 2021; **45**: 32-40 [PMID: 33437154 DOI: 10.1016/j.jgr.2020.09.004]

157 **Bao Y**, Gao Y, Koch E, Pan X, Jin Y, Cui X. Evaluation of pharmacodynamic activities of EPs® 7630, a special extract from roots of *Pelargonium sidoides*, in animals models of cough, secretolytic activity and acute bronchitis. *Phytomedicine* 2015; **22**: 504-509 [PMID: 25925973 DOI: 10.1016/j.phymed.2015.03.004]

158 **Aung H**, Mehendale S, Chang WT, Wang CZ, Xie JT, Yuan CS. *Scutellaria baicalensis* decreases ritonavir-induced nausea. *AIDS Res Ther* 2005; **2**: 12 [PMID: 16368007 DOI: 10.1186/1742-6405-2-12]

159 **Hong GE**, Kim JA, Nagappan A, Yumnam S, Lee HJ, Kim EH, Lee WS, Shin SC, Park HS, Kim GS. Flavonoids Identified from Korean *Scutellaria baicalensis* Georgi Inhibit Inflammatory Signaling by Suppressing Activation of NF- κ B and MAPK in RAW 264.7 Cells. *Evid Based Complement Alternat Med* 2013; **2013**: 912031 [PMID: 24348728 DOI: 10.1155/2013/912031]

160 **Mehendale S**, Aung H, Wang CZ, Tong R, Foo A, Xie JT, Yuan CS. *Scutellaria baicalensis* and a constituent flavonoid, baicalein, attenuate ritonavir-induced gastrointestinal side-effects. *J Pharm Pharmacol* 2007; **59**: 1567-1572 [PMID: 17976269 DOI: 10.1211/jpp.59.11.0015]

161 **Cui L**, Guan X, Ding W, Luo Y, Wang W, Bu W, Song J, Tan X, Sun E, Ning Q, Liu G, Jia X, Feng L. *Scutellaria baicalensis* Georgi polysaccharide ameliorates DSS-induced ulcerative colitis by improving intestinal barrier function and modulating gut microbiota. *Int J Biol Macromol* 2021; **166**: 1035-1045 [PMID: 33157130 DOI: 10.1016/j.ijbiomac.2020.10.259]

162 **Thanh HN,** Minh HPT, Le TA, Ly HDT, Huu TN, Duc LV, Kim TD, Thanh TB. Ethanol extracts of *Scutellaria baicalensis* protect against lipopolysaccharide-induced acute liver injury in mice. *Asian Pac J Trop Biomed* 2015; **5:** 761-767 [DOI: 10.1016/j.apjtb.2015.07.007]

163 **Dai J**, Chen L, Qiu YM, Li SQ, Xiong WH, Yin YH, Jia F, Jiang JY. Activations of GABAergic signaling, HSP70 and MAPK cascades are involved in baicalin's neuroprotection against gerbil global ischemia/reperfusion injury. *Brain Res Bull* 2013; **90**: 1-9 [PMID: 23041106 DOI: 10.1016/j.brainresbull.2012.09.014]

164 **Bui TT**, Piao CH, Song CH, Lee CH, Shin HS, Chai OH. Baicalein, wogonin, and *Scutellaria baicalensis* ethanol extract alleviate ovalbumin-induced allergic airway inflammation and mast cell-mediated anaphylactic shock by regulation of Th1/Th2 imbalance and histamine release. *Anat Cell Biol* 2017; **50**: 124-134 [PMID: 28713616 DOI: 10.5115/acb.2017.50.2.124]

165 **Laub A.** Using species of the Lamiaceae family for musculoskeletal pain. 2018. [cited 10 January 2021]. Available from: https://www.researchgate.net/publication/335156154\_Using\_Species\_of\_the\_Lamiaceae\_Family\_for\_Musculoskeletal\_Pain

166 **Salmalian H**, Saghebi R, Moghadamnia AA, Bijani A, Faramarzi M, Nasiri Amiri F, Bakouei F, Behmanesh F, Bekhradi R. Comparative effect of *Thymus vulgaris* and ibuprofen on primary dysmenorrhea: A triple-blind clinical study. *Caspian J Intern Med* 2014; **5**: 82-88 [PMID: 24778782]

167 **Okazaki K**, Kawazoe K, Takaishi Y. Human platelet aggregation inhibitors from thyme (*Thymus vulgaris* L.). *Phytother Res* 2002; **16**: 398-399 [PMID: 12112303 DOI: 10.1002/ptr.979]

168 **Habashy NH,** Serie MM, Attia WE, Abdelgaleil SA. Chemical characterization, antioxidant and anti-inflammatory properties of Greek *Thymus vulgaris* extracts and their possible synergism with Egyptian *Chlorella vulgaris*. *J Funct Foods* 2018; **40:** 317-328 [DOI: 10.1016/j.jff.2017.11.022]

169 **Salve J**, Pate S, Debnath K, Langade D. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. *Cureus* 2019; **11**: e6466 [PMID: 32021735 DOI: 10.7759/cureus.6466]

170 **Murthy MNK,** Gundagani S, Nutalapati C, Pingali U. Evaluation of analgesic activity of standardised aqueous extract of *Withania somnifera* in healthy human volunteers using mechanical pain model. *J Clin Diagn* 2019; **13:** 1-4 [DOI: 10.7860/jcdr/2019/37590.12441]

171 **Ku SK**, Bae JS. Antiplatelet, anticoagulant, and profibrinolytic activities of withaferin A. *Vascul Pharmacol* 2014; **60**: 120-126 [PMID: 24534482 DOI: 10.1016/j.vph.2014.01.009]

172 **Gupta A**, Singh S. Evaluation of anti-inflammatory effect of *Withania somnifera* root on collagen-induced arthritis in rats. *Pharm Biol* 2014; **52**: 308-320 [PMID: 24188460 DOI: 10.3109/13880209.2013.835325]

173 **Lopresti AL**, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract: A randomized, double-blind, placebo-controlled study. *Medicine (Baltimore)* 2019; **98**: e17186 [PMID: 31517876 DOI: 10.1097/MD.0000000000017186]

174 **Maghbooli M**, Golipour F, Moghimi Esfandabadi A, Yousefi M. Comparison between the efficacy of ginger and sumatriptan in the ablative treatment of the common migraine. *Phytother Res* 2014; **28**: 412-415 [PMID: 23657930 DOI: 10.1002/ptr.4996]

175 **Bartels EM**, Folmer VN, Bliddal H, Altman RD, Juhl C, Tarp S, Zhang W, Christensen R. Efficacy and safety of ginger in osteoarthritis patients: A meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2015; **23**: 13-21 [PMID: 25300574 DOI: 10.1016/j.joca.2014.09.024]

176 **Tóth B**, Lantos T, Hegyi P, Viola R, Vasas A, Benkő R, Gyöngyi Z, Vincze Á, Csécsei P, Mikó A, Hegyi D, Szentesi A, Matuz M, Csupor D. Ginger (*Zingiber officinale*): An alternative for the prevention of postoperative nausea and vomiting. A meta-analysis. *Phytomedicine* 2018; **50**: 8-18 [PMID: 30466995 DOI: 10.1016/j.phymed.2018.09.007]

177 **Khan AM**, Shahzad M, Raza Asim MB, Imran M, Shabbir A. *Zingiber officinale* ameliorates allergic asthma via suppression of Th2-mediated immune response. *Pharm Biol* 2015; **53**: 359-367 [PMID: 25420680 DOI: 10.3109/13880209.2014.920396]

178 **Lee W**, Ku SK, Kim MA, Bae JS. Anti-factor Xa activities of zingerone with anti-platelet aggregation activity. *Food Chem Toxicol* 2017; **105**: 186-193 [PMID: 28414123 DOI: 10.1016/j.fct.2017.04.012]

179 **Bera K**, Nosalova G, Sivova V, Ray B. Structural Elements and Cough Suppressing Activity of Polysaccharides from *Zingiber officinale* Rhizome. *Phytother Res* 2016; **30**: 105-111 [PMID: 26522239 DOI: 10.1002/ptr.5508]

180 **Nanjundaiah SM**, Annaiah HN, Dharmesh SM. Gastroprotective Effect of Ginger Rhizome (*Zingiber officinale*) Extract: Role of Gallic Acid and Cinnamic Acid in H(+), K(+)-ATPase/H. pylori Inhibition and Anti-Oxidative Mechanism. *Evid Based Complement Alternat Med* 2011; **2011**: 249487 [PMID: 19570992 DOI: 10.1093/ecam/nep060]

181 **Ajith TA**, Hema U, Aswathy MS. *Zingiber officinale* Roscoe prevents acetaminophen-induced acute hepatotoxicity by enhancing hepatic antioxidant status. *Food Chem Toxicol* 2007; **45**: 2267-2272 [PMID: 17637489 DOI: 10.1016/j.fct.2007.06.001]

182 **Ajith TA**, Nivitha V, Usha S. *Zingiber officinale* Roscoe alone and in combination with alpha-tocopherol protect the kidney against cisplatin-induced acute renal failure. *Food Chem Toxicol* 2007; **45**: 921-927 [PMID: 17210214 DOI: 10.1016/j.fct.2006.11.014]

183 **Abdelli I**, Hassani F, Bekkel Brikci S, Ghalem S. *In silico* study the inhibition of angiotensin converting enzyme 2 receptor of COVID-19 by *Ammoides verticillata* components harvested from Western Algeria. *J Biomol Struct Dyn* 2021; **39**: 3263-3276 [PMID: 32362217 DOI: 10.1080/07391102.2020.1763199]

184 **Thuy BTP**, My TTA, Hai NTT, Hieu LT, Hoa TT, Thi Phuong Loan H, Triet NT, Anh TTV, Quy PT, Tat PV, Hue NV, Quang DT, Trung NT, Tung VT, Huynh LK, Nhung NTA. Investigation into SARS-CoV-2 Resistance of Compounds in Garlic Essential Oil. *ACS Omega* 2020; **5**: 8312-8320 [PMID: 32363255 DOI: 10.1021/acsomega.0c00772]

185 **Sui H**, Yu Q, Zhi Y, Geng G, Liu H, Xu H. [Effects of apigenin on the expression of angiotensin-converting enzyme 2 in kidney in spontaneously hypertensive rats]. *Wei Sheng Yan Jiu* 2010; **39**: 693-696, 700 [PMID: 21351633]

186 **Dong J**, Xu X, Liang Y, Head R, Bennett L. Inhibition of angiotensin converting enzyme (ACE) activity by polyphenols from tea (*Camellia sinensis*) and links to processing method. *Food Funct* 2011; **2**: 310-319 [PMID: 21779569 DOI: 10.1039/c1fo10023h]

187 **Chen H,** Du Q. Potential natural compounds for preventing SARS-CoV-2 (2019-nCoV) infection. 2020 Preprint. Available from: 2020010358 [DOI: 10.20944/preprints202001.0358.v3]

188 **Senthil Kumar KJ**, Gokila Vani M, Wang CS, Chen CC, Chen YC, Lu LP, Huang CH, Lai CS, Wang SY. Geranium and Lemon Essential Oils and Their Active Compounds Downregulate Angiotensin-Converting Enzyme 2 (ACE2), a SARS-CoV-2 Spike Receptor-Binding Domain, in Epithelial Cells. *Plants (Basel)* 2020; **9** [PMID: 32575476 DOI: 10.3390/plants9060770]

189 **Zi CT,** Zhang N, Yang L, Wang LX, Wu YL, Su YS, Wang XJ. Discovery of a potent angiotensin converting enzyme 2 inhibitor from Chinese medicinal and edible plant via docking-based virtual screening. 2020 Preprint. Available from: rs-32515 [DOI: 10.21203/rs.3.rs-32515/v1]

190 **Takahashi S**, Yoshiya T, Yoshizawa-Kumagaye K, Sugiyama T. Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. *Biomed Res* 2015; **36**: 219-224 [PMID: 26106051 DOI: 10.2220/biomedres.36.219]

191 **Ojeda D**, Jiménez-Ferrer E, Zamilpa A, Herrera-Arellano A, Tortoriello J, Alvarez L. Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa*. *J Ethnopharmacol* 2010; **127**: 7-10 [PMID: 19808084 DOI: 10.1016/j.jep.2009.09.059]

192 **Prasad K**. Secoisolariciresinol Diglucoside (SDG) Isolated from Flaxseed, an Alternative to ACE Inhibitors in the Treatment of Hypertension. *Int J Angiol* 2013; **22**: 235-238 [PMID: 24436618 DOI: 10.1055/s-0033-1351687]

193 **My TTA**, Loan HTP, Hai NTT, Hieu LT, Hoa TT, Thuy BTP, Quang DT, Triet NT, Anh TTV, Dieu NTX, Trung NT, Hue NV, Tat PV, Tung VT, Nhung NTA. Evaluation of the Inhibitory Activities of COVID-19 of *Melaleuca cajuputi* Oil Using Docking Simulation. *Chemistry Select* 2020; **5**: 6312-6320 [PMID: 32572383 DOI: 10.1002/slct.202000822]

194 **Siriwattananon K**, Manopwisedjaroen S, Kanjanasirirat P, Budi Purwono P, Rattanapisit K, Shanmugaraj B, Smith DR, Borwornpinyo S, Thitithanyanont A, Phoolcharoen W. Development of Plant-Produced Recombinant ACE2-Fc Fusion Protein as a Potential Therapeutic Agent Against SARS-CoV-2. *Front Plant Sci* 2020; **11**: 604663 [PMID: 33584747 DOI: 10.3389/fpls.2020.604663]

**Footnotes**

**Conflict-of-interest statement:** Authors declare that they have no conflicts of interest for this article.

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**Manuscript source:** Invited manuscript

**Peer-review started:** March 16, 2021

**First decision:** May 1, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Turkey

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Wang X **S-Editor:** Fan JR **L-Editor: P-Editor:**

**Table 1 Antiviral effects of plants on respiratory viruses**

|  |  |  |  |
| --- | --- | --- | --- |
| **Plant name** | **Preparation** | **Susceptible viruses** | **Ref.** |
| *Allium sativum* (Garlic) | Aqueous extracts | Influenza A (H9N2) | Rasool *et al*[53], 2017 |
| Extract | Infectious bronchitis virus | Mohajer Shojai *et al*[54], 2016 |
| Ethanolic extract | Influenza A (H1N1) | Chavan *et al*[55], 2016 |
| Garlic oil | Influenza A (H1N1) | Choi[56], 2018 |
| Fresh extract | Influenza A (H1N1) | Mehrbod *et al*[57], 2013 |
| Aqueous extract | Adenovirus (ADV3 and ADV41) | Chen *et al*[58], 2011 |
| *Aloe vera* (Aloe) | Aloe anthraquinones and several derivatives (3-O-tetraacetoglupiranosil) | Influenza A | Borges-Argáez *et al*[59], 2019 |
| Aloe-emodin | Influenza A | Li *et al*[60], 2014 |
| *Astragalus mongholicus* (Astragalus) | *Astragalus* polysaccharides | Avian infectious bronchitis virus | Zhang *et al*[61], 2018 |
| *Astragalus* polysaccharide | Influenza A (H9N2) | Kallon *et al*[62], 2013 |
| *Camellia sinensis* (Green tea) | Catechins -EGCG | Adenovirus | Weber *et al*[63], 2003 |
| Catechin | Influenza A | Kuzuhara *et al*[64], 2009 |
| Catechins | Influenza A (H5N1) | Liu *et al*[65], 2012 |
| Polyphenols | Influenza A; Influenza B | Yang *et al*[66], 2014 |
| *Curcuma longa* (Turmeric) | Curcumin | Influenza A virus | Chen *et al*[67], 2013 |
| Dai *et al*[68], 2018 |
| Curcumin | Influenza A (H1N1, H6N1) | Chen *et al*[69], 2010 |
| Curcumin | RSV | Obata *et al*[70], 2013 |
| *Echinacea purpurea* (Purple coneflower) | *E. purpurea* fresh herb and root tinctures | Influenza | Vimalanathan *et al*[71], 2013 |
| Standardized *E. purpurea* extract | Influenza A (H5N1, H7N7, H1N1) | Pleschka *et al*[72], 2009 |
| Standardized *E. purpurea* extract | Rhinoviruses, RSV | Hudson *et al*[73], 2011 |
| *Eucalyptus globulus* (Eucalyptus) | Essential oil- vapor phase | Influenza | Vimalanathan *et al*[74], 2014 |
| *Ginkgo biloba* (Ginkgo) | Leaf extract | Influenza A (H1N1, H3N2) | Haruyama *et al*[75], 2013 |
| *Glycyrrhiza* sp*.* (Licorice) | Water extract of licorice (*Glycyrrhiza uralensis*) | RSV | Feng Yeh *et al*[76], 2013 |
| Glycyrrhizic acid derivatives | SARS-CoV | Hoever *et al*[77], 2005 |
| Extract of *Glycyrrhiza inflata* | Influenza A (H1N1) | Dao *et al*[78], 2011 |
| Glycyrrhizin | Influenza A | Wolkerstorfer *et al*[79], 2009 |
| Glycyrrhizin | Influenza A (H5N1) | Michaelis *et al*[80], 2010 |
| *Lepidium meyenii* (Maca) | Extracted with methanol | Influenza A; Influenza B | Del Valle Mendoza *et al*[81], 2014 |
| *Melaleuca alternifolia* (Tea tree) | Tea tree oil | Influenza A (H1N1) | Garozzo *et al*[82], 2011 |
| Aerosol and vapor of tea tree oil | Influenza A (H11N9) | Usachev *et al*[83], 2013 |
| Tea tree oil | Influenza A (H11N9) | Pyankov *et al*[84], 2012 |
| *Melissa officinalis* (Lemon balm) | Essential oil | Influenza A (H9N2) | Pourghanbari *et al*[85], 2016 |
| Extract | Avian infectious bronchitis | Lelešius *et al*[86], 2019 |
| *Mentha piperita* (Peppermint) | Ethanol extract | RSV | Li *et al*[87], 2017 |
| Extract | Avian infectious bronchitis | Lelešius *et al*[86], 2019 |
| *Nigella sativa* (Black cumin) | Ethanol extracts of | Influenza A (H5N1) | Dorra *et al*[88], 2019 |
| Ethanol extracts of | Influenza A (H9N2) | Umar *et al*[89], 2016 |
| Extract | Coronavirus | Ulasli *et al*[90], 2014 |
| *Panax ginseng* (Ginseng) | Root of plant *Panax ginseng* | RSV | Lee *et al*[91], 2014 |
| Panax Korean red ginseng extract | RSV | Lee *et al*[92], 2014 |
| Red ginseng extract and polysaccharide and saponin fractions | Influenza A (H1N1) | Yin *et al*[93], 2013 |
| Korean red ginseng extract | Influenza A (H1N1, H3N2) | Yoo *et al*[94], 2012 |
| *Pelargonium sidoides* (Pelargonium) | *Pelargonium sidoides* radix extract EPs® 7630 | Rhinovirus | Roth *et al*[95], 2019 |
| EPs® 7630 | Respiratory viruses | Michaelis *et al*[96], 2011 |
| EPs® 7630 | Influenza A (H1N1, H3N2) | Theisen *et al*[97], 2012 |
| *Sambucus nigra* (Black elder) | Extract | Infectious bronchitis virus | Chen *et al*[98], 2014 |
| Standardized elderberry liquid extract | Influenza A; Influenza B | Krawitz *et al*[99], 2011 |
| Concentrated juice of elderberry | Influenza A | Kinoshita *et al*[100], 2012 |
| Elderberry flavonoids | Influenza A (H1N1) | Roschek *et al*[101], 2009 |
| *Scutellaria baicalensis* (Chinese skullcap) | Chemical constituents | Influenza A (H1N1) | Ji *et al*[102], 2015 |
| Baicalin | SARS-CoV | Chen *et al*[103], 2004 |
| *Torreya nucifera* (Japanese nutmeg yew) | Ethanol extract | SARS-CoV | Ryu *et al*[104], 2010 |
| *Thymus vulgaris* (Thyme) | Essential oil- liquid phase | Influenza | Vimalanathan *et al*[74], 2014 |
| Extract | Avian infectious bronchitis | Lelešius *et al*[86], 2019 |
| *Withania somnifera* (Ashwagandha) | Withaferin A | Influenza A (H1N1) | Cai *et al*[105], 2015 |
| *Zingiber officinalis* (Ginger) | Aqueous extracts | Influenza A (H9N2) | Rasool *et al*[53], 2017 |
| Ethanol extracts | Influenza A- (H5N1) | Dorra *et al*[88], 2019 |
| Fresh ginger | RSV | Chang *et al*[106], 2013 |

Influenza A strains: H1N1, H3N2, H5N1, H6N1, H7N7, H9N2, H11N9; RSV: Respiratory syncytial virus; H1N1: Influenza A; SARS-CoV: Severe acute respiratory syndrome coronavirus.

**Table 2 Human clinical studies showing the effect of plants on respiratory infections**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Plant** | **Disease state** | **Participant** | **Dosage** | **Study design** | **Results** |
| Aged garlic extract[107] | Cold and  flu illness | 120 healthy subjects, 2 groups (21-50 yr) | 4 capsules/d (2.56 g); 90 d | Double-blind, randomized, placebo-controlled parallel intervention | Increase in γδ-T cell and NK cell. Reduction in cold and flu severity; decrease in symptom days |
| *E. purpurea* and *E. angustifolia* root[108] | New-onset common cold | 719 patients, 4 parallel groups (12-80 yr) | First 24 h: Equivalent of 10.2 g of root. Next 4 d: 5.1 g | Randomized, controlled trial | Disease duration and severity are not statistically significantly changed |
| *Echinacea purpurea* alcohol extract (Echinaforce®)[109] | Common cold | 755 healthy subjects, 2 groups (≥ 18 yr) | Illness prevention: 3 × 0.9 mL. Acute stages of colds: 5 × 0.9 mL | Randomized, double-blind, placebo-controlled trial | Reduction of the total number of cold episodes, cumulated episode days, and pain-killer medicated episodes. Inhibited virally confirmed colds and especially prevented enveloped virus infections. Maximal effects on recurrent infections. Prophylactic intake of *E. purpurea* over a period of 4 mo to provide a positive risk/benefit ratio |
| *Echinacea* root extract[110] | Respiratory symptoms | 175 adults, 2 groups (18–65 yr) | Tablets: 112.5 mg *E. purpurea* 6:1 extract (equivalent to 675 mg dry root) and 150 mg *E. angustifolia* 4:1 extract (equivalent to 600 mg dry root) 3 × 1 tablet, if required: 3 × 2 tablets | Randomized, double blind, placebo-controlled trial | Lower respiratory symptom scores. Preventive effect against the development of respiratory symptoms during travel, including long-haul flights |
| Green tea catechins and theanine[111] | Influenza | 200 healthcare workers, 2 groups | Capsules: Green tea catechins (378 mg/d) and theanine (210 mg/d). 5 m | Randomized, double-blind, placebo-controlled trial | Lower incidence of influenza infection in the catechin/theanine group |
| Ivy leaf extract[112] | Acute or chronic bronchial inflammatory disease | 9657 patients (5181 children) | Ivy leaves extract [drug-to-extract ratio: 5-7.5:1; extraction solvent: ethanol 30% (w/w)]. 0–5 yr: 3 × 2.5 mL; 6–12 yr: 3 × 5 mL; 12 yr and adults: 3 × 5–7.5 mL. 7 d | Prospective, open, multicenter post marketing study | Healing or improvement in 95% of symptoms. Effective and well tolerated |
| Ivy extract (Hedelix®)[113] | Acute respiratory catarrh and/or chronic recidivating inflammatory bronchial disease | 268 children, 2 groups (syrup and drops groups) (0-12 yr) | 0-1 yr: 1 × 2.5 mL syrup or 3 × 5 drops, 1-4 yr: 3 × 2.5 mL syrup or 3 × 16 drops, 4-10 yr: 4 × 2.5 mL syrup or 3 × 21 drops, 10-12 yr: 3 × 5 mL syrup or 3 × 31 drops. 14 d | Independent open, non‐interventional studies | Effective and safe treatment of cough. Reduction in symptoms (especially rhinitis, cough and viscous mucus) |
| Ivy leaves dry extract (Prospan ®)[114] | Bronchial asthma | 30 children (suffering from partial or uncontrolled mild persistent allergic asthma despite long-term treatment with 400 μg budesonide equivalent), 2 groups (6–11 yr) | 2 × 5 mL (corresponding to 70 mg extract) 28–30 d | Randomized, double blind, placebo-controlled, cross-over study | Improvement of MEF75-25, MEF25 and VC |
| Korean red ginseng extract[115] | Influenza-like illness | 100 healthy adults, 2 groups (30-70 yr) | 9 capsules/d. 3 m | Placebo-controlled trial | Reduced the incidence of influenza-like illness |
| Modified ginseng extracts (GS-3K8 and GINST)[116] | Acute respiratory illness | 45 healthy applicants, 3 groups (39-65 yr) | Capsules: 500 mg; 6 capsules/d; 8 wk | Randomized, double-blind, placebo-controlled pilot study | Reduction in acute respiratory illness development and symptom duration |
| *Panax quinquefolius* extract CVT-E002[117] | Acute respiratory illness and Chronic Lymphocytic Leukemia | 293 patients, 2 groups (≥ 18 yr) | 2 × 200 mg extract. 3 m | Randomized, double-blind, placebo-controlled study | Reduction intense acute respiratory illness and moderately-severe sore throat. Increased antibody responses. |
| *Panax ginseng*[118] | Chronic obstructive pulmonary disease | 14 participants, 2 groups (57–73 yr) | 2 × 200 mg  4 wk | Clinical trial protocol and pilot study | One participant in P. ginseng group reported events of sore throat, cough and fever |
| *Panax ginseng* root extract[119] | Chronic obstructive pulmonary disease | 168 participants, 2 groups | 2 × 100 mg capsules. 24 wk | Randomized, multi-center, double-blind, placebo controlled | Reduction in symptoms |
| *Pelargonium sidoides* extract EPs® 7630[120] | Chronic obstructive pulmonary disease | 199 adults, 2 groups (18 yr and older) | 30 drops. 24 wk | Randomized, double-blind, placebo-controlled, parallel group trial | Improvement in HRQoL (health-related quality-of-life) and PRO (Patient-reported outcomes) |
| *Pelargonium sidoides* extract EPs® 7630[121] | Acute bronchitis | 220 patients (1-18 yr) | 1-6 yr: 3 × 10 drops; 6–12 yr: 3 × 20 drops; 12-18 yr: 3 × 30 drops; 7 d | Randomized, double-blind, placebo-controlled clinical trial | Reduction in the total score of bronchitis-specific symptoms (especially cough and rales at auscultation) |
| *Pelargonium sidoides* extract EPs® 7630[122] | Upper respiratory tract infections | 28 children with a diagnosed transient hypogammaglobulinemia of infancy (1-5 yr) | 3 × 10 drops; 7 d | Randomized, placebo controlled, prospective, monocentric pilot study | Increased appetite. Reduction of nasal congestion |
| *Pelargonium sidoides* root extract EPs® 7630[123] | Upper respiratory tract- asthma attacks | 61 children (1–14 yr) | 1–5 yr: 3 × 10 drops; 6–12 yr: 3 × 20 drops; 12 yr and above: 3 × 30 drops; 5 d | Randomized, placebo controlled | Reduction the severity of symptoms (especially cough and nasal congestion). Shortening of the duration of upper respiratory viral infections. Reduction asthma attack frequency |
| *Pelargonium sidoides* preparation EPs® 7630[124] | Acute non-streptococcal tonsillopharyngitis | 126 children, 2 groups (6–10 yr) | 3 × 20 drops. 6 d | Double-blind, placebo-controlled clinical trial | Decrease in tonsillitis severity score compared to placebo in the EPs® 7630 group after 4 d of treatment |
| *Pelargonium sidoides* extract EPs® 7630[125] | Common cold | 207 adults (18-55 yr) | SD: 3 × 30 drops; HD: 3 × 60 drops; 10 d | Prospective, double-blind, parallel-group, placebo-controlled, phase 3, 2 parts, 2-arm, clinical trial | After 10 d, clinical treatment in 90.4% of the active drug group. Reduction the severity of symptoms and short the duration of the disease. Higher full recovery rates or greater recovery for HD treatment on day 5 |
| *Sambucus nigra* extract[126] | Influenza | 64 patients (16-60 yr) | Lozenge: 175 mg extract; 4 lozenges/d; 2 d | Randomized, double-blind, placebo-controlled, pilot clinical trials | Significant improvement in most symptoms within 24 h (fever, headache, muscle aches and nasal congestion). Significant improvement in all investigated symptoms within 48 h (cough and mucus discharge) |
| *Sambucus nigra* extract[127] | Respiratory health | 312 adults, 2 groups | Capsules: 300 mg. Before travel: 2 capsules/d. During travel and after arrival: 3 capsules/d. 14 d | Randomized, double-blind placebo-controlled clinical trial | Reduction of cold duration and severity in air travelers. Low symptom score |

SD: Standard dose; HD: High dose.

**Table 3 Plants that can have an impact on coronavirus disease 2019 symptoms**

|  |  |  |
| --- | --- | --- |
| **Plant name** | **Effects** | **Ref.** |
| *Allium sativum* (Garlic) | Analgesic | Dehghani *et al*[128], 2018 |
| Anti-inflammatory | Arreola *et al*[129], 2015 |
| Anti-platelet | Hiyasat *et al*[130], 2009 |
| Heart protection | Sultana *et al*[131], 2016 |
| Hepatic protection | Aprioku *et al*[132], 2017 |
| Improving GI function | Chen *et al*[133], 2018 |
| Renal protection | Seckiner *et al*[134], 2014 |
| *Curcuma longa* (Turmeric) | Analgesic | Henrotin *et al*[135], 2020 |
| Eke-Okoro *et al*[136], 2018 |
| Antiemetic | Liu *et al*[137], 2018 |
| Antifatigue | Huang *et al*[138], 2015 |
| Anti-inflammatory | Shimizu *et al*[139], 2019 |
| Antifibrotic | Gouda *et al*[140], 2019 |
| Antipyretic | Haider *et al*[141], 2013 |
| Bronchodilator | Ram *et al*[142], 2003 |
| GI protection | Haider *et al*[141], 2013 |
| Dulbeccoand Savarino[143], 2013 |
| Hepatic protection | Dulbeccoand Savarino[143], 2013 |
| *Glycyrrhiza glabra* (Licorice) | Antitussives | Nosalova *et al*[144], 2013 |
| Kuang *et al*[145], 2018 |
| Anti-inflammatory | Kao *et al*[146], 2010 |
| Respiratory system protection | Shi *et al*[147], 2011 |
| *Nigella sativa* (Black cumin) | Analgesic | Rushmi *et al*[148], 2017 |
| Anticoagulant | Muralidharan-Chari *et al*[149], 2016 |
| Antihistaminic | Ansari *et al*[150], 2010 |
| Alsamarai *et al*[151], 2014 |
| Anti-inflammatory | Majdalawiehand Fayyad[152], 2015 |
| Mahdavi *et al*[153], 2016 |
| Bronchodilation | Boskabady *et al*[154], 2010 |
| Salem *et al*[155], 2017 |
| *Panax ginseng* (Ginseng) | Adaptogenic | Ratan *et al*[156], 2021 |
| *Pelargonium sidoides* (Pelargonium) | Antitussives | Bao *et al*[157], 2015 |
| Secretolytic activity | Bao *et al*[157], 2015 |
| *Scutellaria baicalensis* (Chinese skullcap) | Antiemetic | Aung *et al*[158], 2005 |
| Anti-inflammatory | Hong *et al*[159], 2013 |
| GI protection | Mehendale *et al*[160], 2007 |
| Cui *et al*[161], 2021 |
| Hepatic protection | Thanh *et al*[162], 2015 |
| Neuroprotective | Dai *et al*[163], 2013 |
| Regulation of histamine release-Anti allergic | Bui *et al*[164], 2017 |
| *Thymus vulgaris* (Thyme) | Analgesic | Laub[165], 2018 |
| Salmalian *et al*[166], 2014 |
| Anticoagulant | Okazaki *et al*[167], 2002 |
| Anti-inflammatory | Habashy *et al*[168], 2018 |
| *Withania somnifera* (Ashwagandha) | Adaptogenic | Salve *et al*[169], 2019 |
| Analgesic | Murthy *et al*[170], 2019 |
| Anticoagulant, antithrombotic | Ku *et al*[171], 2014 |
| Anti-inflammatory | Gupta and Singh[172], 2014 |
| Antitussives | Nosalova *et al*[144], 2013 |
| Stress-relieving | Lopresti *et al*[173], 2019 |
| *Zingiber officinale* (Ginger) | Analgesic | Maghbooli *et al*[174], 2014 |
| Bartels *et al*[175], 2015 |
| Antiemetic | Tóth *et al*[176], 2018 |
| Anti-inflammatory | Khan *et al*[177], 2015 |
| Antiplatelet, antithrombotic | Lee *et al*[178], 2017 |
| Antitussives | Bera *et al*[179], 2016 |
| GI protection | Nanjundaiah *et al*[180], 2011 |
| Hepatic protection | Ajith *et al*[181], 2007 |
| Nephroprotective | Ajith *et al*[182], 2007 |

**Table 4** **Angiotensin-converting enzyme inhibitor plant**

|  |  |  |  |
| --- | --- | --- | --- |
| **Plants** | **The compound under study** | **Results** | **Ref.** |
| *Ammoides verticillata* essential oil | Isothymol | SARS-CoV-2/ACE2 inhibition | Abdelli *et al*[183], 2021 |
| *Allium sativum*essential oil | Organosulfur compounds (99.4% of its essential oil) | SARS-CoV-2/ACE2 inhibition. Garlic essential oil can prevent protein maturation of the virus and the spread of infection | Thuy *et al*[184], 2020 |
| *Apium graveolens* | Apigenin | Kidneys of spontaneous hypertensive rats/Regulation in ACE2 expression | Sui *et al*[185], 2010 |
| *Camellia sinensis* | Black tea; Dark tea; Green tea; Oolong tea; White tea | ACE inhibition: Green < oolong < white < black < dark teas | Dong *et al*[186], 2011 |
| *Citrus aurantium* | Hesperetin. Scutellarin. Nicotianamine. Glycyrrhizin. Baicalin | SARS-CoV-2/Connecting to ACE2 and blocking the SARS-CoV-2 input | Chen and Du[187], 2020 |
| *Erigeron breviscapus* |
| *Glycine max* |
| *Glycyrrhiza radix* |
| *Scutellaria baicalensis* |
| Geranium and lemon essential oils | Citronellol and limonene | SARS-CoV-2/ACE2 inhibition | Senthil Kumar *et al*[188], 2020 |
| Ginseng *Glycyrrhiza uralensis* | Ginsenoside Rg6; Ginsenoside F1; Monoammonium glycyrrhizinate; Glycyrrhizic acid methyl ester | SARS-CoV-2/ACE2 kinase inhibition | Zi *et al*[189], 2020 |
| *Glycine max* (soybean) | Nicotianamine | ACE2 inhibition | Takahashi *et al*[190], 2015 |
| *Glycyrrhiza glabra* | Glycyrrhizic acid | SARS-CoV-2/Glycyrrhizic acid disrupts the connection of the virus with the ACE2 receptor at the entry level | Sinha *et al*[43], 2021 |
| *Hibiscus sabdariffa* anthocyanins | Delphinidin- and cyanidin-3-O-sambubiosides | ACE inhibition | Ojeda *et al*[191], 2010 |
| *Linum usitatissimum* (Flaxseed) | Secoisolariciresinol diglucoside | ACE inhibition | Prasad *et al*[192], 2013 |
| *Melaleuca cajuputi* essential oil | Components (70.9% of the oil) | SARS-CoV-2/ACE2 and PDB6LU7 proteins inhibition | My *et al*[193], 2020 |
| *Nicotiana benthamiana* | Recombinant ACE2-Fc fusion protein produced from *N. benthamiana* | SARS-CoV-2/Strong binding to the RBD of SARS-CoV-2 and inhibition | Siriwattananon *et al*[194], 2020 |
| *Withania somnifera* | Withanone | SARS-CoV-2/Docking to the connector interface of the AEC2-RBD complex | Balkrishna *et al*[51], 2020 |

ACE: Angiotensin-converting enzyme; RBD: Receptor binding domain; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme-2.