Review article
Curr. Pers. MAPs, (2021); 4(2): 128-150

Current Perspectives on Medicinal and Aromatic Plants

An International Journal
ISSN: 2619-9645 | e-ISSN: 2667-5722

Natural Substances and Coronavirus: Review and Potential for the Inhibition of SARS-CoV-2

Amal HELALI[1*], Meryem Wafa HAMMADI[1], Manel HOUALEF[1], Khadidja BENCHACHOU[1]

[1] Department of Pharmacy, Faculty of Medecine, University ABOU BEKR BELKAID, 13000, Tlemcen, Algeria
*Corresponding author : amal.helali@univ-tlemcen.dz

https://doi.org/10.38093/cupmap.1029572

Received : 28/11/2021
Accepted : 30/12/2021

Abstract

Coronaviruses are responsible for an increasing economic, social and mortality burden, as the causative agent of diseases such as the severe acute respiratory syndrome (SARS), the Middle East Respiratory Syndrome (MERS) and recently the COVID-19. Existing natural compounds, especially those known for their antiviral activity, may be useful as therapeutic agents against coronavirus infections. This study aims to review the currently available scientific literature on natural substances of plant origin with promising antiviral effects against coronaviruses. PubMed, Science Direct and Biomed Central databases were searched for articles including the keywords "*Coronavirus*", "*SARS-CoV-2*" as well as "*Alkaloids*", "*Polyphenols*", "*Terpenes*" and "*Secondary metabolites*". 145 research articles published between 2003 and 2020 were selected. The majority of the studies on natural substances acting against coronaviruses were performed in the last two years: 2020 (31,72%) and 2021 (60,69%) coinciding with the emergence of the new coronavirus SARS-CoV-2. Most studies were performed by *in silico* methods with a percentage of 66,67%, 25,45% by *in vitro* methods and only 7,88% by *in vivo* tests. Our research resulted in a list of 963 natural substances of plant origin tested against Coronavirus. Polyphenols represent the most tested secondary metabolites against Coronavirus, followed by terpenes and then alkaloids. Quercetin, Catechin, Glycyrrhizin, Kaempferol, Rutin, Curcumin, Myrecitin, Apigenin and Hesperidin were the most cited substances. In the future, we hope that the active ingredients of medicinal plants can be used to treat SARS-CoV-2 infection in humans.

Key Words: SARS-CoV-2, COVID-19, Natural compounds, Secondary metabolites, Review.

© CUPMAP. All rights reserved.

1. Introduction

Coronaviruses were first identified in humans in the 1960s. They are viruses that cause emerging diseases, i.e., new infections due to changes or mutations in viruses. Human coronaviruses mainly cause respiratory infections, ranging from the common cold to severe and sometimes lethal pneumonia (Vabret, Dina, Brison, Brouard, & Freymuth, 2009).

Three coronaviruses cause infections that can be severe or even fatal: severe acute respiratory syndrome (SARS-CoV) that appeared in China and caused the 2003 epidemic, Middle East Respiratory Syndrome (MERS) that caused the 2012 epidemic, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus-2019 (COVID-19) disease (Asrani, Hasan, Sohal, & Hassan, 2020).

In late December 2019, China reported the emergence of a new infectious disease, caused by a virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), initially transmitted from animals to humans and then from humans to humans. Within a short time, SARS-CoV-2 spread to other countries, killing thousands of people. As a result, the World Health Organization (WHO) has declared the Coronavirus-2019 (COVID-19) disease a pandemic and currently it is considered the second leading cause of death after cardiovascular disease.

The WHO states that no effective therapy has been approved to date for the prevention or treatment of this disease. Although vaccines have now been launched, evidence of their safety and efficacy in the population is still awaited. This suggests the need to broaden the scope of research for effective treatments. Among other therapeutic options, natural products and derivatives constitute a vast source of potential drug molecules. Nature provides a huge well of active ingredients that remain to be discovered to treat diseases.

Historically, 80% of clinically important drug developments are still inspired by these nature-derived entities. Therefore, products of natural origin or phytochemicals have continuously served humanity as a noble source of therapeutically important elements. And these products are of considerable importance in the event of a global health crisis and represent one of the most practical and promising approaches to reduce the intensity of pandemics through their therapeutic potential.

The main objective of this study is to review the currently available scientific literature on natural substances of plant origin with promising antiviral effects against Coronavirus.

2. Material and Methods

2.1. Bibliographic research of the data

The databases used were: PubMed, Science Direct and Biomed Central. The bibliographic search and the downloading of articles were carried out during the period from January 1, 2003 to May 31, 2021.

2.2. Search strategy

First, the keywords of the search equation were entered in the search engines of the databases used. We used English keywords related to the virus such as: "***Coronavirus***", "***SARS-CoV-2***", and related to phytotherapy and natural compounds sush as: "***Alkaloids***", "***Polyphenols***", "***Terpenes***" and "***Secondary metabolites***". Afterwards, we used the following filters: between 2000 and 2020, academic articles, in English. The articles we included in the research project met the following criteria:

- Any article design: *in silico* study, *in vitro* trial, *ex vivo* trial, *in vivo* trial, randomized controlled trials, clinical trials and meta-analyses with full text available in Open Access or downloadable;
- Articles written in English or French;
- Articles published during the period from January 1, 2003 to May 31, 2021.

2.3. Data analysis and exploitation

After downloading the considered articles, a deep reading was necessary to classify the articles and note the following informations:

- Year of publication;
- Country;
- Type of study;
- Substance's name;
- Substance's Chemical structure;
- Substance's plant origin;
- Plant's scientific name and botanical family;
- Substance's chemical class;
- Antiviral mechanism of action.

The data collected was then reported on Excel® and Google Sheets® softwares to convert the results into graphs and facilitate the analysis task.

3. Results and Discussion

A total of 5330 articles were identified by electronic search on PubMed, Science Direct, and BioMed Central. A summary of the study selection process is shown in Figure 1. 1881 articles were selected based on title and abstract, and 1368 after duplicate removal. At this stage, full texts were assessed and 1220 articles were excluded for ineligibility. Finally, 145 studies were included in our study. The search yielded a list of 963 natural substances of plant origin tested against Coronaviruses.

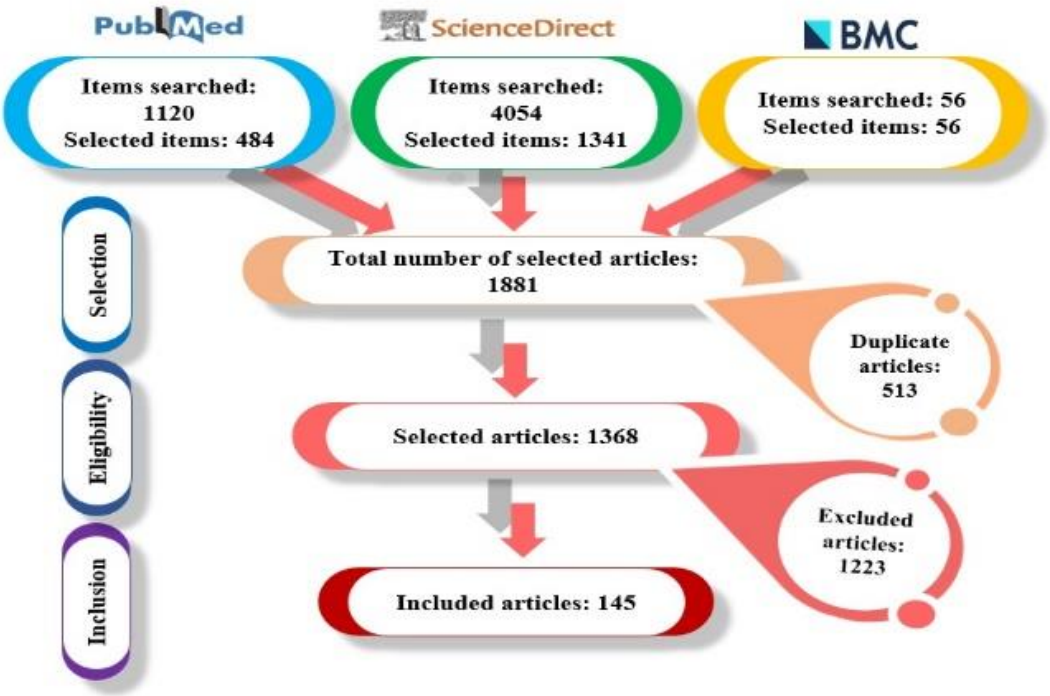

Figure 1. Articles search and selection's flowchart.

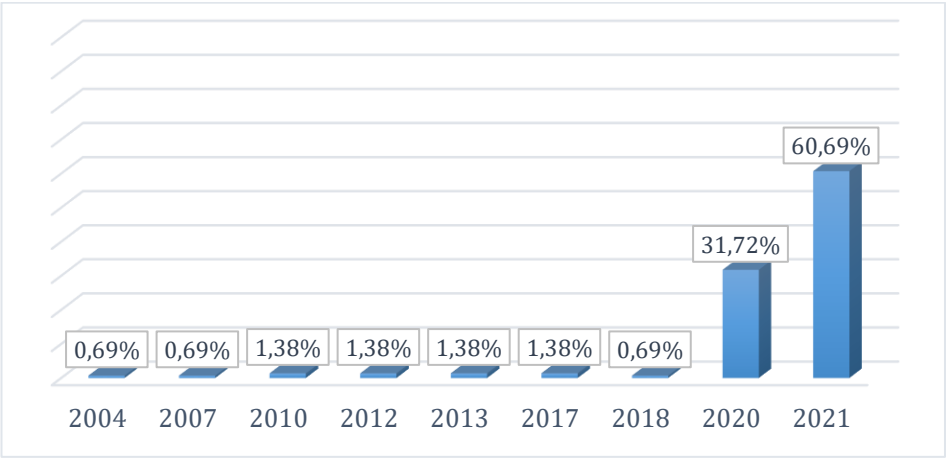

Figure 2. Articles distribution by publication's date.

3.1. Year of publication

The majority of the studies on natural substances acting against Coronaviruses were carried out in the last two years: 2020 (31.72%) and 2021 (60.69%), 2004 represents the year of the first publication and the number of articles published between 2004 and 2020 did not change significantly Figure 2.

This finding can be clearly justified by the emergence of the new coronavirus SARS-CoV-2 and the universal scope and severity of the pandemic caused by it compared to the last two epidemics due to SARS-CoV-1 and MERS-CoV.

3.2. Country

The states producing the most publications are the Asian countries mainly India with a percentage of 35.2% followed by China (16.6%) then South Korea (9.7%). The other countries: Egypt, Germany, Nigeria, USA, Brazil, Taiwan published between 6 and 3 articles and the rest including Algeria published less than 3 articles Figure 3.

Figure 3. Articles distribution by country.

3.3. Type of study

Most of the studies on Coronaviruses and natural substances were carried out by the *in silico* method with a percentage of 66.67%, 25.45% by *in vitro* methods and only 7.88% by i*n vivo* tests Figure 4.

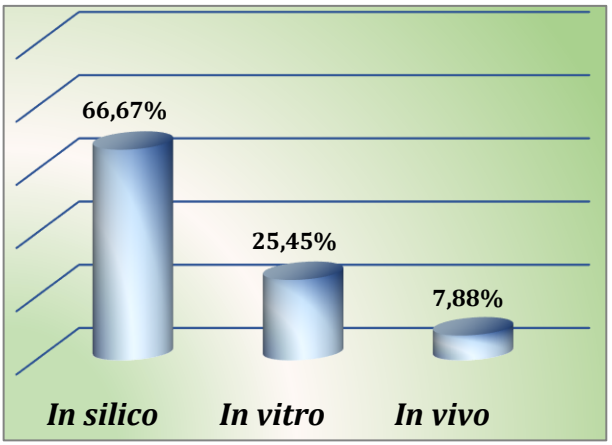

Figure 4. Articles distribution by study's type.

In silico methods are virtual screening approaches or methods based on algorithms developed for screening a large number of molecules in a shorter time and identifying a potential drug candidate (Hariprasad Puttaswamy et al., 2020). The use of these approaches has increased in the last two years, which is expected due to:

- The rapid result provided by these methods;
- The possibility of anticipation and prediction without the need for raw materials, extraction or purification;
- The ethical approach that does not require the use of animals;
- The lower costs and risks compared to traditional methods.

3.4. Substance's chemical classes

Of the 963 natural substances mentioned in the articles studied, polyphenols represent the most tested secondary metabolites against Coronavirus with a percentage of 51%, followed by terpenes (29%) and then alkaloids (18%). The other compounds such

as some primary metabolites constitute only 2% of the studied substances Figure 5.

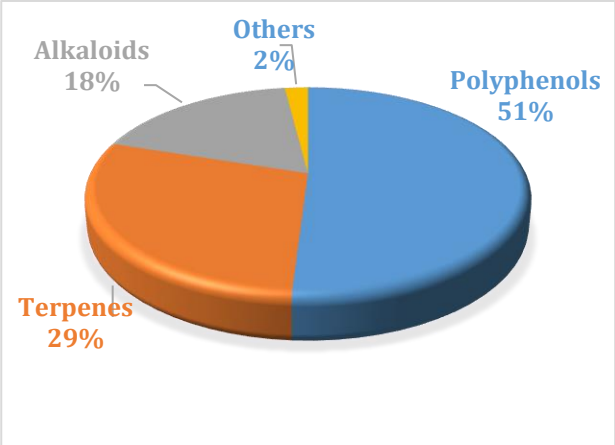

Figure 5. Molecules distribution by chemical classes.

Polyphenols are natural molecules known to have antiviral activity against a wide range of viruses, including HIV-1, HIV-2, HSV-1, HSV-2, influenza virus, dengue virus, HBV, HCV, infectious bronchitis virus (IBV), Murbarg virus, Ebola virus, Newcastle disease virus (NDV), polio virus-1, lentivirus and coronavirus.

In the case of the latter, polyphenols act against coronaviruses using various mechanisms, including activation or inhibition of cell signaling pathways or arrest of the papain-like protease (PL pro) and the enzyme 3-chymotripsin-like protease (3CLpro)(Shin, Oh, & Jeong, 2021).

3.5. Botanical family

Of the 963 natural substances mentioned in the articles studied, the Menispermaceae represents the most studied botanical family against Coronavirus with a percentage of 6.4% followed by the Asteraceae (6.3%) then the Rosaceae (5.6%) and Lamiaceae (5.3%). The other botanical families present a percentage lower than 4.5% Figure 6.

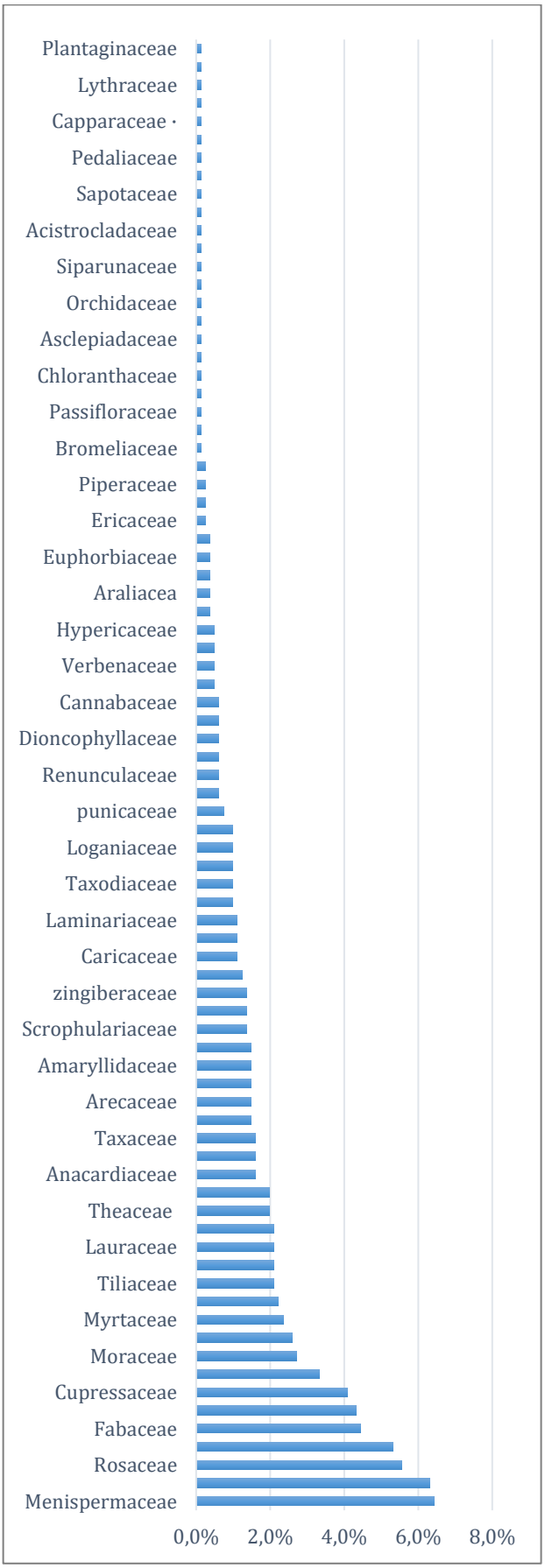

Figure 6. Molecules distribution by origin specie's botanical family.

Table 1. The 10 most quoted natural substances.

Natural substance	Chemical class	Virus	Action mechanism	Study design	References
Catechin and analogs *Camellia sinensis* *Carica papaya* *Mangifera indica* *Moringa oleifera* *Acacia nilotica* *Psidium guajava* *Rosa hybrida*	Polyphenol	SARS-CoV SARS-CoV-2	M^{pro},PL^{pro}, Helicase, protein N, protein S, RBD, ACE2, RdRp, CTSL, Nsp6, Nsp15 and furin inhibitor.Proteine S interaction with GRP78 and replication inhibitor Reduce cytokine storm Antioxidant agent	*In silico* *In vitro* *In vivo*	(Allam et al., 2020; Arokiyaraj, Stalin, Kannan, & Shin, 2020; Attia et al., 2021; Du et al., 2021; Elsbaey, Ibrahim, Bar, & Elgazar, 2021; R. Ghosh, Chakraborty, Biswas, & Chowdhuri, 2020b; Gogoi et al., 2021; Gupta et al., 2020; Halder et al., 2021; Hariyono, Patramurti, Candrasari, & Hariono, 2021; Jang et al., 2021; Jang et al., 2020; Jena, Kanungo, Nayak, Chainy, & Dandapat, 2021; Kumar et al., 2021; Liu, Raghuvanshi, Ceylan, & Bolling, 2020; Meyer-Almes, 2020; Mhatre, Naik, & Patravale, 2021; Mishra et al., 2021; Natesh et al., 2021; Nguyen et al., 2021; Pitsillou, Liang, Hung, & Karagiannis, 2021; Pitsillou, Liang, Ververis, Hung, & Karagiannis, 2021; Roh, 2012; Shin et al., 2021; Singh, Sk, Sonawane, Kar, & Sadhukhan, 2020; Umar et al., 2021; Vardhan & Sahoo, 2021; Yañez et al., 2021; M. Zhao et al., 2021)

Quercetin and analogs *Geranii Herba* *Ephedra sp* *Crocus sativus* *Allium cepa* *Broussonetia papyrifera* *Moringa oleifera* *Psidium guajava* *Camellia sinensis* *Rosa hybrida* *Azadirachta indica* *Mangifera indica* *Ginkgo biloba* *Corchorus olitorius* *Justicia adhatoda* *Psidium guyava* *Lespedeza cuneata* *Polygonum aviculare* *Rhododendron aureum* *Taxillus kaempferi*	Polyphenol	SARS-CoV MERS-CoV SARS-CoV-2	Inhibit SARS-CoV-2 cell entry via ACE2 receptor Inhibit proteolytic process, 3CLpro, PLpro, RdRp and interaction with HR2 domain Decrease inflammation factors Reduces cytokine storm Antioxidant agent	*In silico* *In vitro* *In vivo*	(Arokiyaraj et al., 2020; Attia et al., 2021; Azim et al., 2020; Du et al., 2021; Gao, Song, & Song, 2020; Gheware et al., 2021; K. Ghosh, Amin, Gayen, & Jha, 2021; Ibrahim et al., 2020; Kumar Verma et al., 2021; Kushwaha et al., 2021; Liu et al., 2020; Mesli, Ghalem, Daoud, & Ghalem, 2021; Meyer-Almes, 2020; Nguyen et al., 2021; Niu et al., 2021; Park et al., 2017; H. Puttaswamy et al., 2020; Shaji et al., 2021; P. Sharma & Shanavas, 2020; Shin et al., 2021; Singh et al., 2020; Umar et al., 2021; Xiong et al., 2021; Xu, Gao, Liang, & Chen, 2021; Yañez et al., 2021)
Glycyrrhizin and analogs *Glycyrrhiza uralensis* *Glycyrrhiza glabra*	Terpene	SARS-CoV MERS-CoV SARS-CoV-2	Inhibitor of the inflammatory response / prevents the development of a cytokine storm Inhibitor of 3CLpro, PLpro, RdRp, TMPRSS2, protein S, RBD, ACE2, Nsp1, furin and Endoribonuclease	*In silico* *In vitro* *In vivo*	(F. Chen et al., 2004; L. Chen et al., 2020; Ding et al., 2020; Diniz, Perez-Castillo, Elshabrawy, Filho, & de Sousa, 2021; Gowda, Patrick, Joshi, Kumawat, & Sen, 2021; Gurung, Ali, Lee, Farah, & Al-Anazi, 2021; Hejazi, Beg, Imam, Athar, & Islam, 2021; Luo et al., 2020; Muhseen, Hameed, Al-Hasani, Tahir ul Qamar, & Li, 2020; Patil et al., 2021; H. Puttaswamy et al., 2020; A.

					Sharma, Tiwari, & Sowdhamini, 2020; Toor, Banerjee, Lipsa Rath, & Darji, 2021; van de Sand et al., 2021; Vardhan & Sahoo, 2020, 2021; Yu et al., 2021; Z. Zhao et al., 2021; Zígolo, Goytia, Poma, Rajal, & Irazusta, 2021)
Kaempferol and analogs *Geranii Herba* *Carica papaya* *Ephedra sp* *Crocus sativus* *Senna alexandrina* *Broussonetia papyrifera* *Moringa oleifera* *Mangifera indica* *Ginkgo biloba* *Justicia adhatoda*	Polyphenol	SARS-CoV MERS-CoV SARS-CoV-2	Inhibits SARS-CoV-2 cell entry via ACE2 receptor Inhibits proteolytic process, 3CLpro, PLpro, RdRp, Nsp14, Nsp16 and protein S	*In silico* *In vitro*	(Arokiyaraj et al., 2020; Du et al., 2021; Gao et al., 2020; Gheware et al., 2021; Hariyono et al., 2021; Ibrahim et al., 2020; Mehmood et al., 2021; Natesh et al., 2021; Nguyen et al., 2021; Park et al., 2017; H. Puttaswamy et al., 2020; Shaji et al., 2021; Singh et al., 2020; Umar et al., 2021; Xiong et al., 2021; Yañez et al., 2021)
Rutin *Withania somnifera* *Passiflora incarnata Theobroma cacao*	Polyphenol	SARS-CoV SARS-CoV-2	3CLpro, PLpro, protein E, Nsp 15, ACE2, Endoribonuclease inhibitor Reduce cytokines	*In silico* *In vitro*	(Attia et al., 2021; Bhowmik et al., 2020; A. Ghosh, Chakraborty, Chandra, & Alam, 2021; K. Ghosh et al., 2021; Kumar et al., 2021; Kushwaha et al., 2021; Liu et al., 2020; Meyer-Almes, 2020; Nguyen et al., 2021; Niu et al., 2021; Patil et al., 2021; Pitsillou, Liang, Hung, et al., 2021; Pitsillou, Liang,

					Ververis, et al., 2021; Yañez et al., 2021; Zígolo et al., 2021)
Curcumin and analogs *Curcuma longa*	Polyphenol	SARS-CoV-2 SARS-CoV MERS-CoV	Inhibitor of interaction of protein S with GRP78, Mpro, ACE2, proteinS, RdRp Decrease inflammation factors and cytokines Increase the number of reg T cells	*In silico* *In vitro* *In vivo*	(Allam et al., 2020; L. Chen et al., 2020; A. Ghosh et al., 2021; Gupta et al., 2020; Halder et al., 2021; Ibrahim et al., 2020; Jena et al., 2021; Kodchakorn, Poovorawan, Suwannakarn, & Kongtawelert, 2020; Kumar Verma et al., 2021; Nguyen et al., 2021; Singh et al., 2020; Tahmasebi et al., 2021; Valizadeh et al., 2020; Wen et al., 2007)
Myricetin and analogs *Citrus sinensis* *Camellia sinensis* *Withania somnifera* *Myrica penssylvanica* *Isatis indigotica* *Torreya nucifera* *Moringa oleifera*	Polyphenol	SARS-CoV-2	Inhibitor of Mpro, Nsp 15, TMPRSS2, RdRp Reduce cytokines	*In silico* *In vitro*	(Attia et al., 2021; A. Ghosh et al., 2021; K. Ghosh et al., 2021; Gogoi et al., 2021; Kumar et al., 2021; Nguyen et al., 2021; Niu et al., 2021; Patil et al., 2021; H. Puttaswamy et al., 2020; Singh et al., 2020; Umar et al., 2021; Zígolo et al., 2021)
Apigenin and analogs *Carica papaya* *Hypericum perforatum* *Cocos nucifera*	Polyphenol	SARS-CoV-2	3CLpro, PLpro, RdRp, Nsp 15, ACE2, protein S inhibitor	*In silico* *In vitro*	(Elsbaey et al., 2021; Fayed et al., 2021; Gowrishankar et al., 2021; Hariyono et al., 2021; Kumar et al., 2021; Messaoudi et al., 2021; Natesh et al., 2021; Nguyen et al., 2021; Ryu et

					al., 2010; Singh et al., 2020; Xiong et al., 2021; Yañez et al., 2021)
Luteolin *Ephedra sp* *Ginkgo biloba* *Justicia adhatoda*	Polyphenol	SARS-CoV-2	Inhibitor of 3CLpro, PL pro, ACE2, protein S, Nsp14, Nsp15, RdRp, TMPRSS2 Reduces cytokines	*In silico* *In vitro*	(Du et al., 2021; Gao et al., 2020; Gheware et al., 2021; Kumar et al., 2021; Liu et al., 2020; Nguyen et al., 2021; Niu et al., 2021; Singh et al., 2020; Xiong et al., 2021; Xu et al., 2021; Yañez et al., 2021)
Hesperidin and analogs *Citrus sinensis* *Withania somnifera* *Isatis indigotica*	Polyphenol	SARS-CoV-2	Mpro, Nsp 1, Endoribonuclease, RdRp, TMPRSS2, S protein inhibitor Blocks the 3a channel protein Reduces ARDS	*In silico* *In vitro*	(Attia et al., 2021; A. Ghosh et al., 2021; K. Ghosh et al., 2021; R. Ghosh, Chakraborty, Biswas, & Chowdhuri, 2020a; Gupta et al., 2020; Kodchakorn et al., 2020; Nguyen et al., 2021; Patil et al., 2021; Singh et al., 2020; Vardhan & Sahoo, 2021; Zígolo et al., 2021)

3.6. Antiviral mechanism of action

Most of the studies on natural substances acting against coronaviruses showed that several metabolites acted by inhibition of the main protease (Mpro) with a percentage of 43.71%, others by inhibition of the viral protein RNA-dependent RNA polymerase (RdRp), the angiotensin converting enzyme (ACE2), the surface protein (protein S) or by the inhibition of the papain-like protein (PLpro). Other studies do not show by which mechanisms these secondary metabolites acted against coronavirus.

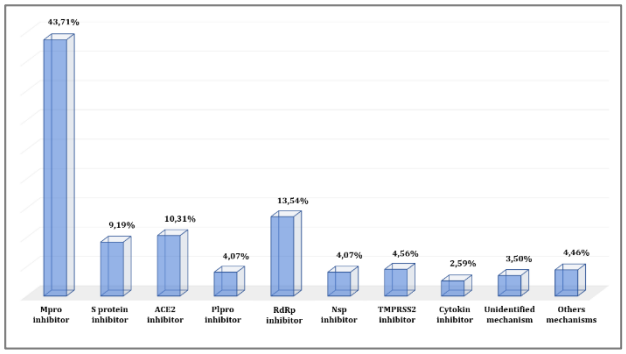

Figure 7. Molecules distribution by action's mechanism.

3.7. Most cited substances

Taking into account the citation's frequency in the articles, we ranked the 10 most cited substances (mentionned in more than 3 studies) in descending order (Table 1). Out of these 963 substances, catechins are the most cited compounds (29), followed by quercetin (25), glycyrrhizin (19) and kaempferol (16). The other substances had a lower mention's frequency.

3.7.1. Polyphenols

- **Quercetin**

Quercetin is a flavonoid widely present in the plant kingdom, found in grapefruit, onions, apples and black tea. A lesser amount exists in green leafy vegetables and beans. Quercetin has a range of pharmacological activities as an antioxidant and anti-inflammatory agent. An experiment confirmed that quercetin could enhance ligand-induced apoptosis of senescent idiopathic pulmonary fibrosis fibroblasts and reduce pulmonary fibrosis *in vivo* (Xu et al., 2021). In 2017, an *in vitro* study showed that quercetin and quercetin-β-galactoside can inhibit the activity of viral proteases (3C-like protease=3CL pro and PL pro) of SARS-CoV and MERS-CoV (Park et al., 2017). In addition, recent studies (*in silico* and *in vitro*) have reported the potential inhibitory effects of quercetin and these analogues on the main protease of SARS-CoV-2 (Attia et al., 2021; Kushwaha et al., 2021; Meyer-Almes, 2020; Nguyen et al., 2021; Umar et al., 2021; Xiong et al., 2021).

Another docking technique was also used to further define the inhibitory activity of the glycosides of this flavonol. This technique revealed that quercetin 3,5-digalactoside recorded the lowest binding energy with Mpro. It was observed that flavonols with two glucose moieties recorded lower binding energy (LE) than flavonols with one or three glucose moieties (H. Puttaswamy et al., 2020).

Quercetagenin, another flavonol could effectively inhibit SARS-CoV-2 replication *in vitro* by 58% with an IC50 of 145 µM. It has also been reported that quercetin and quercetin 3-(6-malonylglucoside) could reduce SARS-CoV-2 entry by blocking ACE2 activity (Mesli et al., 2021; Xu et al., 2021). Quercetin analogs can also bind to RdRp and PL pro (Gheware et al., 2021; Singh et al., 2020).

- **Rutin**

Rutin flavonoid isolated from the extract of different medicinal plants such as *Withania somnifera*, Passion flower and *Theobroma cacao* (A. Ghosh et al., 2021; Yañez et al., 2021) has various biological activities, including anti-inflammatory and antiviral activities. Studies have shown that rutin has

antimicrobial activity and, through *in silico* studies, possible inhibitory activity of several proteins essential for SARS-CoV-2 to complete its viral cycle. However, its antiviral spectrum is broader and it is experimentally tested as an antiviral agent against retroviruses, orthomyxoviruses, herpes viruses, hepatitis B and C viruses and H1N1 influenza virus.

Other experiments performed by different researchers mention that rutin can be used as a potential inhibitor of Mpro and ACE2 of COVID-19(Bhowmik et al., 2020; A. Ghosh et al., 2021; Kumar et al., 2021; Meyer-Almes, 2020; Patil et al., 2021; Yañez et al., 2021). In addition, *in vitro* enzyme inhibition assays also showed that rutin had inhibitory activity against SARS-CoV 3CLpro since the 3CLpro sequence of SARS-CoV-2 is very similar to that of SARS-CoV (Liu et al., 2020; Nguyen et al., 2021).

- **Kaempferol**

Kaempferol is a flavonol that can be extracted from several plants namely *Moringa oleifera*, *Carica papaya* and *Ephedra sp* (Gao et al., 2020; Hariyono et al., 2021; Umar et al., 2021). In an *in vitro* study, kaempferol extracted from *Broussonetia papyrifera* was identified as an inhibitor of viral proteases (PL pro and 3CL pro) in both SARS-CoV and MERS-CoV (86). Studies have recently begun to focus on SARS-CoV-2 infection, kaempferol and its analogues have been tested against various coronavirus target proteins such as 3CL pro, RdRp, ACE2 and protein S both *in silico* and *in vitro* (Du et al., 2021; Gao et al., 2020; Ibrahim et al., 2020; Mehmood et al., 2021; Natesh et al., 2021; Nguyen et al., 2021; Umar et al., 2021; Xiong et al., 2021).

- **Myricetin**

Myricetin is a flavonol that can be extracted from *Isatis indigotica*, *Torreya nucifera* or *Moringa oleifera* (M, Reddy, Hema, Dodoala, & Koganti, 2021; Umar et al., 2021). Myricetin and its analogues have been tested against Mpro, RdRp, Transmembrane serine protease 2 (TMPRSS2), endoribonuclease and IL-6 both *in silico* and *in vitro*. They showed good docking scores especially against TMPRSS2 and RdRp (A. Ghosh et al., 2021; Kumar et al., 2021; M. Reddy et al., 2021; Nguyen et al., 2021; Niu et al., 2021; H. Puttaswamy et al., 2020; Singh et al., 2020; Umar et al., 2021). According to an *in vitro* study, the absence of hydroxyl groups in the C3 and C4 B-ring was the reason for the lower inhibitory activity of kaempferol and quercetin than myricetin (Nguyen et al., 2021).

- **Naringenin**

Naringenin is a flavonone extracted mainly from C*itrus* fruits, *Isatis indigotica*. It has been reported as an antiviral agent against Zika virus (Attia et al., 2021; R. Ghosh et al., 2020a; M. Reddy et al., 2021). Naringenin showed no inhibitory effect against Mpro of SARS-CoV (R. Ghosh et al., 2020a). In contrast, it scored good docking against Mpro, TMPRSS2 and RdRp of SARS-CoV-2(M. Reddy et al., 2021; Singh et al., 2020; Yañez et al., 2021). Naringin, a heteroside of naringenin, also showed good scores with Mpro and non-structural protein 15 (Nsp 15) (Kumar et al., 2021; Yañez et al., 2021).

- **Hesperidin**

Hesperidin and its aglycone hesperitin are flavonones extracted mainly from C*itrus* fruits. Hesperidin has antimicrobial, anti-inflammatory, cardiovascular and antidiabetic (Type II) effects (K. Ghosh et al., 2021). Several studies have noted the possible inhibitory activity of hesperidin and hesperitin against various proteins target namely Mpro, TMPRSS2 and RdRp (R. Ghosh et al., 2020a; Kodchakorn et al., 2020; M. Reddy et al., 2021; Nguyen et al., 2021; Singh et al., 2020; Varghese et al., 2021).

In the flavanones group, the order of M pro inhibitory activity was naringin < hesperidin < naringenin. Naringenin is glycosylated naringin. However, its inhibitory activity was 3.2 times higher than that of naringin. Hesperidin, which contained 7-OH glycosylation at the A ring like naringenin and the methoxy group at the 5′ position of the B ring, was found to have higher inhibitory activity than naringin but lower inhibitory activity than naringenin, indicating that glycosylation at the C7 position enhanced the inhibitory effect of M pro. In contrast, the methoxy group at C5′ in the B ring reduced its inhibitory activity (Nguyen et al., 2021).

- **Catechins and gallate catechins**

Catechins are polyphenols, more precisely they are part of the flavonoid family; the subclass of flavanols, present in some foods, including green tea (*Camellia sinensis*) and *Carica papaya*. The effect of catechin and its analogues in the inhibition of SARS-CoV-2 associated coronavirus replication has been recently studied and various mechanisms of action have been attributed to the antiviral activities of catechin, such as inhibition of protein S, RdRp, ACE2 and Mpro (R. Ghosh et al., 2020b; Halder et al., 2021; Hariyono et al., 2021; Jena et al., 2021; Meyer-Almes, 2020; Singh et al., 2020).

In an *in silico* study, catechins extracted from *Mangifera indica* and *Moringa oleifera* were identified as potent inhibitors of Mpro with a very high docking score (Umar et al., 2021). In addition, epicatechin is a structural analogue of catechin that exhibits in addition to other inhibitory effects, the ability to inhibit furin, protein N and Nsp6 (Mishra et al., 2021; Vardhan & Sahoo, 2021).

Epigallocatechin gallate (EGCG), the main catechin in green tea, is known to exert antiviral activity against several types of viruses including herpes virus, hepatitis virus and influenza A virus. *In silico* studies to test antiviral activity against SARS-CoV-2 showed that epigallocatechin gallate bound well to key targets including Spike, 3CLpro, PLpro and RdRp (R. Ghosh et al., 2020b; Mhatre et al., 2021). In addition, *in vitro* studies have confirmed its efficacy in inhibiting replication and reducing cytokine storm (Shin et al., 2021; M. Zhao et al., 2021).

- **Curcumin**

Curcumin and its analogues are the main constituents of turmeric (*Curcuma longa L.)* and other Curcuma spp. which are widely used around the world as a culinary spice, popular dietary supplement ingredient as well as in traditional medicine due to its wide range of health benefits including anti-inflammatory, anti-cancer, cardiovascular, respiratory and immune benefits. In addition, the suppression of several cytokines by curcumin has suggested that it may be a useful approach in treating Ebola patients against the cytokine storm. Curcumin has a variety of antiviral activities against dengue virus, herpes simplex virus, Zika virus and chikungunya virus. CC also inhibits aminopeptidase N (APN) which has been identified as a cellular receptor for alpha CoV (L. Chen et al., 2020; Halder et al., 2021).

Another study showed that curcumin could effectively inhibit the major protease of SARS-CoV in Vero E6 cells *in vitro* (Wen et al., 2007). Recently numerous researches have shown its potential inhibitory power against SARS-CoV-2 Mpro both *in silico* and *in vitro* (A. Ghosh et al., 2021; Halder et al., 2021). In an *in vitro* study with curcumin and its analogues, the order of inhibitory effects was bisdemethoxycurcumin < curcumin < dimethylcurcumin. In this group, curcumin contained two methoxy groups (C2′ and C4") and showed higher inhibitory activity on M pro than did bisdemethoxycurcumin, which did not have the methoxy group. However, its inhibitory activity was lower than that of dimethylcurcumin, which contained a C2′ methoxy group(Nguyen et al., 2021). Two

double-blind randomized controlled trials showed a significant increase in regulatory T cells and a decrease in cytokine levels (IL-6, IL-1β) as well as an attenuation in the mortality rate in severe patients. Curcumin has major problems of water solubility, high metabolism and rapid excretion from the body. This is solved by the nanoscale formulation namely nanocurcumin (Tahmasebi et al., 2021; Valizadeh et al., 2020). Further molecular docking studies revealed that curcumin can also bind to RdRp, ACE2 and protein S (Jena et al., 2021; S. Singh et al., 2020).

- **Luteolin**

Luteolin is a flavonoid and more specifically a flavone. It has multiple biological activities, including anti-inflammatory, anti-cancer, anti-oxidant, antiviral and cardiac protective. It has been reported that luteolin can interfere with the virus at the beginning of its life cycle, to some extent blocking the absorption and internalization of the flu virus. In addition, various studies have confirmed that luteolin inhibits the NS2B/NS3 protease activity of the dengue virus. It was also documented that luteolin has an anti-Epstein-Barr virus (EBV) effect.
An *in silico* study showed that luteolin extracted from *Ephedra sp* and *Ginkgo biloba* is an inhibitor of SARS-CoV-2 3CLpro. Other studies have also shown that this compound is a potent inhibitor of ACE2 and RdRp. Overall, luteolin has a good antiviral effect, suggesting that luteolin may be a potential drug for the treatment of COVID-19 and their actual effect in the treatment of this disease needs to be verified by further studies (Du et al., 2021; Gao et al., 2020; Kumar et al., 2021; Liu et al., 2020; Singh et al., 2020; Xiong et al., 2021; Yañez et al., 2021).

Luteolin-7-glucoside (Yañez et al., 2021), Luteolin-6-C-arabinosid, Luteolin-6-C-glucoside, Luteolin-6C-glucoside-8C-arabinoside and Luteolin-6-8-di-C-arabinoside are luteolin analogues isolated from *Justicia adhatoda* extract (Gheware et al., 2021). They also exhibit antiviral activity against SARS-CoV-2.

- **Apigenin**

Apigenin is a compound of the flavonoids family, which has anti-inflammatory properties. An *in silico* study done by Indonesian researchers on *Carica papaya* showed the antiviral activity of this natural substance such as the inhbition of Mpro, PLpro and RdRp. In addition, several studies on different apigenin analogues such as Apigeninidin 5-O-glucoside, apigenidin and 6,6'-biapigenin have shown their antiviral efficacy against SARS-CoV-2 via inhibition of Mpro and RdRp (Elsbaey et al., 2021; Ryu et al., 2010).

- **Caffeic acid**

Caffeic acid is a polyphenol, naturally present in all plants as it is a key intermediate in lignin biosynthesis. An *in silico* study by Indonesian researchers showed that caffeic acid extracted from *Carica papaya* decreases the inflammatory factors of SARS-CoV-2 (Hariyono et al., 2021). Other *in silico* studies have confirmed that this compound acts as an inhibitor of Mpro and RdRp (Adem et al., 2021; Bhowmik et al., 2020; Kumar et al., 2021; Nguyen et al., 2021; Singh et al., 2020; Umar et al., 2021; Yañez et al., 2021).

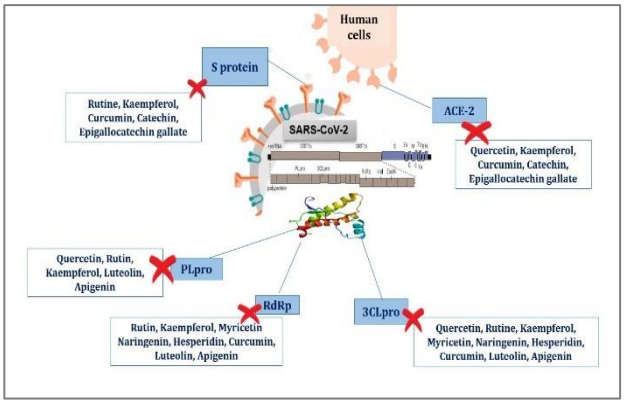

Figure 8. Polyphenols and Anti-SARS-CoV-2 inhbition's mechanisms

3.7.2. Terpenes

- **Glycyrrhizin**

Glycyrrhizin also called glycyrrhizic acid is a triterpene saponin extracted mainly from the root of *Glycyrrhiza glabra* (licorice) and *Glycyrrhiza uralensis*. A large number of studies have shown that licorice and its components have a protective effect on inflammation and lung damage and it is a promising medicinal plant for the treatment of SARS infections. In addition, glycyrrhizin was active against other viruses such as varicella-zoster virus, herpes simplex virus and dengue virus. It is an effective hepato-protective substance in patients with chronic hepatitis C and can protect against a variety of liver diseases such as chronic viral hepatitis, drug-induced and chemical-induced liver damage, non-alcoholic fatty liver, autoimmune hepatitis and hepatocellular carcinoma. It is also used for the treatment of skin inflammation.

The effect of glycyrrhizin in inhibiting the replication of SARS-CoV-2 associated coronavirus has been recently studied and various mechanisms of action have been attributed to the antiviral activities of glycyrrhizin, such as inhibition of endoribonuclease (Patil et al., 2021), inhibition of Mpro, PLpro, RBD, RdRp and ACE2, inhibition of protein S and accessory protein Nsp1 and inhibition of TMPRSS2 (Muhseen et al., 2020; H. Puttaswamy et al., 2020; A. Sharma et al., 2020; Toor et al., 2021; van de Sand et al., 2021; Vardhan & Sahoo, 2020; Yu et al., 2021). In addition, glycyrrhyzin plays an important role in inhibiting immune hyperactivation and the development of cytokine storm factors (Yu et al., 2021).

18β-glycyrrhetinic acid is active against SARS-CoV, SARS-CoV-2 and MERS-CoV by acting on the inhibition of Mpro (Diniz et al., 2021; Vardhan & Sahoo, 2021; Zígolo et al., 2021). Glycyrrhetinic acid is the aglycone of glycyrrhizin (Luo et al., 2020).

- **Andrographolide**

Andrographolide is the major active component isolated from the extract of the herb *Andrographis paniculata* (Banerjee et al., 2021; Sa-Ngiamsuntorn et al., 2021). This labdane-type diterpene lactone possesses a wide range of biological activities, including antiviral, antibacterial, antiparasitic, antitumor, and promotive antidiabetic potential. Previous studies have shown that andrographolide possesses a broad spectrum of antiviral properties, which inhibits various viral infections, including influenza A virus, human immunodeficiency virus (HIV), Chikungunya virus (CHIKV), dengue virus (DENV) by acting on GRP78 and Enterovirus D68 (EV-D68. Andrographolide induces endoplasmic reticulum (ER) stress leading to cancer cell death by apoptosis via induction of increased levels of reactive oxygen species (ROS) that can inhibit virus-induced carcinogenesis (Shi et al., 2020). Additional inhibitory effects of andrographolide include those of cell migration, invasion, matrix metalloproteinase expression, anti-angiogenesis, autophagy, and pathway dysregulation have been reported for inflammatory disorders, including cancer.

In addition, *in silico* studies to test antiviral activity against SARS-CoV-2 also showed that andrographolide bound well to key targets, including Spike protein, 3CLpro, and PLpro, indicating that andrographolide has potential efficacy against SARS-CoV-2 (Banerjee et al., 2021; Kodchakorn et al., 2020; Sa-Ngiamsuntorn et al., 2021; Shi et al., 2020; Verma et al., 2021). Overall, as a plant-derived compound, andrographolide is widely distributed with low cytotoxicity, but its potent antiviral activity against a variety of viruses requires further investigation.

- **Artemisinin**

Artemisinin is the main active component of *Artemisia annua*. It is a sesquiterpenic lactone. Artemisinin is an ancient antimalarial drug, has saved millions of lives, and has been reported to have multiple pharmacological activities, including anticancer, antiviral and immune modulation.

In an *in vitro* study, artemisinin was chosen to test their anti-SARS-CoV-2 potential using African green monkey kidney Vero E6 cells. Cytotoxicity assays were performed prior to the antiviral assay to determine the cytotoxicity of the selected compounds, and viral RNA copies in the supernatants were determined by quantitative real-time PCR (qRT-PCR) to determine the antiviral effects of the compounds. The results of this study show that artemisinin and its derivatives: Arteannuine B showed the highest anti-SARS-CoV-2 potential with an EC50 of 10.28 ± 1.12 M.

Artesunate and dihydroartemisinin showed similar EC50 values of 12.98 ± 5.30 M and 13.31 ± 1.24 M, respectively, which could be achieved clinically in plasma after intravenous administration. Further mode of action analysis revealed that arteannuine B and lumefantrine acted in the post-entry stage of SARS-CoV-2 infection. This research highlights the anti-SARS-CoV-2 potential of artemisinin and provides leading candidates for anti-SARS-CoV-2 drug research and development (Cao et al., 2020). Other *in silico* studies have shown that this chemical compound is a potent inhibitor of BRD2 and the accessory protein Nsp1(Aydın, Altınel, Erdoğmuş, & Son Ç, 2021; Gupta et al., 2020; Li et al., 2021).

3.7.3. Alkaloids

Since the discovery of this class of natural products, several biological activities associated with alkaloids have been reported, including analgesic, antibacterial, antifungal, anti-inflammatory, anticancer and antiviral. Among the alkaloids that have antiviral activity is berberine (Fielding, da Silva Maia Bezerra Filho, Ismail, & Sousa, 2020).

- **Berberin**

Berberin is an isoquinoline alkaloid derived from the Chinese herb *Coptis chinensis* and plants of the genus *Berberis*. Its broad biological properties identified in preclinical studies include anti-inflammatory, anti-arrhythmic, antimicrobial and cholesterol-lowering activity. Berberin has broad-spectrum antiviral activity *in vitro* against viruses from several different families, including influenza A virus, enterovirus, chikungunya virus, hepatitis B and C viruses, HIV, respiratory syncytial virus, human cytomegalovirus, herpes simplex virus, and human papilloma virus (Varghese et al., 2021).

In one study, Berberin showed good binding activities to the S1 subunit of SARS-CoV-2. Then, to determine whether this compound may be a candidate for broad-spectrum anti-coronavirus activity, they performed further evaluation on the S1 subunits of MERS-CoV and SARS-CoV. The results showed similar binding activity with the S1 subunit of MERS-CoV but reduced affinity for SARS-CoV(Yu et al., 2021). In addition, Berberin showed good docking scores against Mpro and Nsp 15 (Kumar et al., 2021; Zígolo et al., 2021).

Another study identified potential therapeutic targets for berberine against SARS-CoV and SARS-CoV-2 using computer modeling. The most important targets for berberine include NF-κB and MAPK, which are cytokine storm-regulating proteins, and CASP and BAX, which are relevant targets for preventing tissue damage by suppressing cell death signaling pathways. Thus, they demonstrated for the first time that berberin significantly reduces viral replication, suppresses viral entry of the host receptor

ACE2 and TMPRSS2, and decreases inflammatory markers, including IL-6, IL-8, IL-1α, and CCL2 in SARS-CoV-2-infected Calu3 cells (Wang et al., 2021). Berberin has also shown efficacy against SARS-CoV-2 at low micromolar concentrations in vitro in Vero E6 cells (Varghese et al., 2021). In a randomized controlled trial of 39 hospitalized patients with severe COVID-19 grouped into 2 groups, the first received berberin plus routine treatment within 14 days of admission and the control group received only routine treatment. No significant differences were observed between the 2 groups in the trend of IL-6, TNF-α, CRP, procalcitonin, and white blood cell levels within 14 days. In subgroup analyses of patients with diarrhea, berberine significantly improved changes in IL-6, TNF-α, and CRP levels. They hypothesized that berberin may reduce serum levels of inflammatory mediators through the protection and maintenance of gastrointestinal function (Zhang et al., 2021).

4. Conclusion

Natural products have long been used as a treasure trove of drug discovery. These structurally diverse molecules exert a wide range of pharmacological activities, including exceptional antiviral activity. Considerable effort has been devoted to the development of anti-coronavirus drugs from natural products, particularly in the context of global public health challenges such as the SARS-CoV outbreaks in 2003 and the current SARS-CoV-2. In order to provide a more systematic understanding of the research on anti-coronavirus activity of natural products, we have reviewed the relevant studies to date, and summarized the properties of many natural bioactive molecules according to their chemical family, mechanism of action... Most of these natural products are listed as inhibitors against SARS-CoV and SARS-CoV-2 and some molecules act on MERS-CoV.

This study compiled data on different types of phytoconstituents with antiviral activity against coronaviruses as well as phytoconstituents with affinities against SARS-CoV-2 therapeutic targets such as RdRP, 3CLpro, PLpro and host cell targets such as ACE-2, mainly based on computational screening methods. Among these substances, polyphenols, terpenes and alkaloids showed very encouraging anti-coronavirus activity, which could provide a large number of promising candidates for anti-coronavirus drug development and offer potential weapons against SARS-CoV-2 in the current dilemma.

However, further *in vivo* and *in vitro* studies are needed to confirm the bioactivity of these compounds against COVID-19.

Overall, the development of phytopharmaceuticals as an alternative approach could be considered a viable therapeutic option against SARS-CoV-2 in the current COVID-19 pandemic.

Acknowledgements

This work was supported by the Departement of pharmacy, Faculty of Medecine, ABOU BEKR BELKAID University, Tlemcen, Algeria.

Author Contribution

Amal HELALI and Khadidja BENCHACHOU conceived and designed the study. Meryem Wafa HAMMADI and Manel HOUALEF performed the data research and exploitation. Amal HELALI wrote the paper.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Adem, Ş., Eyupoglu, V., Sarfraz, I., Rasul, A., Zahoor, A. F., Ali, M., . . . Elfiky, A. A. (2021). Caffeic acid derivatives (CAFDs) as inhibitors of SARS-CoV-2: CAFDs-based functional foods as a potential alternative approach to combat COVID-

19. *Phytomedicine, 85*, 153310. doi:https://doi.org/10.1016/j.phymed.2020.153310
2. Allam, L., Ghrifi, F., Mohammed, H., El Hafidi, N., El Jaoudi, R., El Harti, J., . . . Ibrahimi, A. (2020). Targeting the GRP78-Dependant SARS-CoV-2 Cell Entry by Peptides and Small Molecules. *Bioinformatics and Biology Insights, 14*, 1177932220965505. doi:10.1177/1177932220965505
3. Arokiyaraj, S., Stalin, A., Kannan, B. S., & Shin, H. (2020). Geranii Herba as a Potential Inhibitor of SARS-CoV-2 Main 3CL(pro), Spike RBD, and Regulation of Unfolded Protein Response: An In Silico Approach. *Antibiotics (Basel), 9*(12). doi:10.3390/antibiotics9120863
4. Asrani, P., Hasan, G. M., Sohal, S. S., & Hassan, M. I. (2020). Molecular Basis of Pathogenesis of Coronaviruses: A Comparative Genomics Approach to Planetary Health to Prevent Zoonotic Outbreaks in the 21st Century. *Omics, 24*(11), 634-644. doi:10.1089/omi.2020.0131
5. Attia, G. H., Moemen, Y. S., Youns, M., Ibrahim, A. M., Abdou, R., & El Raey, M. A. (2021). Antiviral zinc oxide nanoparticles mediated by hesperidin and in silico comparison study between antiviral phenolics as anti-SARS-CoV-2. *Colloids and Surfaces B: Biointerfaces, 203*, 111724. doi:https://doi.org/10.1016/j.colsurfb.2021.111724
6. Aydın, A. D., Altınel, F., Erdoğmuş, H., & Son Ç, D. (2021). Allergen fragrance molecules: a potential relief for COVID-19. *BMC Complementary Medecine and Therapies, 21*(1), 41. doi:10.1186/s12906-021-03214-4
7. Azim, K. F., Ahmed, S. R., Banik, A., Khan, M. M. R., Deb, A., & Somana, S. R. (2020). Screening and druggability analysis of some plant metabolites against SARS-CoV-2: An integrative computational approach. *Informatics in Medecine Unlocked, 20*, 100367. doi:https://doi.org/10.1016/j.imu.2020.100367
8. Banerjee, S., Kar, A., Mukherjee, P. K., Haldar, P. K., Sharma, N., & Katiyar, C. K. (2021). Immunoprotective potential of Ayurvedic herb Kalmegh (Andrographis paniculata) against respiratory viral infections - LC-MS/MS and network pharmacology analysis. *Phytochemical Analysis, 32*(4), 629-639. doi:10.1002/pca.3011
9. Bhowmik, D., Nandi, R., Jagadeesan, R., Kumar, N., Prakash, A., & Kumar, D. (2020). Identification of potential inhibitors against SARS-CoV-2 by targeting proteins responsible for envelope formation and virion assembly using docking based virtual screening, and pharmacokinetics approaches. *Infection, Genetics and Evolution, 84*, 104451. doi:https://doi.org/10.1016/j.meegid.2020.104451
10. Cao, R., Hu, H., Li, Y., Wang, X., Xu, M., Liu, J., . . . Zhong, W. (2020). Anti-SARS-CoV-2 Potential of Artemisinins In Vitro. *ACS Infectious Diseases, 6*(9), 2524-2531. doi:10.1021/acsinfecdis.0c00522
11. Chen, F., Chan, K. H., Jiang, Y., Kao, R. Y., Lu, H. T., Fan, K. W., . . . Yuen, K. Y. (2004). In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *Journal of Clinical Virology, 31*(1), 69-75. doi:10.1016/j.jcv.2004.03.003
12. Chen, L., Hu, C., Hood, M., Zhang, X., Zhang, L., Kan, J., & Du, J. (2020). A Novel Combination of Vitamin C, Curcumin and Glycyrrhizic Acid Potentially Regulates Immune and Inflammatory Response Associated with Coronavirus Infections: A Perspective from System Biology Analysis. *Nutrients, 12*(4). doi:10.3390/nu12041193
13. Ding, H., Deng, W., Ding, L., Ye, X., Yin, S., & Huang, W. (2020). Glycyrrhetinic acid and its derivatives as potential alternative medicine to relieve symptoms in nonhospitalized COVID-19 patients. *Journal of Med Virology, 92*(10), 2200-2204. doi:10.1002/jmv.26064
14. Diniz, L. R. L., Perez-Castillo, Y., Elshabrawy, H. A., Filho, C., & de Sousa, D. P. (2021). Bioactive Terpenes and Their Derivatives as Potential SARS-CoV-2 Proteases Inhibitors from Molecular Modeling Studies. *Biomolecules, 11*(1). doi:10.3390/biom11010074
15. Du, A., Zheng, R., Disoma, C., Li, S., Chen, Z., Li, S., . . . Xia, Z. (2021). Epigallocatechin-3-gallate, an active ingredient of Traditional Chinese Medicines, inhibits the 3CLpro activity of SARS-CoV-2. *International journal of biological macromolecules, 176*, 1-12. doi:10.1016/j.ijbiomac.2021.02.012
16. Elsbaey, M., Ibrahim, M. A. A., Bar, F. A., & Elgazar, A. A. (2021). Chemical constituents from coconut waste and their in silico evaluation as potential antiviral agents against SARS-CoV-2. *South African Journal of Botany, 141*, 278-289. doi:https://doi.org/10.1016/j.sajb.2021.05.018
17. Fayed, M. A. A., El-Behairy, M. F., Abdallah, I. A., Abdel-Bar, H. M., Elimam, H., Mostafa, A., . . . Elshaier, Y. A. M. M. (2021). Structure- and Ligand-Based in silico Studies towards the Repurposing of Marine Bioactive Compounds to Target SARS-CoV-2. *Arabian Journal of Chemistry, 14*(4), 103092. doi:https://doi.org/10.1016/j.arabjc.2021.103092
18. Fielding, B. C., da Silva Maia Bezerra Filho, C., Ismail, N. S. M., & Sousa, D. P. (2020). Alkaloids: Therapeutic Potential against Human Coronaviruses. *Molecules, 25*(23). doi:10.3390/molecules25235496
19. Gao, K., Song, Y.-P., & Song, A. (2020). Exploring active ingredients and function mechanisms of

Ephedra-bitter almond for prevention and treatment of Corona virus disease 2019 (COVID-19) based on network pharmacology. *BioData Mining, 13*(1), 19. doi:10.1186/s13040-020-00229-4

20. Gheware, A., Dholakia, D., Kannan, S., Panda, L., Rani, R., Pattnaik, B. R., . . . Prasher, B. (2021). Adhatoda Vasica attenuates inflammatory and hypoxic responses in preclinical mouse models: potential for repurposing in COVID-19-like conditions. *Respiratory Research, 22*(1), 99. doi:10.1186/s12931-021-01698-9
21. Ghosh, A., Chakraborty, M., Chandra, A., & Alam, M. P. (2021). Structure-activity relationship (SAR) and molecular dynamics study of withaferin-A fragment derivatives as potential therapeutic lead against main protease (M(pro)) of SARS-CoV-2. *Journal of Molecular Modeling, 27*(3), 97. doi:10.1007/s00894-021-04703-6
22. Ghosh, K., Amin, S. A., Gayen, S., & Jha, T. (2021). Chemical-informatics approach to COVID-19 drug discovery: Exploration of important fragments and data mining based prediction of some hits from natural origins as main protease (Mpro) inhibitors. *Journal of Molecular Structure, 1224*, 129026. doi:https://doi.org/10.1016/j.molstruc.2020.129026
23. Ghosh, R., Chakraborty, A., Biswas, A., & Chowdhuri, S. (2020a). Depicting the inhibitory potential of polyphenols from Isatis indigotica root against the main protease of SARS CoV-2 using computational approaches. *Journal of Biomolecular Structure and Dynamics*, 1-12. doi:10.1080/07391102.2020.1858164
24. Ghosh, R., Chakraborty, A., Biswas, A., & Chowdhuri, S. (2020b). Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors - an in silico docking and molecular dynamics simulation study. *Journal of Biomolecular Structure and Dynamics*, 1-13. doi:10.1080/07391102.2020.1779818
25. Gogoi, B., Chowdhury, P., Goswami, N., Gogoi, N., Naiya, T., Chetia, P., . . . Handique, P. J. (2021). Identification of potential plant-based inhibitor against viral proteases of SARS-CoV-2 through molecular docking, MM-PBSA binding energy calculations and molecular dynamics simulation. *Molecular Diversity*, 1-15. doi:10.1007/s11030-021-10211-9
26. Gowda, P., Patrick, S., Joshi, S. D., Kumawat, R. K., & Sen, E. (2021). Glycyrrhizin prevents SARS-CoV-2 S1 and Orf3a induced high mobility group box 1 (HMGB1) release and inhibits viral replication. *Cytokine, 142*, 155496. doi:10.1016/j.cyto.2021.155496
27. Gowrishankar, S., Muthumanickam, S., Kamaladevi, A., Karthika, C., Jothi, R., Boomi, P., . . . Pandian, S. K. (2021). Promising phytochemicals of traditional Indian herbal steam inhalation therapy to combat COVID-19 – An in silico study. *Food and Chemical Toxicology, 148*, 111966. doi:https://doi.org/10.1016/j.fct.2020.111966
28. Gupta, S., Singh, V., Varadwaj, P. K., Chakravartty, N., Katta, A., Lekkala, S. P., . . . Reddy Lachagari, V. B. (2020). Secondary metabolites from spice and herbs as potential multitarget inhibitors of SARS-CoV-2 proteins. *Journal of Biomolecular Structure and Dynamics*, 1-20. doi:10.1080/07391102.2020.1837679
29. Gurung, A. B., Ali, M. A., Lee, J., Farah, M. A., & Al-Anazi, K. M. (2021). The potential of Paritaprevir and Emetine as inhibitors of SARS-CoV-2 RdRp. *Saudi Journal of Biological Sciences, 28*(2), 1426-1432. doi:https://doi.org/10.1016/j.sjbs.2020.11.078
30. Halder, P., Pal, U., Paladhi, P., Dutta, S., Paul, P., Pal, S., . . . Ghosh, S. (2021). Evaluation of potency of the selected bioactive molecules from Indian medicinal plants with MPro of SARS-CoV-2 through in silico analysis. *Journal of Ayurveda and Integrative Medicine*. doi:https://doi.org/10.1016/j.jaim.2021.05.003
31. Hariyono, P., Patramurti, C., Candrasari, D. S., & Hariono, M. (2021). An integrated virtual screening of compounds from Carica papaya leaves against multiple protein targets of SARS-Coronavirus-2. *Results in chemistry, 3*, 100113-100113. doi:10.1016/j.rechem.2021.100113
32. Hejazi, I. I., Beg, M. A., Imam, M. A., Athar, F., & Islam, A. (2021). Glossary of phytoconstituents: Can these be repurposed against SARS CoV-2? A quick in silico screening of various phytoconstituents from plant Glycyrrhiza glabra with SARS CoV-2 main protease. *Food and Chemical Toxicology, 150*, 112057. doi:https://doi.org/10.1016/j.fct.2021.112057
33. Ibrahim, M. A. A., Abdelrahman, A. H. M., Hussien, T. A., Badr, E. A. A., Mohamed, T. A., El-Seedi, H. R., . . . Hegazy, M.-E. F. (2020). In silico drug discovery of major metabolites from spices as SARS-CoV-2 main protease inhibitors. *Computers in Biology and Medecine, 126*, 104046. doi:https://doi.org/10.1016/j.compbiomed.2020.104046
34. Jang, M., Park, R., Park, Y. I., Cha, Y. E., Yamamoto, A., Lee, J. I., & Park, J. (2021). EGCG, a green tea polyphenol, inhibits human coronavirus replication in vitro. *Biochemical and Biophysical Research Communications, 547*, 23-28. doi:10.1016/j.bbrc.2021.02.016
35. Jang, M., Park, Y. I., Cha, Y. E., Park, R., Namkoong, S., Lee, J. I., & Park, J. (2020). Tea Polyphenols EGCG and Theaflavin Inhibit the Activity of SARS-CoV-2 3CL-Protease In Vitro. *Evidence-based Complementary and Alternative Medicine, 2020*, 5630838. doi:10.1155/2020/5630838

36. Jena, A. B., Kanungo, N., Nayak, V., Chainy, G. B. N., & Dandapat, J. (2021). Catechin and curcumin interact with S protein of SARS-CoV2 and ACE2 of human cell membrane: insights from computational studies. *Scientific Reports, 11*(1), 2043. doi:10.1038/s41598-021-81462-7
37. Kodchakorn, K., Poovorawan, Y., Suwannakarn, K., & Kongtawelert, P. (2020). Molecular modelling investigation for drugs and nutraceuticals against protease of SARS-CoV-2. *Journal of Molecular Graphics & Modelling, 101*, 107717. doi:10.1016/j.jmgm.2020.107717
38. Kumar, S., Kashyap, P., Chowdhury, S., Kumar, S., Panwar, A., & Kumar, A. (2021). Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication. *Phytomedicine, 85*, 153317. doi:10.1016/j.phymed.2020.153317
39. Kumar Verma, A., Kumar, V., Singh, S., Goswami, B. C., Camps, I., Sekar, A., . . . Lee, K. W. (2021). Repurposing potential of Ayurvedic medicinal plants derived active principles against SARS-CoV-2 associated target proteins revealed by molecular docking, molecular dynamics and MM-PBSA studies. *Biomedicine and Pharmacotherapy, 137*, 111356. doi:10.1016/j.biopha.2021.111356
40. Kushwaha, P. P., Singh, A. K., Prajapati, K. S., Shuaib, M., Gupta, S., & Kumar, S. (2021). Phytochemicals present in Indian ginseng possess potential to inhibit SARS-CoV-2 virulence: A molecular docking and MD simulation study. *Microbial Pathogenesis, 157*, 104954. doi:https://doi.org/10.1016/j.micpath.2021.104954
41. Li, G., Yuan, M., Li, H., Deng, C., Wang, Q., Tang, Y., . . . Song, J. (2021). Safety and efficacy of artemisinin-piperaquine for treatment of COVID-19: an open-label, non-randomised and controlled trial. *International Journal of Antimicrobial Agents, 57*(1), 106216. doi:10.1016/j.ijantimicag.2020.106216
42. Liu, X., Raghuvanshi, R., Ceylan, F. D., & Bolling, B. W. (2020). Quercetin and Its Metabolites Inhibit Recombinant Human Angiotensin-Converting Enzyme 2 (ACE2) Activity. *Journal of Agricultural and Food Chemistry, 68*(47), 13982-13989. doi:10.1021/acs.jafc.0c05064
43. Luo, L., Jiang, J., Wang, C., Fitzgerald, M., Hu, W., Zhou, Y., . . . Chen, S. (2020). Analysis on herbal medicines utilized for treatment of COVID-19. *Acta Pharmaceutica Sinica B, 10*(7), 1192-1204. doi:https://doi.org/10.1016/j.apsb.2020.05.007
44. M, P., Reddy, G. J., Hema, K., Dodoala, S., & Koganti, B. (2021). Unravelling high-affinity binding compounds towards transmembrane protease serine 2 enzyme in treating SARS-CoV-2 infection using molecular modelling and docking studies. *European Journal of Pharmacology, 890*, 173688. doi:https://doi.org/10.1016/j.ejphar.2020.173688
45. Mehmood, A., Khan, S., Khan, S., Ahmed, S., Ali, A., xue, M., . . . Bai, Q. (2021). In silico analysis of quranic and prophetic medicinals plants for the treatment of infectious viral diseases including corona virus. *Saudi Journal of Biological Sciences, 28*(5), 3137-3151. doi:https://doi.org/10.1016/j.sjbs.2021.02.058
46. Mesli, F., Ghalem, M., Daoud, I., & Ghalem, S. (2021). Potential inhibitors of angiotensin converting enzyme 2 receptor of COVID-19 by Corchorus olitorius Linn using docking, molecular dynamics, conceptual DFT investigation and pharmacophore mapping. *Journal of Biomolecular Structure and Dynamics*, 1-13. doi:10.1080/07391102.2021.1896389
47. Messaoudi, O., Gouzi, H., El-Hoshoudy, A. N., Benaceur, F., Patel, C., Goswami, D., . . . Bendahou, M. (2021). Berries anthocyanins as potential SARS-CoV–2 inhibitors targeting the viral attachment and replication; molecular docking simulation. *Egyptian Journal of Petroleum, 30*(1), 33-43. doi:https://doi.org/10.1016/j.ejpe.2021.01.001
48. Meyer-Almes, F.-J. (2020). Repurposing approved drugs as potential inhibitors of 3CL-protease of SARS-CoV-2: Virtual screening and structure based drug design. *Computational Biology and Chemistry, 88*, 107351. doi:https://doi.org/10.1016/j.compbiolchem.2020.107351
49. Mhatre, S., Naik, S., & Patravale, V. (2021). A molecular docking study of EGCG and theaflavin digallate with the druggable targets of SARS-CoV-2. *Computers in Biology and Medicine, 129*, 104137. doi:10.1016/j.compbiomed.2020.104137
50. Mishra, C. B., Pandey, P., Sharma, R. D., Malik, M. Z., Mongre, R. K., Lynn, A. M., . . . Prakash, A. (2021). Identifying the natural polyphenol catechin as a multi-targeted agent against SARS-CoV-2 for the plausible therapy of COVID-19: an integrated computational approach. *Briefings in Bioinformatics, 22*(2), 1346-1360. doi:10.1093/bib/bbaa378
51. Muhseen, Z. T., Hameed, A. R., Al-Hasani, H. M. H., Tahir ul Qamar, M., & Li, G. (2020). Promising terpenes as SARS-CoV-2 spike receptor-binding domain (RBD) attachment inhibitors to the human ACE2 receptor: Integrated computational approach. *Journal of Molecular Liquids, 320*, 114493. doi:https://doi.org/10.1016/j.molliq.2020.114493
52. Natesh, J., Mondal, P., Kaur, B., Abdul Salam, A. A., Kasilingam, S., & Meeran, S. M. (2021). Promising phytochemicals of traditional Himalayan

medicinal plants against putative replication and transmission targets of SARS-CoV-2 by computational investigation. *Computers in Biology and Medicine, 133*, 104383. doi:https://doi.org/10.1016/j.compbiomed.2021.104383

53. Nguyen, T. T. H., Jung, J. H., Kim, M. K., Lim, S., Choi, J. M., Chung, B., . . . Kim, D. (2021). The Inhibitory Effects of Plant Derivate Polyphenols on the Main Protease of SARS Coronavirus 2 and Their Structure-Activity Relationship. *Molecules, 26*(7). doi:10.3390/molecules26071924
54. Niu, W. H., Wu, F., Cao, W. Y., Wu, Z. G., Chao, Y. C., & Liang, C. (2021). Network pharmacology for the identification of phytochemicals in traditional Chinese medicine for COVID-19 that may regulate interleukin-6. *Bioscience Reports, 41*(1). doi:10.1042/bsr20202583
55. Park, J. Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., . . . Lee, W. S. (2017). Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry, 32*(1), 504-515. doi:10.1080/14756366.2016.1265519
56. Patil, R., Chikhale, R., Khanal, P., Gurav, N., Ayyanar, M., Sinha, S., . . . Gurav, S. S. (2021). Computational and network pharmacology analysis of bioflavonoids as possible natural antiviral compounds in COVID-19. *Informatics in Medicine Unlocked , 22*, 100504. doi:10.1016/j.imu.2020.100504
57. Pitsillou, E., Liang, J., Hung, A., & Karagiannis, T. C. (2021). Inhibition of interferon-stimulated gene 15 and lysine 48-linked ubiquitin binding to the SARS-CoV-2 papain-like protease by small molecules: In silico studies. *Chemical Physics Letters, 771*, 138468. doi:https://doi.org/10.1016/j.cplett.2021.138468
58. Pitsillou, E., Liang, J., Ververis, K., Hung, A., & Karagiannis, T. C. (2021). Interaction of small molecules with the SARS-CoV-2 papain-like protease: In silico studies and in vitro validation of protease activity inhibition using an enzymatic inhibition assay. *Journal of Molecular Graphics and Modelling, 104*, 107851. doi:https://doi.org/10.1016/j.jmgm.2021.107851
59. Puttaswamy, H., Gowtham, H. G., Ojha, M. D., Yadav, A., Choudhir, G., Raguraman, V., . . . Chauhan, L. (2020). In silico studies evidenced the role of structurally diverse plant secondary metabolites in reducing SARS-CoV-2 pathogenesis. *Scientific Reports, 10*(1), 20584. doi:10.1038/s41598-020-77602-0
60. Puttaswamy, H., Gowtham, H. G., Ojha, M. D., Yadav, A., Choudhir, G., Raguraman, V., . . . Chauhan, L. (2020). In silico studies evidenced the role of structurally diverse plant secondary metabolites in reducing SARS-CoV-2 pathogenesis. *Scientific Reports, 10*(1), 20584. doi:10.1038/s41598-020-77602-0
61. Roh, C. (2012). A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. *International journal of nanomedicine, 7*, 2173-2179. doi:10.2147/IJN.S31379
62. Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J.-Y., Kim, D., . . . Lee, W. S. (2010). Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. *Bioorganic & Medicinal Chemistry, 18*(22), 7940-7947. doi:https://doi.org/10.1016/j.bmc.2010.09.035
63. Sa-Ngiamsuntorn, K., Suksatu, A., Pewkliang, Y., Thongsri, P., Kanjanasirirat, P., Manopwisedjaroen, S., . . . Hongeng, S. (2021). Anti-SARS-CoV-2 Activity of Andrographis paniculata Extract and Its Major Component Andrographolide in Human Lung Epithelial Cells and Cytotoxicity Evaluation in Major Organ Cell Representatives. *Journal of Natural Products, 84*(4), 1261-1270. doi:10.1021/acs.jnatprod.0c01324
64. Shaji, D., Yamamoto, S., Saito, R., Suzuki, R., Nakamura, S., & Kurita, N. (2021). Proposal of novel natural inhibitors of severe acute respiratory syndrome coronavirus 2 main protease: Molecular docking and ab initio fragment molecular orbital calculations. *Biophysical Chemistry, 275*, 106608. doi:https://doi.org/10.1016/j.bpc.2021.106608
65. Sharma, A., Tiwari, V., & Sowdhamini, R. (2020). Computational search for potential COVID-19 drugs from FDAapproved drugs and small molecules of natural origin identifies several anti-virals and plant products. *Journal of Biosciences, 45*(1). doi:10.1007/s12038-020-00069-8
66. Sharma, P., & Shanavas, A. (2020). Natural derivatives with dual binding potential against SARS-CoV-2 main protease and human ACE2 possess low oral bioavailability: a brief computational analysis. *Journal of Biomolecular Structure and Dynamics*, 1-12. doi:10.1080/07391102.2020.1794970
67. Shi, T. H., Huang, Y. L., Chen, C. C., Pi, W. C., Hsu, Y. L., Lo, L. C., . . . Lin, C. H. (2020). Andrographolide and its fluorescent derivative inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage. *Biochemical and Biophysical Research Communications, 533*(3), 467-473. doi:10.1016/j.bbrc.2020.08.086
68. Shin, J. A., Oh, S., & Jeong, J.-M. (2021). The potential of BEN815 as an anti-inflammatory, antiviral and antioxidant agent for the treatment of COVID-19. *Phytomedicine Plus, 1*(4), 100058. doi:https://doi.org/10.1016/j.phyplu.2021.100058

69. Singh, S., Sk, M. F., Sonawane, A., Kar, P., & Sadhukhan, S. (2020). Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: an in-silico analysis. *Journal of Biomolecular Structure and Dynamics*, 1-16. doi:10.1080/07391102.2020.1796810
70. Tahmasebi, S., Saeed, B. Q., Temirgalieva, E., Yumashev, A. V., El-Esawi, M. A., Navashenaq, J. G., . . . Roshangar, L. (2021). Nanocurcumin improves Treg cell responses in patients with mild and severe SARS-CoV2. *Life Sciences, 276*, 119437. doi:https://doi.org/10.1016/j.lfs.2021.119437
71. Toor, H. G., Banerjee, D. I., Lipsa Rath, S., & Darji, S. A. (2021). Computational drug re-purposing targeting the spike glycoprotein of SARS-CoV-2 as an effective strategy to neutralize COVID-19. *European Journal of Pharmacology, 890*, 173720. doi:https://doi.org/10.1016/j.ejphar.2020.173720
72. Umar, H. I., Josiah, S. S., Saliu, T. P., Jimoh, T. O., Ajayi, A., & Danjuma, J. B. (2021). In-silico analysis of the inhibition of the SARS-CoV-2 main protease by some active compounds from selected African plants. *Journal of Taibah University Medical Sciences, 16*(2), 162-176. doi:https://doi.org/10.1016/j.jtumed.2020.12.005
73. Vabret, A., Dina, J., Brison, E., Brouard, J., & Freymuth, F. (2009). [Human coronaviruses]. *Pathologie Biologie (Paris), 57*(2), 149-160. doi:10.1016/j.patbio.2008.02.018
74. Valizadeh, H., Abdolmohammadi-vahid, S., Danshina, S., Ziya Gencer, M., Ammari, A., Sadeghi, A., . . . Ahmadi, M. (2020). Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *International Immunopharmacology, 89*, 107088. doi:https://doi.org/10.1016/j.intimp.2020.107088
75. van de Sand, L., Bormann, M., Alt, M., Schipper, L., Heilingloh, C. S., Steinmann, E., . . . Krawczyk, A. (2021). Glycyrrhizin Effectively Inhibits SARS-CoV-2 Replication by Inhibiting the Viral Main Protease. *Viruses, 13*(4). doi:10.3390/v13040609
76. Vardhan, S., & Sahoo, S. K. (2020). In silico ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19. *Computers in Biology and Medicine, 124*, 103936. doi:10.1016/j.compbiomed.2020.103936
77. Vardhan, S., & Sahoo, S. K. (2021). Virtual screening by targeting proteolytic sites of furin and TMPRSS2 to propose potential compounds obstructing the entry of SARS-CoV-2 virus into human host cells. *Journal of Traditional and Complementary Medecine*. doi:10.1016/j.jtcme.2021.04.001
78. Varghese, F. S., van Woudenbergh, E., Overheul, G. J., Eleveld, M. J., Kurver, L., van Heerbeek, N., . . . van Rij, R. P. (2021). Berberine and Obatoclax Inhibit SARS-Cov-2 Replication in Primary Human Nasal Epithelial Cells In Vitro. *Viruses, 13*(2). doi:10.3390/v13020282
79. Verma, D., Mitra, D., Paul, M., Chaudhary, P., Kamboj, A., Thatoi, H., . . . Das Mohapatra, P. K. (2021). Potential inhibitors of SARS-CoV-2 (COVID 19) proteases PLpro and Mpro/ 3CLpro: molecular docking and simulation studies of three pertinent medicinal plant natural components. *Current Research in Pharmacology and Drug Discovery, 2*, 100038. doi:https://doi.org/10.1016/j.crphar.2021.100038
80. Wang, Z. Z., Li, K., Maskey, A. R., Huang, W., Toutov, A. A., Yang, N., . . . Li, X. M. (2021). A small molecule compound berberine as an orally active therapeutic candidate against COVID-19 and SARS: A computational and mechanistic study. *The FASEB Journal, 35*(4), e21360. doi:10.1096/fj.202001792R
81. Wen, C. C., Kuo, Y. H., Jan, J. T., Liang, P. H., Wang, S. Y., Liu, H. G., . . . Yang, N. S. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *Journal of Medicinal Chemistry, 50*(17), 4087-4095. doi:10.1021/jm070295s
82. Xiong, Y., Zhu, G.-H., Wang, H.-N., Hu, Q., Chen, L.-L., Guan, X.-Q., . . . Ge, G.-B. (2021). Discovery of naturally occurring inhibitors against SARS-CoV-2 3CLpro from Ginkgo biloba leaves via large-scale screening. *Fitoterapia, 152*, 104909. doi:https://doi.org/10.1016/j.fitote.2021.104909
83. Xu, J., Gao, L., Liang, H., & Chen, S.-d. (2021). In silico screening of potential anti–COVID-19 bioactive natural constituents from food sources by molecular docking. *Nutrition, 82*, 111049. doi:https://doi.org/10.1016/j.nut.2020.111049
84. Yañez, O., Osorio, M. I., Areche, C., Vasquez-Espinal, A., Bravo, J., Sandoval-Aldana, A., . . . Tiznado, W. (2021). Theobroma cacao L. compounds: Theoretical study and molecular modeling as inhibitors of main SARS-CoV-2 protease. *Biomedicine & Pharmacotherapy, 140*, 111764. doi:https://doi.org/10.1016/j.biopha.2021.111764
85. Yu, S., Zhu, Y., Xu, J., Yao, G., Zhang, P., Wang, M., . . . Zhang, J. (2021). Glycyrrhizic acid exerts inhibitory activity against the spike protein of SARS-CoV-2. *Phytomedicine, 85*, 153364. doi:10.1016/j.phymed.2020.153364
86. Zhang, B. Y., Chen, M., Chen, X. C., Cao, K., You, Y., Qian, Y. J., & Yu, W. K. (2021). Berberine reduces circulating inflammatory mediators in patients

with severe COVID-19. *British Journal of Surgery, 108*(1), e9-e11. doi:10.1093/bjs/znaa021

87. Zhao, M., Yu, Y., Sun, L. M., Xing, J. Q., Li, T., Zhu, Y., . . . Li, T. (2021). GCG inhibits SARS-CoV-2 replication by disrupting the liquid phase condensation of its nucleocapsid protein. *Nature Communications, 12*(1), 2114. doi:10.1038/s41467-021-22297-8
88. Zhao, Z., Xiao, Y., Xu, L., Liu, Y., Jiang, G., Wang, W., . . . Shan, H. (2021). Glycyrrhizic Acid Nanoparticles as Antiviral and Anti-inflammatory Agents for COVID-19 Treatment. *ACS Applied Materials & Interfaces, 13*(18), 20995-21006. doi:10.1021/acsami.1c02755
89. Zígolo, M. A., Goytia, M. R., Poma, H. R., Rajal, V. B., & Irazusta, V. P. (2021). Virtual screening of plant-derived compounds against SARS-CoV-2 viral proteins using computational tools. *Science of The Total Environment, 781*, 146400. doi:https://doi.org/10.1016/j.scitotenv.2021.146400