

Philippine Medicinal Plants with Potential Immunomodulatory and Anti-SARS-CoV-2 Activities

Fabian M. Dayrit^{1,2*}, Armando M. Guidote Jr.^{1,2}, Nina G. Gloriani³,
Sheriah Laine M. de Paz-Silava³, Irene M. Villaseñor⁴, Rene Angelo S. Macahig^{1,5},
Mario A. Tan⁶, John Ross N. Chua¹, and Isidro C. Sia⁷

¹Department of Chemistry, School of Science and Engineering
Ateneo de Manila University, Loyola Heights, Quezon City, Philippines

²Philippine Institute of Pure and Applied Chemistry (PIPAC)

Ateneo de Manila University, Loyola Heights, Quezon City, Philippines

³College of Public Health, University of the Philippines Manila, Taft Avenue, Manila, Philippines

⁴Institute of Chemistry, College of Science, University of the Philippines Diliman, Quezon City, Philippines

⁵Andrew Moore and Associates Ltd., Singapore

⁶Department of Chemistry, College of Science, Research Center for the Natural and Applied Sciences
University of Santo Tomas, España, Manila, Philippines

⁷Integrative Medicine for Alternative Healthcare Systems (INAM) Philippines,
Inc. Diliman, Quezon City, Philippines

Coronavirus disease 2019 (COVID-19) continues to devastate the world's health and economy, affecting all aspects of life leading to widespread social disruption. Even as several vaccines have been developed, their availability in developing countries is limited and their efficacy against the variants of SARS-CoV-2 (severe acute respiratory syndrome–coronavirus 2) needs to be continuously assessed. The World Health Organization (WHO) has acknowledged that vaccines alone will not overcome the global challenges of COVID-19. Medicinal plants may provide the needed support. Herein, we identify Philippine medicinal plants that possess phytochemicals with potential anti-SARS-CoV-2 activity and/or immunomodulatory properties that may strengthen one's immune system against COVID-19. These plants were selected from 100 of the best-studied Philippine medicinal plants with antiviral and immunomodulatory properties. The general antiviral and specific anti-SARS-CoV-2 activities and immunomodulatory properties of the phytochemicals that these plants contained were searched. While many compounds assessed individually using *in vitro* and *in silico* techniques suggest potential anti-SARS-CoV-2 or immunomodulatory effects, this review sought to identify the medicinal plants which contain these compounds and which, based on literature, have the best potential application against COVID-19. These plants are *Allium spp.* bulbs (bawang), *Andrographis paniculata* (Burm.f.) Nees leaves (sinta), *Cocos nucifera* L. oil (niyog), *Euphorbia hirta* L. leaves (tawa-tawa), *Euphorbia neriifolia* L. leaves (sorosoro), *Moringa oleifera* Lam. leaves (malunggay), *Ocimum basilicum* L. leaves (balanoy), *Piper nigrum* L. seeds (paminta), *Vitex negundo* L. leaves (lagundi), and *Zingiber officinale* Roscoe rhizome (luya). This review provides a shortlist that can guide research on possible solutions to COVID-19 using Philippine medicinal plants.

Keywords: antiviral, COVID-19, immunomodulatory, Philippine medicinal plants, SARS-CoV-2

*Corresponding Author: fdayrit@ateneo.edu

INTRODUCTION

Today, more than one year after it broke out, COVID-19 continues to devastate the world's health and economy, affecting all aspects of life, leading to widespread social disruption. COVID-19 is caused by a virus which was named SARS-CoV-2. The high infectivity of SARS-CoV-2, coupled with the expansion of global travel, resulted in the rapid spread of this disease. The transmission of the virus continues to surge in many countries and regions and the rise of variants has caused additional concern.

The solution to COVID-19 must be global and inclusive. The attention of the medical community during the last quarter of 2020 was almost exclusively focused on the development of vaccines. However, even under the best conditions of vaccination programs, it is estimated that to attain herd immunity, vaccination of the global population may take until 2023–2024 (Mullard 2020). With the uncertainty regarding the effective period of immunity, whether from a previous infection or through vaccination, a multipronged strategy should be implemented, which includes consideration of context-specific situations of different individuals, societies, and economies (WHO 2020). Considering the fast emergence of multiple variants having the ability of immune escape and higher transmissibility, it also remains unclear if natural immunity or vaccination can end the pandemic (Altmann *et al.* 2021). Moreover, the global demand for COVID-19 vaccines and drugs does not ensure adequate supply to the Philippines – a country that is completely dependent on imports of these essential medical products. As the WHO Director-General Tedros Adhanom Ghebreyesus repeatedly warned: “A vaccine on its own will not end the pandemic” (inquirer.net 2020).

One option that is affordable and accessible to most people, especially in developing countries, is medicinal plants. From its very beginnings, humankind has had to deal with viral diseases. However, since the scientific concept of the virus was not known until the late-19th century, there can be no reference to the antiviral activity of medicinal plants earlier than this time. The early use of medicinal plants against viral diseases can be surmised from conditions that are now known to be caused by viruses, such as smallpox, herpes, and influenza (Garcia 2020). More recently, medicinal plants were studied against previous coronavirus outbreaks – in particular, SARS-CoV which broke out in 2002, and the Middle East respiratory syndrome-coronavirus (MERS-CoV) (Boukhatem and Setzer 2020). Phytochemicals from medicinal plants are also important in strengthening the human immunomodulatory system to fight off viruses and other pathogens. In the same manner that established drugs are being studied and repurposed to fight COVID-19,

these medicinal plants should be studied for their possible efficacy against this new disease.

This review paper aims to identify Philippine medicinal plants that possess phytochemicals with potential activity against the SARS-CoV-2 virus, as well as beneficial properties for the treatment of COVID-19, including immunomodulatory and anti-inflammatory properties. The objective of this paper is not to analyze the immunomodulatory and antiviral mechanisms of COVID-19, but to recommend Philippine medicinal plants that can be used in clinical studies against COVID-19 based on their phytochemical constituents. While medicinal plants are recognized for particular benefits, their effective and safe use against COVID-19 needs to be carefully studied to avoid conflicting outcomes. For example, the angiotensin-converting enzyme 2 (ACE2) has been identified as the main route of entry of the coronavirus. While upregulation of ACE2 is normally seen as beneficial for lowering blood pressure, this may make people more vulnerable to COVID-19. Therefore, medicinal plants and phytochemicals that upregulate ACE2 expression may put people at greater threat of COVID-19. This is the case for phytochemicals that are normally seen as beneficial, such as baicalin (from *Scutellaria baicalensis*) and rosmarinic acid (from *Rosmarinus officinalis*) (de Lange-Jacobs *et al.* 2020). Similarly, medicinal plants may modulate the immune system by stimulating or suppressing the innate or adaptive mechanisms that synthesize and release pro-inflammatory or anti-inflammatory mediators (Jantan *et al.* 2019). Curcumin, a well-known phytochemical, presents an interesting case: it is anti-inflammatory (Hewlings and Kalman 2017) and is able to bind and potentially block the ACE2 receptor (Manoharan *et al.* 2020), but it also enhances ACE2 expression (Pang *et al.* 2015). Thus, the beneficial use of a medicinal plant in another disease does not automatically mean that it will be beneficial for use against COVID-19.

The initial list of Philippine medicinal plants was based on one hundred medicinal plants from three volumes of the “Encyclopedia of Philippine Medicinal Plants” (Dayrit *et al.* 2014, 2016, 2021) (Table 1). These are the Philippine medicinal plants with the highest number of botanical, pharmacological, and phytochemical publications, and with the longest history of documented use. From this initial list of 100 plants, scientific literature related to the following were searched: recent studies on SARS-CoV-2, earlier studies on other coronaviruses – including SARS-CoV and MERS-CoV, and other viruses – and *in vitro* and *in silico* studies on compounds that are found in these medicinal plants. The recommendations are based on the antiviral and immunomodulatory activities of key phytochemicals found in the medicinal plants, as well as studies on the whole plant. The

Table 1. List of Philippine medicinal plants that were included in this review.

Scientific name	Common name	Scientific name	Common name
<i>Acorus calamus</i> L.	Lubigan	<i>Garcinia mangostana</i> L.	Mangosteen
<i>Agathis dammara</i> (Lamb.) Rich. & A.Rich.	Almasiga	<i>Gliricidia sepium</i> (Jacq.) Walp.	Kakawate
<i>Aleurites moluccana</i> (L.) Willd.	Lumbang	<i>Goniothalamus amuyon</i> (Blanco) Merr.	Amuyong
<i>Allium ascalonicum</i> L.	Sibuyas Tagalog	<i>Imperata cylindrica</i> (L.) Raeusch.	Kogon
<i>Allium cepa</i> L.	Sibuyas	<i>Jatropha curcas</i> L.	Tubang bakod
<i>Allium sativum</i> L.	Bawang	<i>Lagerstroemia speciosa</i> (L.) Pers.	Banaba
<i>Alocasia macrorrhizos</i> (L.) G.Don	Biga	<i>Leucaena leucocephala</i> (Lam.) deWit	Ipil-ipil
<i>Aloe barbadensis</i> Mill.	Sabila	<i>Litsea glutinosa</i> (Lour.) C.B.Rob.	Lauat
<i>Alpinia elegans</i> (C.Presl) K.Schum.	Tagbak	<i>Mallotus philippinensis</i> (Lam.) Mull.Arg.	Banato
<i>Alstonia scholaris</i> L.	Dita	<i>Melastoma malabathricum</i> L.	Tagpo
<i>Anacardium occidentale</i> L.	Kasoy	<i>Mentha x cordifolia</i> Opiz ex Fresen.	Yerba buena
<i>Andrographis paniculata</i> (Burm.f.) Nees	Sinta	<i>Mimosa pudica</i> L.	Makahiya
<i>Annona muricata</i> L.	Guyabano	<i>Momordica charantia</i> L.	Ampalaya
<i>Annona squamosa</i> L.	Atis	<i>Morinda citrifolia</i> Roxb.	Noni
<i>Antidesma bunius</i> (L.) Spreng.	Bignay	<i>Moringa oleifera</i> Lam.	Malunggay
<i>Arcangelisia flava</i> (L.) Merr.	Abutra	<i>Murraya paniculata</i> (L.) Jacq.	Kamuning
<i>Areca catechu</i> L.	Bunga	<i>Musa paradisiaca</i> L.	Saging na saba
<i>Artemisia vulgaris</i> L.	Damong Maria	<i>Nauclea orientalis</i> (L.) L.	Bangkal
<i>Averrhoa bilimbi</i> L.	Kamias	<i>Ocimum basilicum</i> L.	Balanoy
<i>Azadirachta indica</i> A. Juss.	Neem	<i>Origanum vulgare</i> L.	Oregano
<i>Blumea balsamifera</i> (L.) DC.	Sambong	<i>Orthosiphon aristatus</i> (Bl.) Miq.	Kabling gubat
<i>Caesalpinia sappan</i> L.	Sapang	<i>Pandanus amaryllifolius</i> Roxb.	Pandan mabango
<i>Calamus ornatus</i> Blume	Rattan/Yantok	<i>Peperomia pellucida</i> (L.) HBK.	Pansit-pansitan
<i>Calophyllum inophyllum</i> L.	Bitao	<i>Phyllanthus niruri</i> L.	Sampasampalukan
<i>Cananga odorata</i> (Lam.) Hook.f. & Thoms.	Ilang-ilang	<i>Piper betle</i> L.	Ikmo
<i>Canarium ovatum</i> Engl.	Pili	<i>Piper nigrum</i> L.	Paminta
<i>Capsicum frutescens</i> L.	Siling labuyo	<i>Pistia stratiotes</i> L.	Kiyapo
<i>Carica papaya</i> L.	Papaya	<i>Plumeria rubra</i> L.	Kalatsutsi
<i>Carmona retusa</i> (Vahl) Masam.	Tsaang gubat	<i>Pogostemon cablin</i> (Blco.) Benth.	Kabling
<i>Cassia fistula</i> L.	Kanya pistula	<i>Pongamia pinnata</i> (L.) Pierre	Bani
<i>Centella asiatica</i> (L.) Urb.	Takipkohol	<i>Premna odorata</i> Blco.	Alagaw
<i>Cinnamomum mercadoi</i> Vid.	Kalingag	<i>Psidium guajava</i> L.	Bayabas
<i>Citrus hystrix</i> DC.	Kabuyaw	<i>Pterocarpus indicus</i> Willd.	Narra
<i>Clausena anisum-olens</i> (Blanco) Merr.	Kayumanis	<i>Pueraria montana</i> (Lour.) Merr.	Baay
<i>Clausena excavata</i> Burm.f.	Buringit	<i>Quassia indica</i> (Gaertn.) Noot.	Manunggal
<i>Cocos nucifera</i> L.	Niyog	<i>Quisqualis indica</i> L.	Niyug-niyogan
<i>Corchorus olitorius</i> L.	Saluyot	<i>Reutealis trisperma</i> (Blanco) Airy Shaw	Philippine tung
<i>Curcuma longa</i> L.	Luyang dilaw	<i>Rhizophora apiculata</i> Blume	Bakawan
<i>Cycas edentata</i> de Laub.	Pitogong dagat	<i>Senna alata</i> (L.) Roxb.	Akapulko
<i>Cymbopogon citratus</i> (DC. ex Nees) Stapf	Tanglad	<i>Smilax bracteata</i> C.Presl	Banag
<i>Datura metel</i> L.	Talumpunay	<i>Syzygium cumini</i> (L.) Skeels	Duhat
<i>Dillenia philippinensis</i> Rolfe	Katmon	<i>Syzygium jambos</i> (L.) Alston	Tampoy
<i>Dioscorea hispida</i> Dennst.	Nami	<i>Tabernaemontana pandacaqui</i> Poir.	Pandakaki
<i>Diospyros maritima</i> Blume	Malatinta	<i>Talinum triangulare</i> (Jacq.) Willd.	Talinum
<i>Diplazium esculentum</i> (Retz.) Sw.	Pako	<i>Tamarindus indica</i> L.	Sampalok
<i>Eclipta prostrata</i> (L.) L.	Tinta-tinta	<i>Vitex negundo</i> L.	Lagundi
<i>Ehretia philippinensis</i> A.DC.	Alibungog	<i>Zea mays</i> L.	Mais
<i>Entada phaseoloides</i> (L.) Merr.	Gugo	<i>Zingiber officinale</i> Roscoe	Luya
<i>Euphorbia hirta</i> L.	Tawa-tawa		
<i>Euphorbia nerifolia</i> L.	Sorosoro		
<i>Ficus benamina</i> L.	Balete		

keywords used for searching references were “antiviral,” “immunomodulating,” “immune system,” and “immune-enhancing.” Search engines used were Scopus and Google Scholar.

This review is divided into four sections:

- Section I briefly describes the SARS-CoV-2 virus.
- Section II presents phytochemicals and Philippine medicinal plants with immunomodulatory properties.
- Section III focuses on phytochemicals and Philippine medicinal plants with potential anti-SARS-CoV-2 activity.
- Section IV identifies the most promising Philippine medicinal plants against COVID-19 which should be further studied.

Only a few medicinal plants have actually undergone clinical trials against COVID-19 and it is hoped that this review will help identify those which have scientific evidence to be considered.

The SARS-CoV-2 Virus

The causative agent of COVID-19 – SARS-CoV-2 – is a lipid enveloped virus. It has a single-strand positive sense ribonucleic acid (RNA), which functions as messenger RNA (mRNA). This virus has characteristic club-shaped spikes on the surface, which gives it a crown-like appearance, and thus the classification under coronaviruses. These spikes are made up of a highly glycosylated protein, the spike protein. Three other structural proteins on the surface of the virus are the envelope, membrane, and nucleocapsid proteins.

SARS-CoV-2 consists of two large overlapping open reading frames, which encode 16 nonstructural proteins – including the RNA-dependent RNA polymerase (RdRp), RNA helicase, and other proteins that form the viral replicase complex that is important in the propagation of viral mRNAs. These non-structural proteins are considered potential targets for antiviral therapy.

When a person is infected, the biggest challenge in COVID-19 management is how to prevent severe or critical disease, and even death. Cytokine storms and dysregulated immune responses have been hypothesized as central mechanisms of disease severity. Proinflammatory cytokines such as interleukin 6 (IL-6), IL-8, IL-2R, and tumor necrosis factor-alpha (TNF-alpha) have been shown to be significantly elevated among patients with severe disease (Mulchandani *et al.* 2021). This explains how corticosteroids, such as dexamethasone, decrease all-cause mortality and composite progression in severe

COVID-19 patients (Ma *et al.* 2021). Immunomodulation should, therefore, be an important treatment strategy to prevent disease progression and mortality.

II. Phytochemicals and Philippine Medicinal Plants with Immunomodulatory Properties

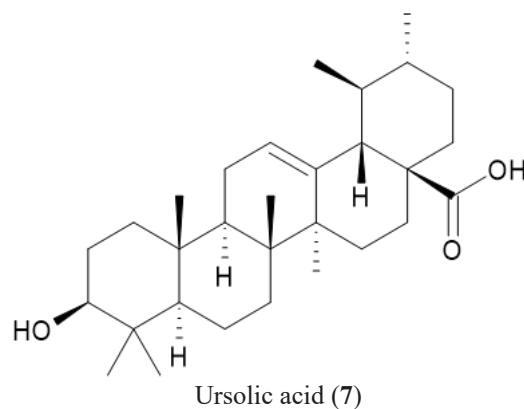
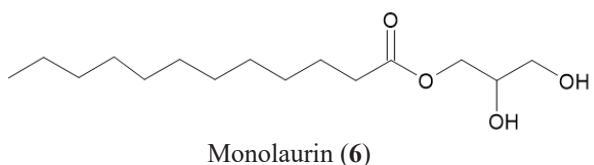
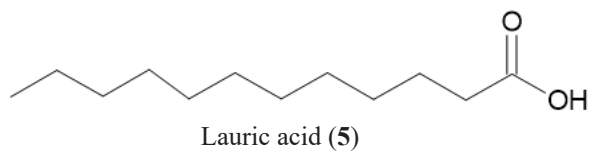
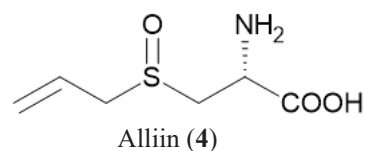
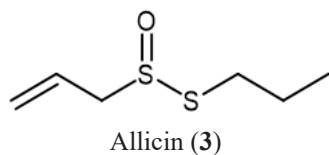
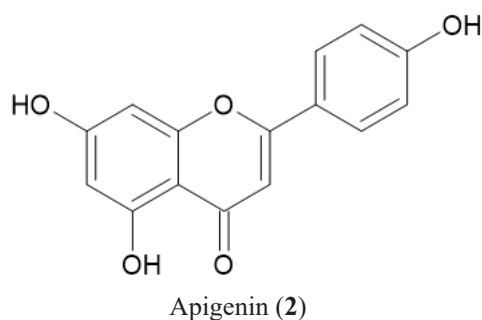
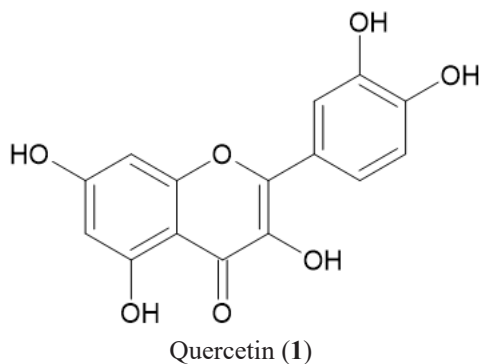
Herbal immunomodulators are plants that can stimulate or suppress the innate or adaptive responses of the immune system. Medicinal plants are multi-component agents that are able to modulate the complex immune system to defend itself against viral infections rather than directly act against the virus. Numerous phytochemical constituents have been identified in medicinal plants that exhibit favorable immunomodulatory properties. These include anthraquinones, flavonoids, terpenoids, alkaloids, polyphenolics, polysaccharides, proteins, fatty acids, and sulfur-containing compounds. Among these compound classes, the flavonoids and their glycosides have the highest number of documented cases. Table 2 lists the phytochemicals that may be responsible for the immunomodulatory activities of the selected Philippine medicinal plants. The structures of these compounds are presented in Figure 1. It should be noted that many flavonoids occur naturally in plants as glycosides. *In vivo*, the glycoside forms have been shown to confer higher bioavailability and, consequently, better activity. Isoquercetin (**21**) and isoquercitrin (**22**) are glycoside isomers of the same aglycone, which is quercetin (**1**). The biological activity of isoquercetin (**21**) and isoquercitrin (**22**) is the same after hydrolysis of the sugar (Appleton 2010). This phenomenon may explain the numerous reports of biological activity among the flavonoids.

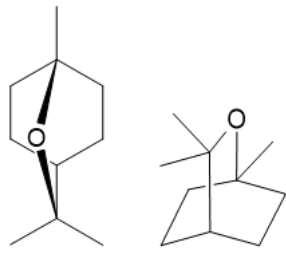
Quercetin (1). The immunomodulatory action of quercetin (**1**) was shown in the following activities: 1) inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and signal transducer and activator of transcription 1 (STAT-1) (Hämäläinen *et al.* 2007); 2) modulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and C-reactive protein (CRP), and down-regulation of NF- κ B activation (Garcia-Mediavilla *et al.* 2007); 3) suppression of immunoglobulin E (IgE)-mediated allergic inflammation (Lee *et al.* 2010); 4) inhibition of nitric oxide (NO) production and iNOS gene expression by Ralph and William’s cell line 264.7 (RAW 264.7) stimulated with lipopolysaccharide/interferon-gamma (LPS/IFN-gamma); and 5) inhibition of COX-2 gene, IL-6 gene, and IL-1beta mRNA expression. Quercetin was found to be active against adenovirus (ADV-3, ADV-8), hepatitis C virus (HCV), herpes simplex virus (HSV), human immunodeficiency virus (HIV) type 1 integrase, influenza A virus (H1N1, H3N2, H5N1), poliovirus, respiratory syncytial virus, rhinovirus, and the sindbis virus. Quercetin has been identified in *Allium ascalonicum* and *Moringa oleifera*.

Table 2. Phytochemicals and plants with immunomodulatory activity.

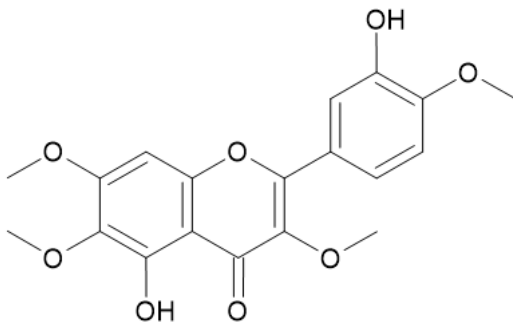
Phytochemical	Immunomodulatory activity	Plant species	Reference/s
Flavonoids and their glycosides			
Quercetin (1)	<ul style="list-style-type: none"> Inhibition or modulation of COX-2, IL-6, IL-1b, NF-κB, iNOS, CRP and STAT-1 Suppression of IgE-mediated allergic inflammation 	<i>A. ascalonicum</i>	Hämäläinen <i>et al.</i> (2007), Garcia-Mediavilla <i>et al.</i> (2007), Lee <i>et al.</i> (2010), Daikonya <i>et al.</i> (2004), Jantan <i>et al.</i> (2019)
Apigenin (2)	<ul style="list-style-type: none"> Inhibition of allergen-induced airway inflammation and switching of immune response Reduction of miR-155 and NF-κB activity Modulation of dendritic cell and other immune cell functions 	<i>O. basilicum</i>	Li <i>et al.</i> (2010), Arango <i>et al.</i> (2015), Cardenas <i>et al.</i> (2016), Ginwala <i>et al.</i> (2016)
Casticin (9)	<ul style="list-style-type: none"> Alleviates eosinophilic airway inflammation and oxidative stress 	<i>V. negundo</i>	Liou <i>et al.</i> (2018)
Epigallocatechin gallate (14)	<ul style="list-style-type: none"> Inhibits STAT and NF-κB transcription factors 	<i>E. hirta</i>	Menegazzi <i>et al.</i> (2020)
Alkaloids			
Piperine (13)	<ul style="list-style-type: none"> Inhibition of the cytokines TNF-α, IFN-α4, IFN-β, STAT-1, IRF-1, IRF-7 mRNA Phosphorylation and nuclear translocation of IRF-3 macrophages Reduction of methacholine-induced airway hyper responsiveness and airway inflammation in ovalbumin-sensitized Balb/c mice Decreased total number of leukocytes, number of total lung cells, absolute number of eosinophils in BALF cells, eosinophils, numbers of CD4+, CD8+, CCR3+, Gr-1+CD11b+, CD69+, CD3+ and CD25+ cells, IL-4, IL-5 and eotaxin levels, IgE and histamine production, IL-4 production Increased IFN-γ production and TGF-β gene expression 	<i>P. nigrum</i>	Bae <i>et al.</i> (2010), Kim and Lee (2009), Vaidya and Rathod (2014)
Terpenoids			
1,8-Cineol (8)	<ul style="list-style-type: none"> Amplifies immune response dependent on the IRF3/IFNβ pathway 	<i>V. negundo</i>	Müller <i>et al.</i> (2016)
Andrographolide (10)	<ul style="list-style-type: none"> Inhibition of furin, PC1, PC7 Suppression of M1 and M2 cytokines Reduction of IL-12/IL-10 ratio Inhibition of the increase of MHC-1, CD40, CD80 and CD86 Suppression IL-4 induced expression of CD40 and CD206 Inhibition on the phosphorylation of ERK 1/2 and AKT Inhibition of anti-HBsAg antibody titers and reduction of IL-4 producing cells 	<i>A. paniculata</i>	Basak <i>et al.</i> (1999), Wang <i>et al.</i> (2010)
Neoandrographolide (11)	<ul style="list-style-type: none"> Inhibition of furin, PC1, PC7 	<i>A. paniculata</i>	Basak <i>et al.</i> (1999)
Dehydroandrographolide succinic acid monoester (12)	<ul style="list-style-type: none"> Inhibition of furin, PC1, PC7 	<i>A. paniculata</i>	Basak <i>et al.</i> (1999)
Andrograpanin (28)	<ul style="list-style-type: none"> Enhancement of SDF-1-induced chemotaxis Reduction of SDF-1α-induced CXCR4 internalization 	<i>A. paniculata</i>	Ji <i>et al.</i> (2005)

Ursolic acid (7)	<ul style="list-style-type: none"> • Increase IL-10 and IL-12 • Reduction of IL-1, IL-6, IL-17, TNF-α IL-17 and IgG2b 	<i>O. basilicum</i>	Choi and Lee (2019) Xu <i>et al.</i> (2015) Chiang <i>et al.</i> (2005)
Sulfur-containing compounds			
Alliin (4)	<ul style="list-style-type: none"> • Immunomodulatory effect on peripheral blood and intestinal epithelial cells and macrophage secretory and cellular activity • Suppression of iNOS expression 	<i>A. ascalonicum</i> <i>A. sativum</i>	Salman <i>et al.</i> (1999), Kang <i>et al.</i> (2001), Lang <i>et al.</i> (2004), Haase <i>et al.</i> (2012)
Allicin (3)	<ul style="list-style-type: none"> • Immunomodulatory effect on peripheral blood and intestinal epithelial cells and macrophage secretory and cellular activity • Suppression of iNOS expression 	<i>A. ascalonicum</i> <i>A. sativum</i>	Salman <i>et al.</i> (1999), Kang <i>et al.</i> (2001), Lang <i>et al.</i> (2004), Haase <i>et al.</i> (2012)
Fatty acids			
Lauric acid (5)	<ul style="list-style-type: none"> • Upregulation of immune system 	<i>C. nucifera</i>	Weatherill <i>et al.</i> (2005)
Monolaurin (6)	<ul style="list-style-type: none"> • Induction of proliferation of T-cells 	<i>C. nucifera</i>	Witcher <i>et al.</i> (1996)
Polysaccharides and proteins			
Fructans	<ul style="list-style-type: none"> • Immunostimulation of murine lymphocytes and macrophages 	<i>A. sativum</i>	Chandrashekara and Venkatesh (2016)
Fructo-oligosaccharides	<ul style="list-style-type: none"> • Stimulation of mouse lymphocytes and macrophages • Increased NO production 	<i>A. cepa</i>	Kumar <i>et al.</i> (2015)

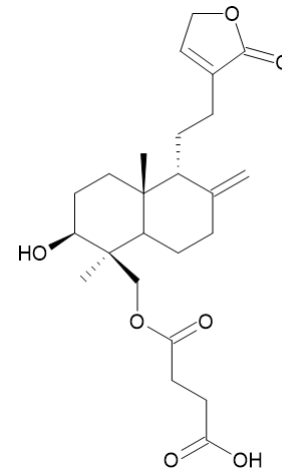




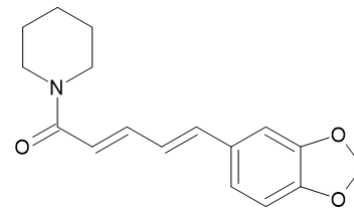
1,8-Cineol (8)



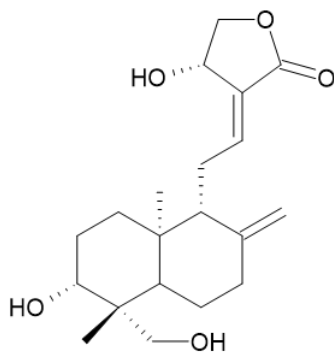
Casticin (9)



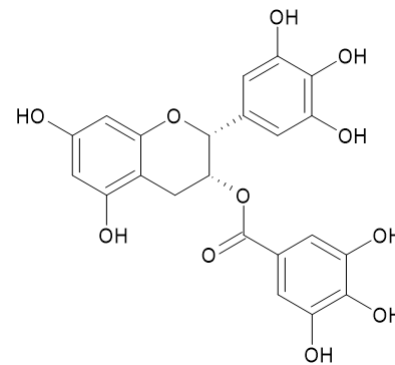
Dehydroandrographolide succinic acid monoester (12)



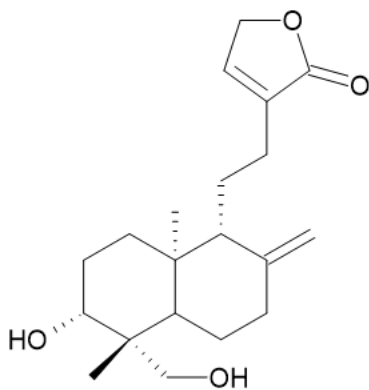
Piperine (13)



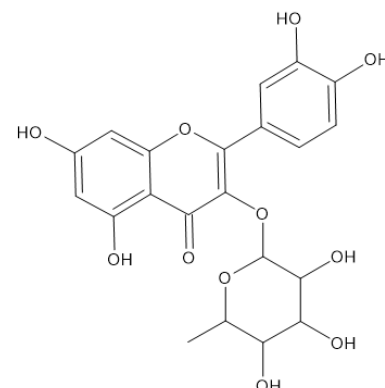
Andrographolide (10)



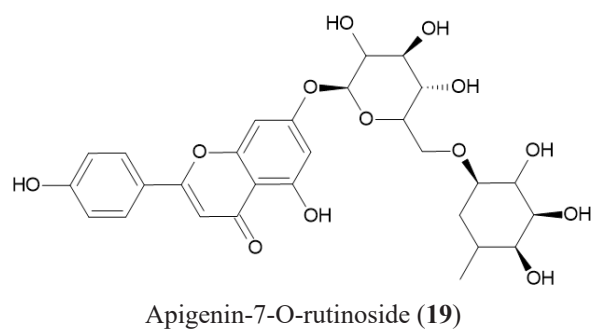
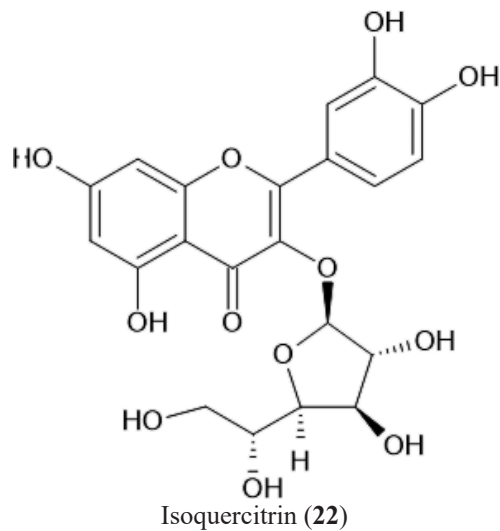
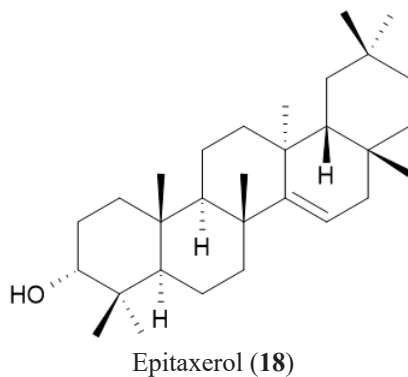
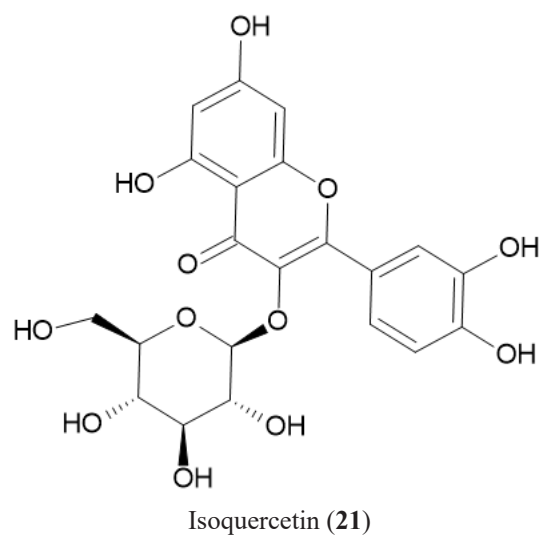
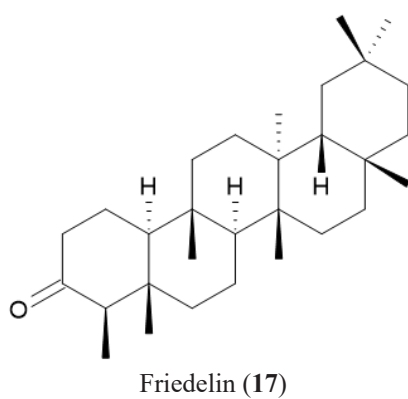
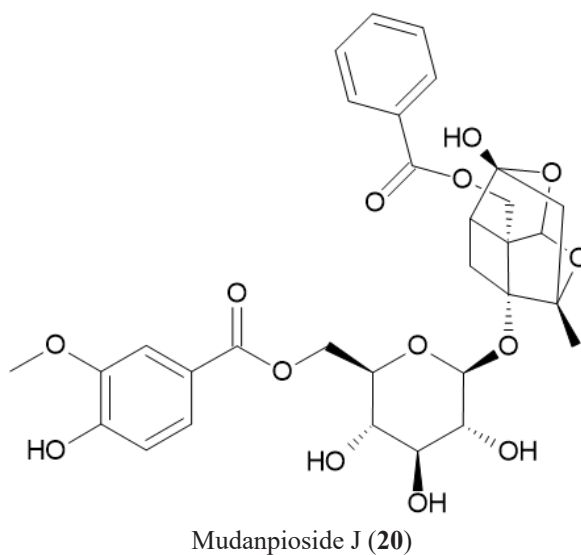
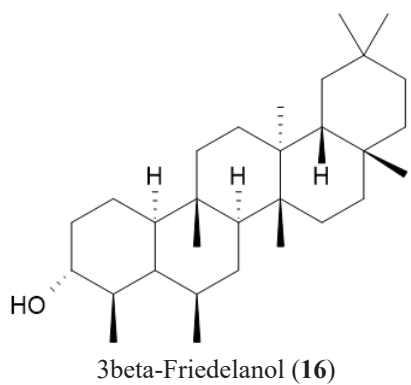
Epigallocatechin gallate (14)



Neoandrographolide (11)



Quercetin-3-rhamnoside (15)



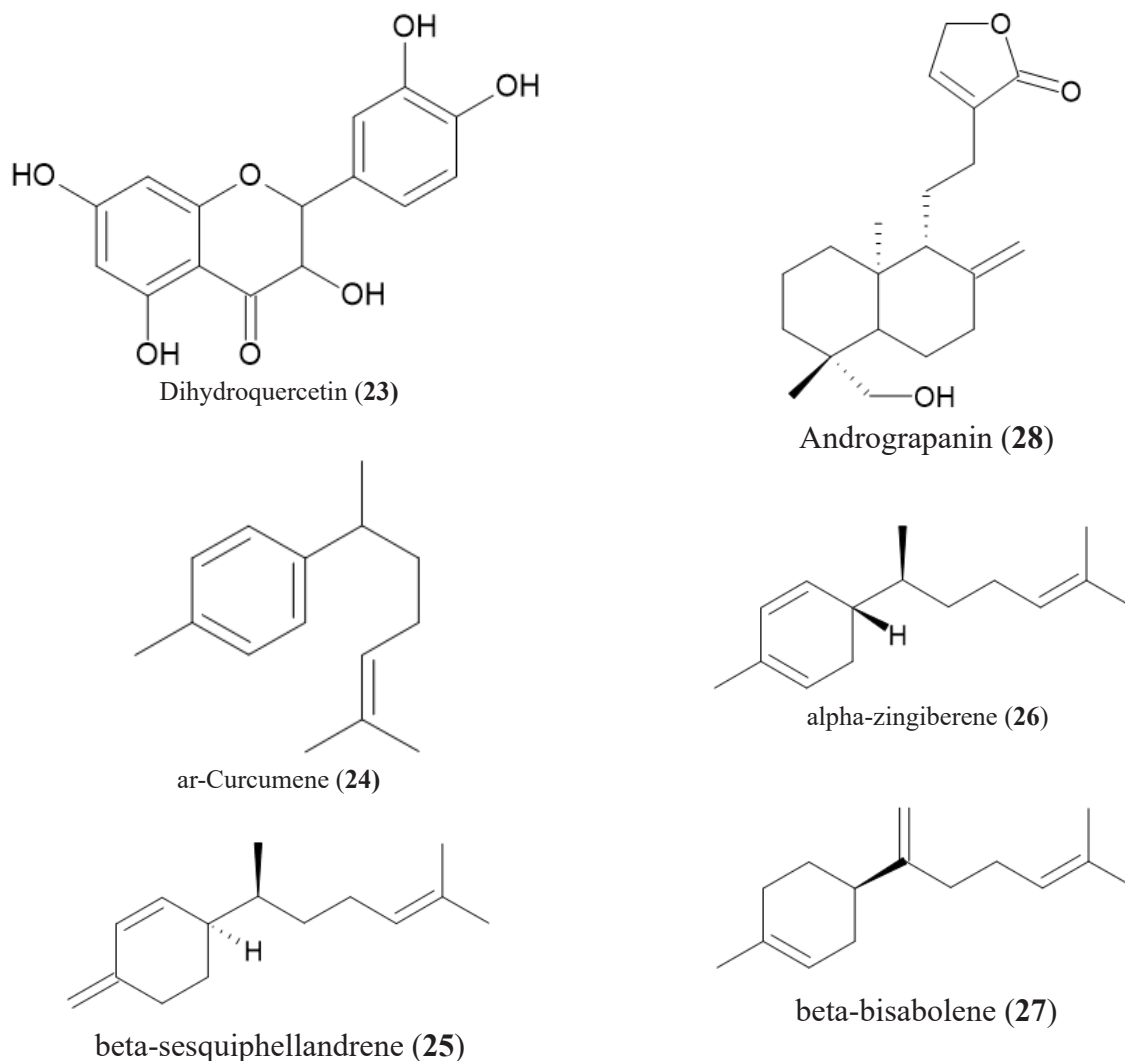


Figure 1. Structures of phytochemicals with potential immunomodulatory and anti-SARS-CoV-2 activities.

Apigenin (2). Apigenin (2) inhibited allergen-induced inflammation and switched immune response toward Th1 cells that produce IL-2 that promotes cell-mediated immunity and production of antibodies that promote phagocytosis (Li *et al.* 2010). Apigenin was active against HSV-1 at half-maximal effective concentration (EC₅₀) of 6.7 mg/L, and selectivity index (SI) of 9.0 and HSV-2 strain 196 (EC₅₀ 9.7 mg/L; SI 6.2), and coxsackievirus (CVB1) (EC₅₀ 0.4 mg/L; SI 7.5). It had the highest antiviral activity against ADV3 (EC₅₀ 11.1 mg/L; SI 5.4), hepatitis B surface antigen (EC₅₀ 7.1 mg/L; SI 2.3), and hepatitis B e antigen (EC₅₀ 12.8 mg/L; SI 1.3) (Chiang *et al.* 2005). Apigenin has been identified in *Ocimum basilicum*.

Alliin (3) and alliin (4). Compounds derived from *Allium sativum* have been reported to decrease the expression of proinflammatory cytokines and to reverse the immunological abnormalities to more acceptable levels

(Donma and Donma 2020). *A. sativum* was suggested as a beneficial preventive measure before being infected with the SARS-CoV-2 virus. It appeared to reverse most immune system dysfunctions observed in patients with COVID-19.

Consistent with this observation, it was shown that alliin (3) increased the production of TNF-alpha and NO in a dose-dependent manner and modulated macrophage function (Haase *et al.* 2012), and inhibited spontaneous and TNF-alpha-induced secretion of proinflammatory cytokines and chemokines from intestinal epithelial cells (Lang *et al.* 2004). It was concluded that alliin is an efficient immunomodulator of macrophage secretory and cellular activities and showed a differential effect on the production of cytokines and cytotoxic molecules (Kang *et al.* 2001). Aliin (4) caused an increase in the production of IL-1beta and TNF-alpha, as well as in the capacity of phagocytosing cells (Salman *et al.* 1999).

In their review of medicinal plants with potential benefit for use in COVID-19 treatment, Silveira and coworkers (2020) selected *A. sativum* to have promising efficacy with a good safety margin.

Lauric acid (5) and monolaurin (6). Lauric acid (5) and monolaurin (6) are released by lipase upon ingestion of coconut oil. Dendritic cells treated with lauric acid showed increased capacity for activation of T cells (Weatherill *et al.* 2005), while monolaurin induced T cell formation in mouse spleen cells (Witcher *et al.* 1996). Two human clinical trials on HIV patients using coconut oil alone and with added monolaurin have shown increases in cluster of differentiation 4 (CD4) and CD8 levels in the blood (Dayrit 2000; Widhiarta 2016). A double-blind clinical trial on 57 mild COVID-19 patients showed the efficacy of virgin coconut oil (VCO) as measured by symptomatic relief and decrease in C-reactive protein (Agdeppa 2021). Further clinical trials are ongoing including the use of VCO by COVID-19 patients with severe symptoms.

Ursolic acid (7). Ursolic acid (7) is a triterpene that has been previously found to have beneficial effects on the immune system. Used as a treatment against the zoonotic parasite *Toxoplasma gondii*, ursolic acid increased the production of the anti-inflammatory mediators IL-10 and IL-12, and reduced the inflammatory cytokines IL-1, IL-6, and TNF- α in infected immune cells (Choi and Lee 2019). Ursolic acid has also been shown to have immunomodulatory effects against autoimmune diseases. It ameliorated the symptoms of the autoimmune condition myasthenia gravis by inhibiting IL-17 and reduced high concentrations of IgG2b antibodies (Xu *et al.* 2015). Ursolic acid is found in *O. basilicum*. Among the pure compounds isolated from *O. basilicum*, ursolic acid was the most active against HSV-1 KOS (Kendell O. Smith) strain (EC₅₀ 6.6 mg/L; SI 15.2), ADV8 (EC₅₀ 4.2 mg/L; SI 23.8), ADV11 (EC₅₀ 24.5 mg/L, SI 4.1), CVB1 (EC₅₀ 0.4 mg/L; SI 251.3), and enterovirus (EV71) (EC₅₀ 0.5 mg/L; SI 201).

Phytochemicals from *Vitex negundo*. *Vitex negundo* contains the monoterpene 1,8-cineol (8) and flavonoid casticin (9), which are able to manage inflammatory responses, in particular from airway inflammation (Liou *et al.* 2018). This may be useful in the management of inflammation in COVID-19. Many severe cases of COVID-19 have patients having difficulty in breathing and later developing pneumonia (Sudhoff *et al.* 2015; Müller *et al.* 2016).

Phytochemicals from *Andrographis paniculata*. *Andrographis paniculata* contains several compounds that have been identified as having both antiviral and immunomodulatory activities – in particular, andrographolide (10), neoandrographolide (11), and

dehydroandrographolide succinic acid monoester (12). In addition, four more compounds have been identified as having either antiviral or immunomodulatory activity. In their review of medicinal plants with potential COVID-19 activity, Silveira and coworkers (2020) selected this plant as having potential benefits and a good safety margin.

Phytochemicals and Philippine Medicinal Plants with Potential Anti-SARS-CoV-2 Activity

The availability of crystallographic structures of target proteins and enzymes of SARS-CoV-2 combined with the large database of known phytochemicals and *in silico* techniques, such as molecular docking and virtual screening, has accelerated the identification of compounds with potential anti-SARS-CoV-2 activity. The compound candidates from *in silico* techniques were combined with results from previous work to identify Philippine medicinal plants with potential anti-SARS-CoV-2 activity. Table 3 lists the potential anti-SARS-CoV-2 phytochemicals in Philippine medicinal plants and the elements that are targeted by these compounds.

Quercetin. The anti-COVID-19 potential of quercetin (1) has been cited in a number of publications and a clinical trial, mainly in combination with other treatments. A number of *in silico* studies suggest that quercetin could inhibit the major druggable targets of SARS-CoV-2, such as 3-chymotrypsin-like protease (3CL^{Pro}) and papain-like protease (PL^{Pro}), with favorable binding energies of –6.25 and –4.62 kcal/mol, respectively (Derosa *et al.* 2020). Evidence has been presented for the synergistic antiviral action of quercetin and vitamin C (Biancatelli *et al.* 2020) and a small case series on 22 COVID-19 patients who successfully used quercetin (800 mg), bromelain (165 mg), zinc acetate (50 mg), and ascorbic acid (1 g) once daily as supplements for 3–5 d to manage SARS-CoV-2 infection (Kamel *et al.* 2020). A clinical trial was undertaken in a research hospital in Turkey on the use of quercetin for prophylaxis and treatment of COVID-19 (Onal and Semerci 2020). In hospitalized COVID-19 patients, quercetin – in combination with vitamin C and bromelain – showed a decrease in CRP, procalcitonin, and ferritin levels, and an increase in platelet and lymphocyte counts (Onal *et al.* 2021).

Allicin and alliin. Allicin (3) and alliin (4) are organosulfur compounds that have been found to be active against various viruses. Modeling studies have shown possible inhibition of the main protease (M^{Pro}) of SARS-CoV-2 through hydrogen bonding with allicin (Khubber *et al.* 2020).

Alliin and allicin are found in readily available and popular plants: *A. sativum* and *A. ascalonicum*, but not in *Allium cepa*.

Lauric acid and monolaurin. Lauric acid (5) and

Table 3. Antiviral phytochemicals in Philippine medicinal plants and the SARS-CoV-2 elements that are targeted.

Target	Phytochemical	Medicinal plant	Reference
SARS-CoV-2 structural elements			
Spike glycoprotein	Piperine (13)	<i>P. nigrum</i>	Maurya <i>et al.</i> (2020)
Lipid membrane	Lauric acid (5), Monolaurin (6)	<i>C. nucifera</i>	Hierholzer and Kabara (1982) Agdeppa <i>et al.</i> (2021)
Enzymes encoded by SARS-CoV-2			
RNA-dependent RNA polymerase (RdRp)	Ursolic acid (7)	<i>O. basilicum</i>	Shady <i>et al.</i> (2021)
3-chymotrypsin-like protease (3CL ^{pro}) or main protease (M ^{pro})	Quercetin (1)	<i>M. oleifera</i> <i>A. ascalonicum</i>	Derosa <i>et al.</i> (2020)
	Allicin (3)	<i>A. sativum</i> <i>A. ascalonicum</i>	Khubber (2020)
	Epigallocatechin gallate (14)	<i>E. hirta</i>	Cherrak <i>et al.</i> (2020)
	Quercetin-3-rhamnoside (15)	<i>E. hirta</i>	Cherrak <i>et al.</i> (2020)
	Piperine (13)	<i>P. nigrum</i>	Gonzalez-Paz <i>et al.</i> (2020)
Papain like protease (PL ^{pro})	Quercetin (1)	<i>M. oleifera</i>	Derosa <i>et al.</i> (2020)
		<i>A. ascalonicum</i>	

monolaurin (**6**) disrupt the membrane of lipid-coated viruses (Sands 1979; Hierholzer and Kabara 1982; Thormar *et al.* 1987). Hierholzer and Kabara showed that monolaurin was able to reduce the infectivity of 14 human RNA and DNA lipid-coated viruses in cell culture by > 99.9% and showed electron microscope images showing disintegration of the virus envelope by monolaurin.

Ursolic acid. An *in vitro* study has shown that ursolic acid (**7**) inhibited the replication of rotavirus with a half-maximal inhibitory concentration (IC₅₀) of 10 microM and suppressed HCV NS5B RdRp activity as a non-competitive inhibitor (Shady *et al.* 2021).

Piperine. Piperine (**13**) is extracted from *Piper nigrum* seed. Piperine has antiviral activity against Hepatitis B virus (Hep G 2.2.15 cell line) and human rhinovirus type 2. Computational studies revealed other possible antiviral activities: 1) docked against methyltransferase and nonstructural protein 3 (NS3) protease-helicase of dengue and viral protein 35 (VP35) interferon inhibitory domain of Ebola virus (Nag and Chowdhury 2020); 2) docked against spike glycoprotein of SARS-CoV-2

(6VXX) (Maurya *et al.* 2020); and 3) docked against viral protease of COVID-19, 3CL^{pro} structure (Gonzalez-Paz *et al.* preprint 2020).

Phytochemicals from *Euphorbia hirta*. *Euphorbia hirta* contains flavonoids that were calculated by *in silico* modeling studies to have potentially strong binding to key proteins of SARS-CoV-2: epigallocatechin gallate (**14**) binding with the SARS-CoV 3CL hydrolase, and quercetin-3-rhamnoside (**15**) to the active site of SARS-CoV-2 M^{pro} (Cherrak *et al.* 2020). Epigallocatechin gallate (**14**) also has well-known immunomodulatory and anti-inflammatory properties (Menegazzi *et al.* 2020).

Phytochemicals from *Euphorbia neriifolia*. *Euphorbia neriifolia* contains compounds that may improve cell survival against coronaviruses. The compounds, 3beta-friedelanol (**16**), friedelin (**17**), and epitaraxerol (**18**) from *E. neriifolia* were compared with actinomycin D as the positive control (0.02 g/mL). The % cell survival or % of viability was compared with a non-treated control at 5 mg/mL. Exposure to 3beta-friedelanol, friedelin, and epitaraxerol improved cell viability resulting in the

multiplication and survival of a larger number of cells with the inhibited virus (Chang *et al.* 2012).

Phytochemicals from *Moringa oleifera*. *M. oleifera* contains the flavonoid quercetin (1). In addition, it also contains compounds that have favorable *in silico* binding energy with the SARS CoV-2 M^{Pro}, in particular: apigenin-7-O-rutinoside (19), mudanpioside J (20), isoquercetin (21), isoquercitrin (22), and dihydroquercetin (23) (Nair and James 2020). In addition, *M. oleifera* contains numerous minerals and vitamins (Ca, Fe, Vitamin C, and carotenoids) that provide nutritional support that is expected to be beneficial in maintaining general health (Meireles *et al.* 2020).

Phytochemicals from *Zingiber officinale*. *Z. officinale* contains four sesquiterpenes with antiviral activity – in particular, ar-curcumene (24), beta-sesquiphellandrene (25), alpha-zingiberene (26), and beta-bisabolene (27). In their review of medicinal plants with potential COVID-19 activity, Silveira and coworkers (2020) selected this plant as having potential benefit, safety, and high acceptability.

Table 4. List of Philippine medicinal plants with potential immunomodulatory and/or anti-SARS-CoV-2 activity and the active constituents that can be used for standardization of the plant extract.

Philippine medicinal plant	Active constituent/s for standardization
<i>A. sativum</i> (bawang)	Alliin (4), allicin (3)
<i>A. ascalonicum</i> (sibuyas tagalog)	Quercetin (1)
<i>A. paniculata</i> (sinta)	Andrographolide (10), neoandrographolide (11), dehydroandrographolide succinic acid monoester (12)
<i>C. nucifera</i> (niyog)	Lauric acid (5)
<i>E. hirta</i> (tawa-tawa)	Epigallocatechin gallate (14), quercetin-3-rhamnoside (15)
<i>E. neriifolia</i> (sorosoro)	3beta-Friedelanol (16), friedelin (17), epitaraxerol (18)
<i>M. oleifera</i> (malunggay)	Quercetin (1)
<i>O. basilicum</i>	Apigenin (2), ursolic acid (7)
<i>V. negundo</i> (lagundi)	1,8-Cineol (8), Casticin (9)
<i>Z. officinale</i> (luya)	Ar-curcumene (24), beta-sesquiphellandrene (25), alpha-zingiberene (26), beta-bisabolene (27)

Table 5. In addition to their antiviral and immunomodulatory property, the selected medicinal plants have beneficial effects against co-morbidities of COVID-19.

Plant	Co-morbidity			
	Cardiovascular disease	Chronic kidney disease	Chronic respiratory disease	Diabetes mellitus
<i>A. sativum</i>	Zeng <i>et al.</i> (2017)	Trejo <i>et al.</i> (2017)	Donma and Donma (2020)	Thomson <i>et al.</i> (2007)
<i>A. paniculata</i>	Islam (2017)	Singh <i>et al.</i> (2009)	Hu <i>et al.</i> (2017)	Komalasari and Harimurti (2015)
<i>C. nucifera</i>	–	Akinnuga <i>et al.</i> (2017)	Vasconcelos <i>et al.</i> (2020)	Akinnuga <i>et al.</i> (2017)
<i>E. hirta</i>	Anandhi <i>et al.</i> (2017)	–	Ekpo and Pretorius (2007)	Kumar <i>et al.</i> (2010)
<i>E. neriifolia</i>	–	–	Salehi <i>et al.</i> (2019)	–
<i>M. oleifera</i>	Mabrouki <i>et al.</i> (2020)	Meireles <i>et al.</i> (2020)	–	–
<i>O. basilicum</i>	Umar <i>et al.</i> (2010)	–	Eftekhar <i>et al.</i> (2019)	Ezeani <i>et al.</i> (2017)
<i>P. nigrum</i>	–	–	Stojanovic-Radic <i>et al.</i> (2019)	Atal <i>et al.</i> (2012)
<i>V. negundo</i>	–	–	Tirpude <i>et al.</i> (2021)	Prasanna Raja <i>et al.</i> (2012)
<i>Z. officinale</i>	–	Hamed <i>et al.</i> (2012)	Çifci <i>et al.</i> (2018)	Shidfar <i>et al.</i> (2015)

RECOMMENDATIONS

This review has revealed the significant potential of medicinal plants found in the Philippines that can be used in the management of COVID-19. The strategy can range from dietary recommendations to strengthen the immune system of people to their use as an adjuvant in the treatment of mild cases of COVID-19. Since these medicinal plants will be used as dried plant material or extracts, it is important that they be standardized using chromatographic or spectroscopic techniques. Table 4 lists the medicinal plants with potential immunomodulatory and/or anti-SARS-CoV-2 activity and the active constituents that can be used for standardization of the plant extract.

Even as vaccines are gradually being made available, these will only work if the immune function is competent. Numerous plants covered in this review show positive benefits in this regard. Given the availability of vaccines and their logistical and practical challenges, readily available and affordable strategies to support such a vaccination program are needed. Medicinal plants may provide the needed support.

Although it is beyond the scope of this review, many of the identified medicinal plants also have beneficial effects against comorbidities that are known risk factors for COVID-19 (Table 5). These are important additional benefits that are not found in many drug candidates.

Given the urgent need for a response to the COVID-19 pandemic, it is recommended that a strategy based on prioritized plant sources be implemented. The plant sources should have a good safety margin, are available and affordable, and contain identified active constituents that can be standardized accordingly. However, it is important that clinical studies be done on standardized plant preparations.

ACKNOWLEDGMENTS

This work was supported by the PITAHC (Philippine Institute of Traditional and Alternative Health Care) of the Department of Health. FMD and AMG are grateful for the research support from the Col. Jaime C. Velasquez Professorial Chair and Senator Gil J. Puyat Professorial Chair, respectively, for the school year 2020–2021.

STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- AGDEPPA IA, NACIS JS, CAPANZANA MV, DAYRIT FM, TANDA KV. 2021. Virgin coconut oil is effective in lowering C-reactive protein levels among suspect and probable cases of COVID-19. *J Funct Foods* 83: 104557.
- AKINNUGAAM, JEJE SO, BAMIDELE O, SUNDAY VE. 2014. Dietary consumption of virgin coconut oil ameliorates lipid profiles in diabetic rats. *Physiol J* 2014: 256236.
- ALTMANN DM, BOYTON RJ, BEALE R. 2021. Immunity to SARS-CoV-2 variants of concern. *Science* 371(6534): 1103–1104.
- ANANDHI, DOSS VA, SOWNDARYA R. 2017. Cardioprotective activity of *Euphorbia hirta* in isoproterenol induced myocardial infarction in rats. *J Med Plants Stud* 5(3): 335–337.
- APPLETON J. 2010. Evaluating the Bioavailability of Isoquercetin. *Nat Med J* 2: 1–6.
- ARANGO D, DIOSA-TORO M, ROJAS-HERNANDEZ LS, COOPERSTONE JL, SCHWARTZ SJ, MO X, JIANG J, SCHMITTGEN TD, DOSEFF AI. 2015. Dietary apigenin reduces LPS-induced expression of miR-155 restoring immune balance during inflammation. *Mol Nutr Food Res* 59(4): 763–772.
- ATAL S, AGRAWAL RP, VYAS S, PHADNIS P, RAI N. 2012. Evaluation of the effect of piperine *per se* on blood glucose level in alloxan-induced diabetic mice. *Acta Pol Pharm* 69(5): 965–969.
- BAE GS, KIM MS, JUNG WS, SEO SW, YUN SW, KIM SG, PARK RK, KIM EC, SONG HJ, PARK SJ. 2010. Inhibition of lipopolysaccharide-induced inflammatory responses by piperine. *Eur J Pharmacol* 642(1–3): 154–162.
- BASAK A, COOPER S, ROBERGE A, BANIK UK, CHRETIEN M, SEIDAH NG. 1999. Inhibition of proprotein convertases-1, -7 and furin by diterpines of *Andrographis paniculata* and their succinoyl esters. *Biochemistry* 338(1): 107–113.
- BIANCATELLI RMLC, BERRILL M, CATRAVAS JD AND MARIK PE. 2020. Quercetin and vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Front Immunol* 11: 1451.
- BOUKHATEM MN, SETZER WN. 2020. Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. *Plants* 9: 800.

- CARDENAS H, ARANGO D, NICHOLAS C, DUARTE S, NUOVO GJ, HE W, VOSS OH, GONZALEZ-MEJIA M, GUTTRIDGE DC, GROTEWOLD E, DOSEFF AI. 2016. Dietary apigenin exerts immunoregulatory activity *in vivo* by reducing NF- κ B activity, halting leukocyte infiltration and restoring normal metabolic function. *Int J Mol Sci* 17(3): 323.
- CHANDRASHEKARA PM, VENKATESH YP. 2016. Immunostimulatory properties of fructans derived from raw garlic (*Allium sativum* L.). *Bioact Carbohydr Diet Fibre* 8(2): 65–70.
- CHANG FR, YEN CT, EI-SHAZLY M, LIN WH, YEN MH, LIN KH, WU YC. 2012. Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of *Euphorbia nerifolia*. *Nat Prod Commun* 7(11): 1415–1417.
- CHERRAK SA, MERZOUK H, MOKHTARI-SOULIMANEN. 2020. Potential bioactive glycosylated flavonoids as SARS-CoV-2 main protease inhibitors: a molecular docking and simulation studies. *PLoS One* 15(10): e0240653.
- CHIANG L-C, NG L-T, CHENG P-W, CHIANG W, LIN C-C. 2005. Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. *Clin Exp Pharmacol Physiol* 32(10): 811–816.
- CHOI WH, LEE IA. 2019. The mechanism of action of ursolic acid as a potential anti-toxoplasmosis agent, and its immunomodulatory effects. *Pathogens* 8: 61.
- ÇİFCİ A, TAYMAN C, YAKUT HI, HALİL H, ÇAKIR E, ÇAKIR U, AYDEMİR S. 2018. Ginger (*Zingiber officinale*) prevents severe damage to the lungs due to hyperoxia and inflammation. *Turk J Med Sci* 48: 892–900.
- DAIKONYA A, KATSUKI S, KITANAKA S. 2004. Antiallergic agents from natural sources 9. Inhibition of nitric oxide production by novel chalcone derivatives from *Mallotus philippinensis* (Euphorbiaceae). *Chem Pharm Bull (Tokyo)* 52(11): 1326–1329.
- DAYRIT CS. 2000. Coconut oil in health and disease: its and monolaurin's potential as cure for HIV/AIDS. XXXVII Cocotech Meeting; Chennai, India; 25 Jul 2000.
- DAYRIT F, GUIDOTE A, MADULID D, SIA I, VILLASEÑOR I, ABELLO M, AGOO EM, ALVERO RG, CALIMAG MM, CHAN M, MACAHIG RA, PAANO AM, QUIROGA MC, TAGLE M, TAN M. 2016. Encyclopedia of medicinal plants of the Philippines, Vol. 2. Philippine Institute of Traditional and Alternative Health Care, Quezon City. 421p.
- DAYRIT F, GUIDOTE A, MADULID D, SIA I, VILLASEÑOR I, ABELLO M, AGOO EM, ALVERO RG, CALIMAG MM, LOQUIAS M, MACAHIG RA, NAYNES R, REYES AL, TAGLE M, TAN M. 2021. Encyclopedia of Medicinal Plants of the Philippines, Vol. 3. Philippine Institute of Traditional and Alternative Health Care, Quezon City. 365p.
- DAYRIT F, MACAHIG RA, MADULID D, AGOO EM, SIA I, ABELLO M, ALVERO RG, CALIMAG MM, QUITAIN AJ, VILLASEÑOR I, NONATO M. 2014. Encyclopedia of common medicinal plants of the Philippines, Vol. 1. Philippine Institute of Traditional and Alternative Health Care, Quezon City. 382p.
- DE LANGE-JACOBS P, SHAIKH-KADERA, THOMAS B, NYAKUDYA TT. 2020. An overview of the potential use of ethno-medicinal plants targeting the renin-angiotensin system in the treatment of hypertension. *Molecules* 25: 2114.
- DEROSA G, MAFFIOLI P, D'ANGELO A, DI PIERRO F. 2020. A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytother Res* 2020: 1–7.
- DONMA MM, DONMA O. 2020. The effects of *Allium sativum* on immunity within the scope of COVID-19 infection. *Med Hypotheses* 144: 109934.
- EFTEKHAR N, MOGHIMI A, ROSHAN NM, SAADAT S, BOSKABADY MH. 2019. Immunomodulatory and anti-inflammatory effects of hydro-ethanolic extract of *Ocimum basilicum* leaves and its effect on lung pathological changes in an ovalbumin-induced rat model of asthma. *BMC Complement Altern Med* 19: 349.
- EKPO OE, PRETORIUS E. 2007. Asthma, *Euphorbia hirta* and its anti-inflammatory properties. *S Afr J Sci* 103: 201–203.
- EZEANI C, EZENYI I, OKOYE T, OKOLI C. 2017. *Ocimum basilicum* extract exhibits antidiabetic effects via inhibition of hepatic glucose mobilization and carbohydrate metabolizing enzymes. *J Intercult Ethnopharmacol.* 6(1): 22–28.
- GARCIA S. 2020. Pandemics and traditional plant-based remedies: a historical-botanical review in the era of COVID19. *Front Plant Sci.* 11: 571042.
- GARCIA-MEDIAVILLA V, CRESPO I, COLLADO PS, ESTELLER A, SÁNCHEZ-CAMPOS S, TUÑÓN MJ, GONZÁLEZ-GALLEGO J. 2007. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang liver cells. *Eur J Pharmacol* 557(2–3): 221–229.
- GINWALA R, MCTISH E, RAMAN C, SINGH N, NAGARKATTI M, NAGARKATTI P, SAGAR D, JAIN P, KHAN ZK. 2016. Apigenin, a natural

- flavonoid, attenuates EAE severity through the modulation of dendritic cell and other immune cell functions. *J Neuroimmune Pharmacol* 11(1): 36–47.
- GONZALEZ-PAZ LA, LOSSADA CA, MONCAYO LS, ROMERO F, PAZ JL, VERA-VILLALOBOS J, PÉREZ AE, SAN-BLAS E, ALVARADO YJ. 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. *Research Square* 2020 Preprint.
- HAASE H, HIEKE N, PLUM LM, GRUHLKE MC, SLUSARENKO AJ, RINK L. 2012. Impact of allicin on macrophage activity. *Food Chem* 134(1): 141–148.
- HÄMÄLÄINEN M, NIEMINEN R, VUORELA P, HEINONEN M, MOILANEN E. 2007. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF- κ B activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF- κ B activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators Inflamm* 45673.
- HAMED MA, ALI SA, EL-RIGAL NS. 2012. Therapeutic potential of ginger against renal injury induced by carbon tetrachloride in rats. *Sci World J* 2012: Article ID 840421.
- HEWLINGS SJ, KALMAN DS. 2017. Curcumin: A review of its effects on human health. *Foods* 2017(6): 92.
- HIERHOLZER JC, KABARA JJ. 1982. *In vitro* effects of monolaurin compounds on enveloped RNA and DNA viruses. *J Food Saf* 4(1): 1–12.
- HU X-Y, WU R-H, LOGUE M, BLONDEL C, LAI LYW, STUART B, FLOWER A, FEI Y-T, MOORE M, SHEPHERD J, LIU JP, LEWITH G. 2017. *Andrographis paniculata* (Chuān Xīn Lian) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis. *PLoS One* 12(8): e0181780.
- INQUIRER.NET. 2020. Vaccine will not be enough to stop pandemic, says WHO chief Retrieved on 16 Nov 2020 from <https://newsinfo.inquirer.net>
- ISLAM MT. 2017. Andrographolide, a new hope in the prevention and treatment of metabolic syndrome. *Front Pharmacol* 8: 571.
- JANTAN I, HAQUE MA, ILANGKOVAN M, ARSHAD L. 2019. An insight into the modulatory effects and mechanisms of action of *Phyllanthus* species and their bioactive metabolites on the immune system. *Front Pharmacol* 10(7): 878.
- JI L-L, WANG Z, DONG F, ZHANG W-B, WANG Z-T. 2005. Andrograpanin, a compound isolated from anti-inflammatory traditional Chinese medicine *Andrographis paniculata*, enhances chemokine SDF-1 α -induced leukocytes chemotaxis. *J Cell Biochem* 95(5): 970–978.
- KAMEL A, ABDELSEED H, ALBALAWI Y, ASLSALAMEEN E, ALMUTAIRI Y, ALKATTAN A. Evaluation of the effect of zinc, quercetin, bromelain and vitamin C on COVID-19 patients. *medRxiv preprint* 24 Dec 2020.
- KANG NS, MOON EY, CHO CG, PYO S. 2001. Immunomodulating effect of garlic component, allicin, on murine peritoneal macrophages. *Nutr Res* 21(4): 617–626.
- KHUBBER S, HASHEMIFESHARAKI R, MOHAMMADI M, GHARIBZAHEDI SMT. 2020. Garlic (*Allium sativum* L.): a potential unique therapeutic food rich in organosulfur and flavonoid compounds to fight with COVID19. *Nutr J* 19: 124.
- KIM S-H, LEE Y-C. 2009. Piperine inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in the ovalbumin-induced asthma model. *J Pharm Pharmacol* 61: 353–359.
- KOMALASARI T, HARIMURTI S. 2015. A review on the anti-diabetic activity of *Andrographis paniculata* (Burm. f.) Nees based *in vivo* study. *Int J Public Health Sci* 4(4): 256–263.
- KUMAR S, RASHMI, KUMAR D. 2010. Evaluation of antidiabetic activity of *Euphorbia hirta* Linn. in streptozotocin induced diabetic mice. *Indian J Nat Prod Resour* 1(2): 200–203.
- KUMAR VP, PRASHANTH KVH, VENKATESH YP. 2015. Structural analyses and immunomodulatory properties of fructo-oligosaccharides from onion (*Allium cepa*). *Carbohydr Polym* 117: 115–122.
- LANG A, LAHAV M, SAKHNINI E, BARSHACK I, FIDDER HH, AVIDAN B, BARDAN E, HERSHKOVIZ R, BAR-MEIR S, CHOWERS Y. 2004. Allicin inhibits spontaneous and TNF- α induced secretion of proinflammatory cytokines and chemokines from intestinal epithelial cells. *Clin Nutr* 23(5): 1199–1208.
- LEE EJ, JI GE, SUNG MK. 2010. Quercetin and kaempferol suppress immunoglobulin E-mediated allergic inflammation in RBL-2H3 and Caco-2 cells. *Inflamm Res* 59(10): 847–854.

- LI RR, PANG LL, DU Q, SHI Y, DAI WJ, YIN KS. 2010. Apigenin inhibits allergen-induced airway inflammation and switches immune response in a murine model of asthma. *Immunopharmacol Immunotoxicol* 32(3): 364–370.
- LIU C-J, CHENG C-Y, YEH K-W, WU Y-H, HUANG W-C. 2018. Protective effects of casticin from *Vitex trifolia* alleviate eosinophilic airway inflammation and oxidative stress in a murine asthma model. *Front Pharmacol* 9: 635.
- MA S, XU C, LIU S, SUN X, LI R, MAO M, FENG S, WANG X. 2021. Efficacy and safety of systematic corticosteroids among severe COVID-19 patients: a systematic review and meta-analysis of randomized controlled trials. *Sig Transduct Target Ther* 6: 83.
- MABROUKI L, RJEIBI I, TALEB J, ZOURGUI L. 2020. cardiac ameliorative effect of *Moringa oleifera* leaf extract in high-fat diet-induced obesity in rat model. *BioMed Res Int* 2020: Article ID 6583603.
- MANOHARAN Y, HARIDAS V, VASANTHAKUMAR KC, MUTHU S, THAVOORULLAH FF, SHETTY P. 2020. Curcumin: a wonder drug as a preventive measure for COVID-19 management. *Indian J Clin Biochem* 35(3): 373–375.
- MAURYA VK, KUMAR S, PRASAD AK, BHATT MLB, SAXENA SK. 2020. Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor. *Virusdisease* 31(2): 179–193.
- MEIRELES D, GOMES J, LOPES L, HINZMANN M, MACHADO J. 2020. A review of properties, nutritional and pharmaceutical applications of *Moringa oleifera*: Integrative approach on conventional and traditional Asian medicine. *Adv Tradit Med* 20: 495–515.
- MENEGAZZI M, DI PAOLA R, CAMPAGNARI R, BERTOLDI M, CRUPI R, CUZZOCREA S. 2020. Protective effect of epigallocatechin-3-gallate (EGCG) in diseases with uncontrolled immune activation: could such a scenario be helpful to counteract COVID-19? *Int J Mol Sci* 21: 5171.
- MULCHANDANI R, LYNGDOH T, KAKKARAK. 2021. Deciphering the COVID-19 cytokine storm: Systematic review and meta-analysis. *Eur J Clin Investig* 51(1): 1–21.
- MULLARD A. 2020. How COVID vaccines are being divvied up around the world. *Nature News*. Retrieved on 30 Nov 2020 from <https://www.nature.com/articles/d41586-020-03370-6>
- MÜLLER J, GREINER JF, ZEUNER M, BROTZMANN V, SCHÄFERMANN J, WIETERS F, WIDERA D, SUDHOFF H, KALTSCHMIDT B, KALTSCHMIDT C. 2016. 1,8-Cineole potentiates IRF3-mediated antiviral response in human stem cells and in an *ex vivo* model of rhinosinusitis. *Clin Sci* 130: 1339–1352.
- NAGA, CHOWDHURY RR. 2020. Piperine, an alkaloid of black pepper seeds can effectively inhibit the antiviral enzymes of dengue and ebola viruses, an *in silico* molecular docking study. *Virusdisease* 31: 308–315.
- NAIR AD, JAMES TJ. Computational screening of phytocompounds from *Moringa oleifera* leaf as potential inhibitors of SARS-CoV-2 M^{Pro}. *Research Square preprint* 2020.
- ONAL H, SEMERCI SY. 2020. Effect of quercetin on prophylaxis and treatment of COVID-19. Retrieved on 20 Feb 2021 from <https://clinicaltrials.gov/ct2/show/NCT04377789>
- ONAL H, ARSLAN B, ERGUN NU, TOPUZ S, SEMERCI SY, KURNAZ M, BOLU Y, BOZKURT M, SUNER N, KOCATAS A. 2021. Treatment of COVID-19 Patients with Quercetin: A Prospective, Single-centre, Randomized, Controlled Trial. Preprint from Authorea, 19 Jan 2021. DOI: 10.22541/au.161106492.28349832/v1
- PANG XF, ZHANG LH, BAI F, WANG NP, GARNER RE, MCKALLIP RJ, ZHAO ZQ. 2015. Attenuation of myocardial fibrosis with curcumin is mediated by modulating expression of angiotensin II AT1/AT2 receptors and ACE2 in rats. *Drug Des Dev Ther* (9): 6043–6054.
- PRASANNARAJAP, SIVAKUMAR V, RIYAZULLAH MS. 2012. Antidiabetic potential of aqueous and ethanol leaf extracts of *Vitex negundo*. *Int J Pharmacogn Phytochem Res* 4(2): 38–40
- SALEHI B, IRITI M, VITALINI S, ANTOLAK H, EWELINA PAWLIKOWSKA E, KREGIEL D, SHARIFI-RAD J, OYELEYE SI *et al.* 2019. *Euphorbia*-derived natural products with potential for use in health maintenance. *Biomolecules* 9: 337.
- SALMAN H, BERGMAN M, BESSLER H, PUNSKY I, DJALDETTI M. 1999. Effect of a garlic derivative (alliin) on peripheral blood cell immune responses. *Int J Immunopharmacol* 21(9): 589–597.
- SANDS JA, LANDIN P, AUPERIN D, REINHARDT A. 1979. Enveloped virus inactivation by fatty acid derivatives. *Antimicrob Agents Chemother* 15(1): 27–31.
- SHADY NH, YOUSSEF KA, SAYED AM, BELBAHRI L, OSZAKO T, HASSAN HM, ABDELMOHSEN UR. 2021. Sterols and triterpenes: antiviral potential supported by *in silico* analysis. *Plants* 10: 41.

- SHIDFAR F, RAJAB A, RAHIDEH T, KHANDOUZI N, HOSSEINI S, SHAHRZAD SHIDFAR S. 2015. The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J Complement Integr Med* 12(2): 165–170.
- SILVEIRA D, PRIETO-GARCIA JM, BOYLAN F, ESTRADA O, FONSECA-BAZZO YM, JAMAL CM, MAGALHÃES PO, PEREIRA EO, TOMCZYK M AND HEINRICH M. 2020. COVID-19: is there evidence for the use of herbal medicines as adjuvant symptomatic therapy? *Front Pharmacol* 11: 581840.
- SINGH P, SRIVASTAVA MM, KHEMANI LD. 2009. Renoprotective effects of *Andrographis paniculata* (Burm.f.) Nees in rats. *Ups J Med Sci* 114(3): 136–139.
- STOJANOVIC-RADIC Z, PEJCIC M, DIMITRIJEVIC M, ALEKSIC A, KUMAR NVA, SALEHI B, CHO WC, SHARIFI-RAD J. 2019. Piperine – a major principle of black pepper: a review of its bioactivity and studies. *Appl Sci* 2019(9): 4270.
- SUDHOFF H, KLENKE C, GREINER JFW, MULLER J, BROTZMANN V, EBMEYER J *et al.* 2015. 1,8-Cineol reduces mucus-production in a novel human *ex vivo* model of late rhinosinusitis. *PLoS One* 10(7): e0133040.
- THOMSON M, AL-AMIN ZM, AL-QATTAN KK, SHABAN LH, ALI M. 2007. Anti-diabetic and hypolipidaemic properties of garlic (*Allium sativum*) in streptozotocin-induced diabetic rats. *Int J Diabetes Metab* 15: 108–115.
- THORMAR H, ISAACS CE, BROWN HR, BARSHATZKY MR, PESSOLANO T. 1987. Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides. *Antimicrob Agents Chemother* 31(1): 27–31.
- TIRPUDE NV, SHARMA A, JOSHI R, KUMARI M, ACHARYA V. 2021. *Vitex negundo* Linn. extract alleviates inflammatory aggravation and lung injury by modulating AMPK/PI3K/Akt/p38-NF-κB and TGF-β/Smad/Bcl2/caspase/LC3 cascade and macrophages activation in murine model of OVA-LPS induced allergic asthma. *J Ethnopharmacol* 271: 113894.
- TREJO EMAG, BUENDÍA ASA, REYES OS, ARROYO FEG, GARCÍA RA, MENDOZA MLL, TAPIA E, LOZADA LGS, ALONSO HO. 2017. Beneficial effects of allicin in chronic kidney disease are comparable to losartan. *Int J Mol Sci* 2017(18): 1980.
- UMAR A, IMAM G, YIMIN W, KERIM P, TOHTI I, BERKE B, MOORE N. 2010. Antihypertensive effects of *Ocimum basilicum* L. (OBL) on blood pressure in renovascular hypertensive rats. *Hypertens Res* 33: 727–730.
- VAIDYA A, RATHOD M. 2014. An *in vitro* study of the immunomodulatory effects of *Piper nigrum* (black pepper) and *Elettaria cardamomum* (cardamom) extracts using a murine macrophage cell line. *Am Int J Res Formal Appl Nat Sci* 8(1): 18–27.
- VASCONCELOS LHC, SILVA MCC, COSTA AC, DE OLIVEIRA GA, DE SOUZA ILL, RIGHETTI RF, QUEIROGA FR *et al.* 2020. Virgin coconut oil supplementation prevents airway hyperreactivity of guinea pigs with chronic allergic lung inflammation by antioxidant mechanism. *Oxid Med Cell Longev* 2020: 5148503.
- WANG W, WANG J, DONG SF, LIU C-H, ITALIANI, P, SUN S-H, XU J, BORASCHI D, MA S-P, QU D. 2010. Immunomodulatory activity of andrographolide on macrophage activation and specific antibody response. *Acta Pharmacol Sin* 31(2): 191–201.
- WEATHERILL AR, LEE JY, ZHAO L, LEMAY DG, YOUN HS, HWANG DH. 2005. Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. *J Immunol* 174: 5390–5397.
- WIDHIARTA K. 2016. Virgin coconut oil for HIV-positive people. *Cord* 32(1): 50–57.
- WITCHER KJ, NOVICK RP, SCHLIEVERT PM. 1996. Modulation of immune cell proliferation by glycerol monolaurate. *Clin Diagn Lab Immunol* 3(1): 10–13.
- [WHO] World Health Organization. 2020. Strategy and planning. Retrieved on 28 Dec 2020 from <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/strategies-and-plans>
- XU H, ZHANG M, LI X-L, LI H, YUE L-T, ZHANG X-X, WANG C-C, WANG S, DUAN R-S. 2015. Low and high doses of ursolic acid ameliorate experimental autoimmune myasthenia gravis through different pathways. *J Neuroimmunol* 281: 61–67.
- ZENG Y, LI Y, YANG J, PU X, DU J, YANG X, YANG T, YANG S. 2017. Therapeutic role of functional components in alliums for preventive chronic disease in human being. *Evid-Based Compl Alt Med* 2017: 9402849.