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

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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

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

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

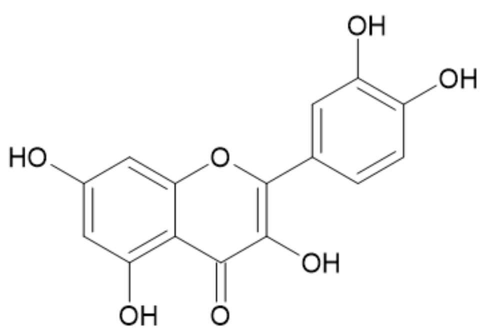
Herbal immunomodulators are plants that can stimulate or suppress the innate or adaptive responses of the immune system. Medicinal plants are multi-component agents that are able to modulate the complex immune system to defend itself against viral infections rather than directly act against the virus. 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.

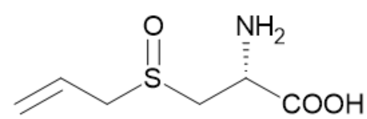
Quercetin (1). The immunomodulatory action of quercetin (**1**) was shown in the following activities: 1) inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 1 (STAT-1) (Hämäläinen *et al.* 2007); 2) modulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and C-reactive protein (CRP), and down-regulation of NF-κB 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*.

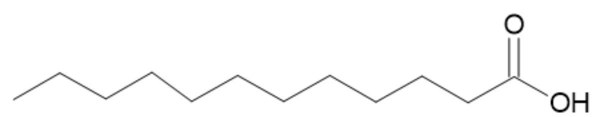
Table 2. Phytochemicals and plants with immunomodulatory activity.

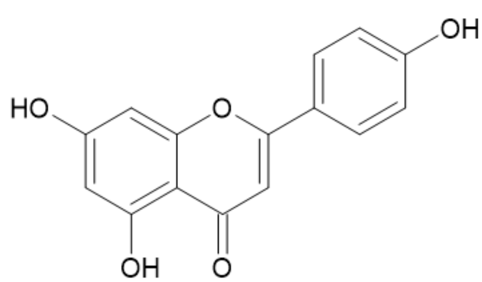
Phytochemical	Immunomodulatory activity	Plant species	Reference/s
Flavonoids and their glycosides			
Quercetin (**1**)	• Inhibition or modulation of COX-2, IL-6, IL-1b, NF-κB, iNOS, CRP and STAT-1 • Suppression of IgE-mediated allergic inflammation	*A. ascalonicum*	Hämäläinen *et al.* (2007), Garcia-Mediavilla *et al.* (2007), Lee *et al.* (2010), Daikonya *et al.* (2004), Jantan *et al.* (2019)
Apigenin (**2**)	• 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	*O. basilicum*	Li *et al.* (2010), Arango *et al.* (2015), Cardenas *et al.* (2016), Ginwala *et al.* (2016)
Casticin (**9**)	• Alleviates eosinophilic airway inflammation and oxidative stress	*V. negundo*	Liou *et al.* (2018)
Epigallocatechin gallate (**14**)	• Inhibits STAT and NF-κB transcription factors	*E. hirta*	Menegazzi *et al.* (2020)
Alkaloids			
Piperine (**13**)	• 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-b gene expression	*P. nigrum*	Bae *et al.* (2010), Kim and Lee (2009), Vaidya and Rathod (2014)
Terpenoids			
1,8-Cineol (**8**)	• Amplifies immune response dependent on the IRF3/IFNβ pathway	*V. negundo*	Müller *et al.* (2016)
Andrographolide (**10**)	• 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	*A. paniculata*	Basak *et al.* (1999), Wang *et al.* (2010)
Neoandrographolide (**11**)	• Inhibition of furin, PC1, PC7	*A. paniculata*	Basak *et al.* (1999)
Dehydroandrographolide succinic acid monoester (**12**)	• Inhibition of furin, PC1, PC7	*A. paniculata*	Basak *et al.* (1999)
Andrograpanin (**28**)	• Enhancement of SDF-1-induced chemotaxis • Reduction of SDF-1α-induced CXCR4 internalization	*A. paniculata*	Ji *et al.* (2005)

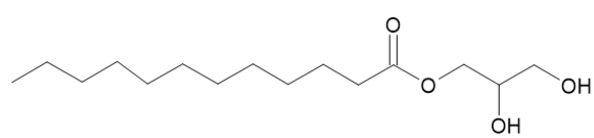
Ursolic acid (**7**)	• Increase IL-10 and IL-12 • Reduction of IL-1, IL-6, IL-17, TNF-□ IL-17 and IgG2b	*O. basilicum*	Choi and Lee (2019) Xu *et al.* (2015) Chiang *et al.* (2005)
Sulfur-containing compounds			
Alliin (**4**)	• Immunomodulatory effect on peripheral blood and intestinal epithelial cells and macrophage secretory and cellular activity • Suppression of iNOS expression	*A. ascalonicum* *A. sativum*	Salman *et al.* (1999), Kang *et al.* (2001), Lang *et al.* (2004), Haase *et al.* (2012)
Allicin (**3**)	• Immunomodulatory effect on peripheral blood and intestinal epithelial cells and macrophage secretory and cellular activity • Suppression of iNOS expression	*A. ascalonicum* *A. sativum*	Salman *et al.* (1999), Kang *et al.* (2001), Lang *et al.* (2004), Haase *et al.* (2012)
Fatty acids			
Lauric acid (**5**)	• Upregulation of immune system	*C. nucifera*	Weatherill *et al.* (2005)
Monolaurin (**6**)	• Induction of proliferation of T-cells	*C. nucifera*	Witcher *et al.* (1996)
Polysaccharides and proteins			
Fructans	• Immunostimulation of murine lymphocytes and macrophages	*A. sativum*	Chandrashekara and Venkatesh (2016)
Fructo-oligosaccharides	• Stimulation of mouse lymphocytes and macrophages • Increased NO production	*A. cepa*	Kumar *et al.* (2015)

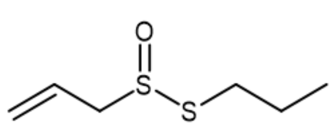

Quercetin (**1**)


Alliin (**4**)


Lauric acid (**5**)


Apigenin (**2**)


Monolaurin (**6**)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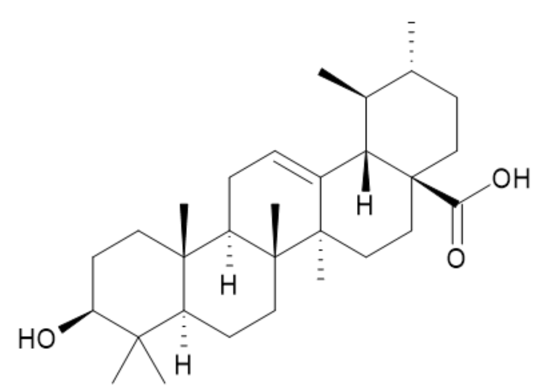
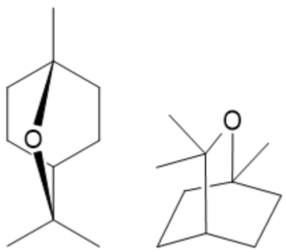
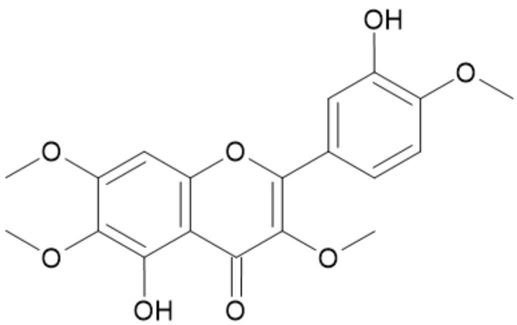
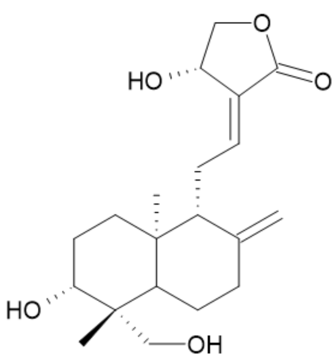
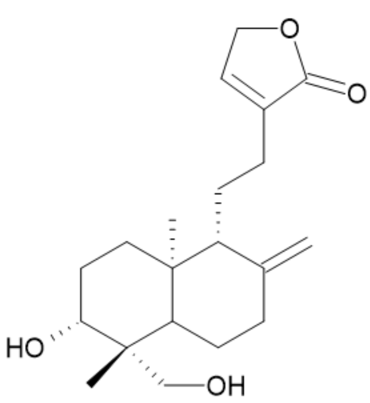
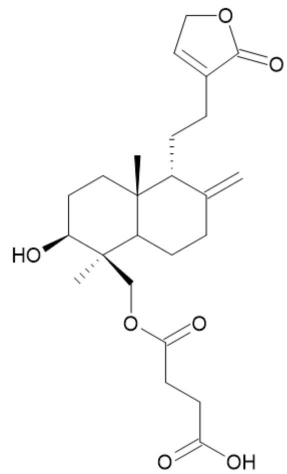

Ursolic acid (**7**)

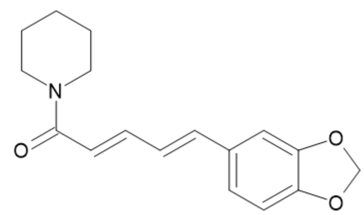

1,8-Cineol (**8**)

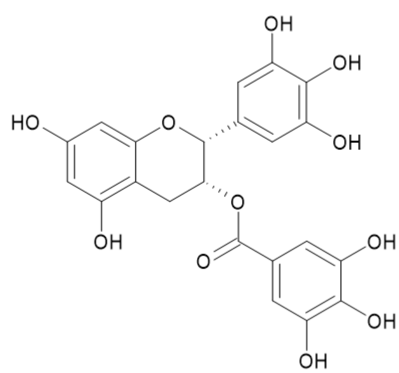

Casticin (**9**)

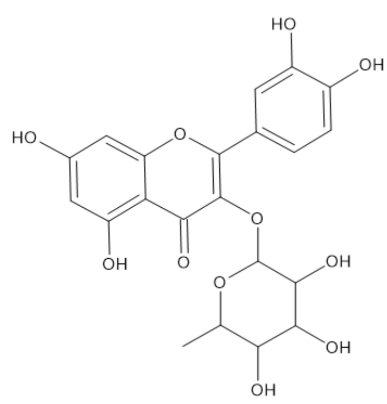

Andrographolide (**10**)

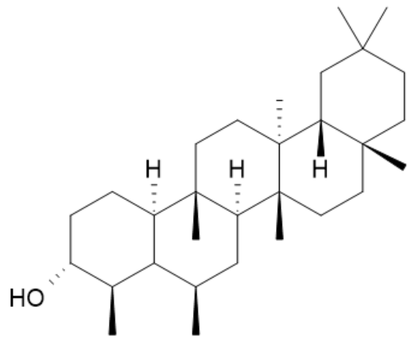

Neoandrographolide (**11**)


Dehydroandrographolide succinic acid monoester (**12**)

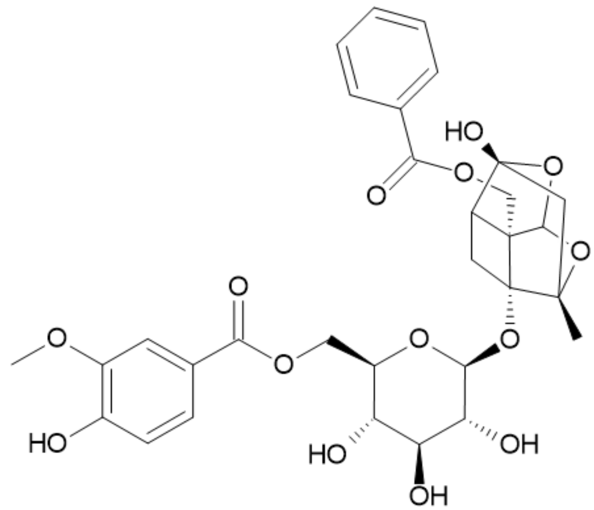

Piperine (**13**)


Epigallocatechin gallate (**14**)

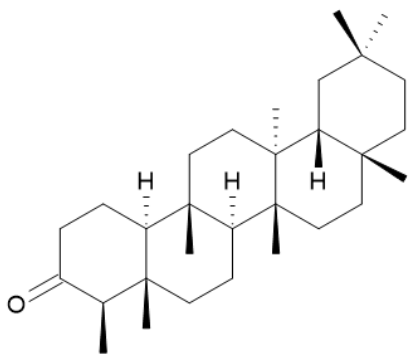

Quercetin-3-rhamnoside (**15**)



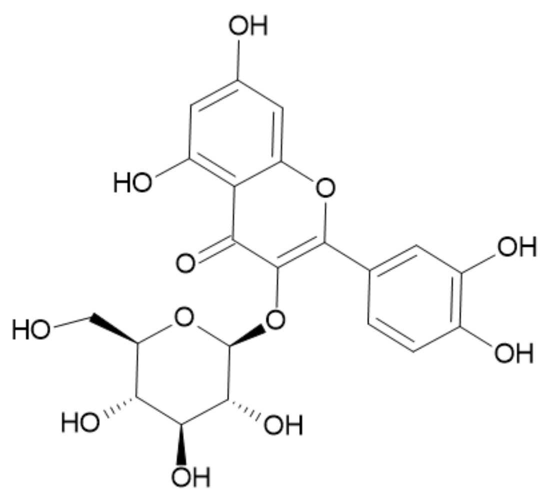
3beta-Friedelanol (**16**)



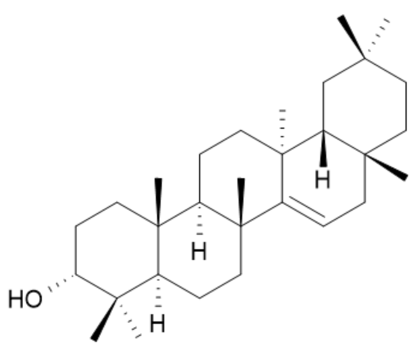
Mudanpioside J (**20**)



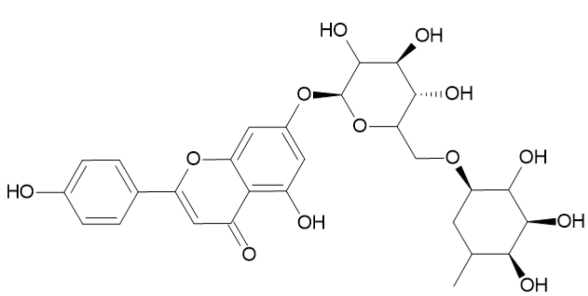
Friedelin (**17**)



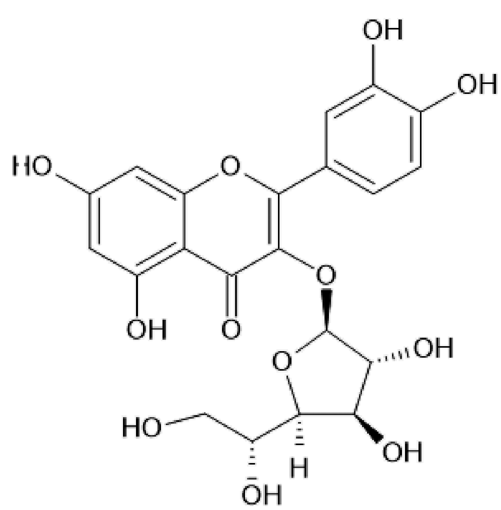
Isoquercetin (**21**)



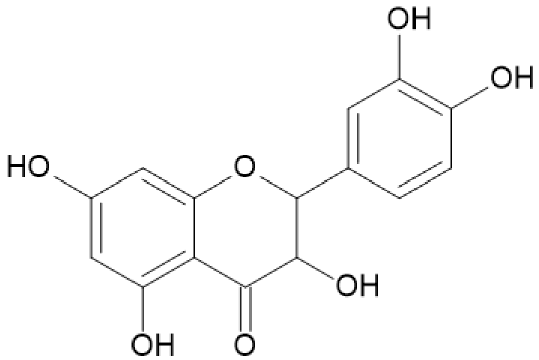
Epitaxerol (**18**)



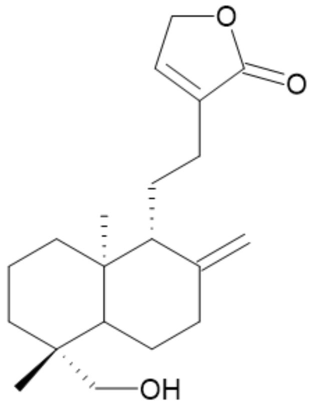
Apigenin-7-O-rutinoside (**19**)



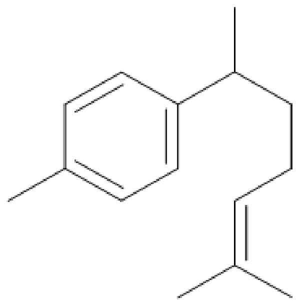
Isoquercitrin (**22**)

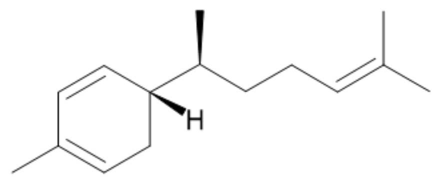


Dihydroquercetin (**23**)

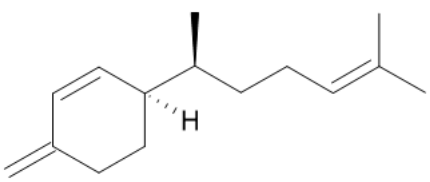


Andrograpanin (**28**)


ar-Curcumene (**24**)



alpha-zingiberene (**26**)



beta-sesquiphellandrene (**25**)

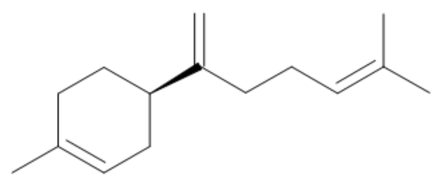

beta-bisabolene (**27**)

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*.

Allicin (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 allicin (**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 allicin 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 phagocyting 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. Dendric 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-alpha 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**)	*P. nigrum*	Maurya *et al.* (2020)
Lipid membrane	Lauric acid (**5**), Monolaurin (**6**)	*C. nucifera*	Hierholzer and Kabara (1982) Agdeppa *et al*. (2021)
Enzymes encoded by SARS-CoV-2			
RNA-dependent RNA polymerase (RdRp)	Ursolic acid (**7**)	*O. basilicum*	Shady *et al.* (2021)
3-chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro})	Quercetin (**1**)	*M. oleifera* *A. ascalonicum*	Derosa *et al.* (2020)
	Allicin (**3**)	*A. sativum* *A. ascalonicum*	Khubber (2020)
	Epigallocatechin gallate (**14**)	*E. hirta*	Cherrak *et al.* (2020)
	Quercetin-3-rhamnoside (**15**)	*E. hirta*	Cherrak *et al.* (2020)
	Piperine (**13**)	*P. nigrum*	Gonzalez-Paz *et al.* (2020)
	Apigenin-7-O-rutinoside (**19**), Mudanpioside J (**20**), Isoquercetin (**21**), Isoquercitrin (**22**), Dihydroquercetin (**23**)	*M. oleifera*	Nair and James (2020)
Papain like protease (PL^{pro})	Quercetin (**1**)	*M. oleifera* *A. ascalonicum*	Derosa *et al.* (2020)

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 (IC_{50}) 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
A. sativum (bawang)	Alliin (**4**), allicin (**3**)
A. ascalonicum (sibuyas tagalog)	Quercetin (**1**)
A. paniculata (sinta)	Andrographolide (**10**), neoandrographolide (**11**), dehydroandrographolide succinic acid monoester (**12**)
C. nucifera (niyog)	Lauric acid (**5**)
E. hirta (tawa-tawa)	Epigallocatechin gallate (**14**), quercetin-3-rhamnoside (**15**)
E. neriifolia (sorosoro)	3beta-Friedelanol (**16**), friedelin (**17**), epitaraxerol (**18**)
M. oleifera (malunggay)	Quercetin (**1**)
O. basilicum	Apigenin (**2**), ursolic acid (**7**)
V. negundo (lagundi)	1,8-Cineol (**8**), Casticin (**9**)
Z. officinale (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
A. sativum	Zeng *et al*. (2017)	Trejo *et al*. (2017)	Donma and Donma (2020)	Thomson *et al*. (2007)
A. paniculata	Islam (2017)	Singh *et al*. (2009)	Hu *et al*. (2017)	Komalasari and Harimurti (2015)
C. nucifera	–	Akinnuga *et al*. (2017)	Vasconcelos *et al*. (2020)	Akinnuga *et al*. (2017)
E. hirta	Anandhi *et al*. (2017)	–	Ekpo and Pretorius (2007)	Kumar *et al*. (2010)
E. neriifolia	–	–	Salehi *et al*. (2019)	–
M. oleifera	Mabrouki *et al*. (2020)	Meireles *et al*. (2020)	–	–
O. basilicum	Umar *et al*. (2010)	–	Eftekhar *et al*. (2019)	Ezeani *et al*. (2017)
P. nigrum	–	–	Stojanovic-Radic *et al*. (2019)	Atal *et al*. (2012)
V. negundo	–	–	Tirpude *et al*. (2021)	Prasanna Raja *et al*. (2012)
Z. officinale	–	Hamed *et al*. (2012)	Çifci *et al*. (2018)	Shidfar *et al*. (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.

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STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflict of interest.

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