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Therapy Against COVID-19: Medicinal Plant Extracts Can Be a Solution

Bouopda Tamo Sylvain Parfait[1, *], Mundene-Timothee Junior Lawrence[2]

[1]Department of Biochemistry, University of Yaounde I, Yaounde, Cameroon

[2]Department of Industrial Chemistry, University of Douala, Douala, Cameroon

Email address:

sylvainbouopda@gmail.com (Bouopda Tamo Sylvain Parfait)

[*]Corresponding author

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Abstract: Coronavirus disease 2019 (COVID-19) was declared by the World Health Organization (WHO) as a pandemic on March 11, 2020. Despite the development of anti-COVID-19 vaccine, the disease continues to kill thousands of people, mainly due to a lack of sufficient doses for all populations and to the prioritization of populations to be vaccinated. According to epidemiological data from April 06, 2022, the COVID-19 pandemic has already killed more than 6,184,299 people around the world with nearly 494,286,073confirmed cases. To date, no antiviral drug has been officially approved to fight this pandemic. Medical professionals and researchers all over the globe are in pursuit for the discovery therapies against this disease. One of the strategies is the use of medicinal plants. Indeed, plant extracts can inhibit viral growth and their effectiveness has been demonstrated on many viruses encountered in human pathology including SARS-CoV-1, poliovirus, varicella-zoster virus, HIV, human papillomavirus, HSV-1, HSV-2, influenza virus, cytomegalovirus and many others. Besides, it has been shown that plant extracts can regulate immune system and make the body able to prevent the establishment of viral infection or to fight against its deleterious effects. The exploration of plant extracts with anti-viral and immunostimulatory properties could be exploitable in the development of drug against COVID-19. This review promotes medicinal plant extracts as potential anti-COVID-19 drugs.

Keywords: COVID-19, Drug Research, Medicinal Plants

1. Introduction

Coronavirus disease 2019 (COVID-19) was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020. The disease gradually spread across the world and was subsequently declared a pandemic on March 11, 2020. According to epidemiological data from January 25, 2021, the COVID-19 pandemic has already killed more than 6,184,299 people around the world with nearly 494,286,073 confirmed cases. It is an infectious disease with severe acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new type of coronavirus first discovered in the city of Wuhan, China, at the end of December 2019. The SARS-CoV-2 infects the lower respiratory system induce a severe pneumonia. It can develop other disorders in the digestive system, heart, liver, kidneys, and nervous system, causing multi-organ failure. COVID-19-infected pneumonia is characterized by flu-like symptoms including fever, cough, and severe acute respiratory distress syndrome [1-4].

Since the outbreak of COVID-19, there has been no specific antiviral medication for treatment of the infection where supportive care and prevention of complications is the current management strategy. Despite the approval of the anti-COVID-19 vaccine by WHO, the disease continues to kill thousands of people, mainly due to a lack of sufficient doses for all populations and to the prioritization of

populations to be vaccinated. No antiviral drug is available to fight COVID-19 although there are many efforts around the world to develop one as quickly as possible. Enormous efforts have been made to protect, alleviate and cure the disease, though no specific treatment has been approved. Many countries infected by this virus, have done various proceedings such as distraction of traveling, isolation of patients and continuous medical care to reduce and prevent coronavirus spreading. The lack of treatment options for COVID-19 has led to many attempts to find alternative options to prevent the transmission of the disease or to alleviate the progression of the infection, including focusing more on preventive measures and the use of natural products and herbal extracts to increase immunity and decrease the probability of getting infected. Historically, the use of natural products was known to be the only treatment method against many infections and diseases. Medicinal plant species can provide a solution as a source of natural antiviral compounds by the accumulation of secondary metabolites and lectins as well as acting as a platform to express the viral immunogenic proteins [6-10].

The elderly patients or people who have existing chronic medical conditions such as heart failure, cancer, type 2 diabetes, severe obesity, chronic kidney disease, sickle cell disease, weakened immune system from solid organ transplants have a higher risk of serious illness from COVID-19. This can be due to the lower immune system. In order to combat SARS-CoV-2, many drug and vaccine development studies at experimental and clinical levels are currently conducted worldwide. Some traditional herbal medicines prevented SARS-CoV-2 infection of healthy persons and improved the health state of patients with mild or severe symptoms. Herbal drugs can effectively relieve symptoms, such as fever, cough, and fatigue, and reduce the probability of patients developing severe conditions. The contribution of traditional medicine in the management of Covid-19 may complement healthcare prevention and medical care services [14]. In China for example, the National Health Commission of China had recommended to use Chinese herbal medicine like QingfeiPaidu Decoction (QPD) to treat COVID-19 patients. Medicinal plants such as *Artemisia annua* are being considered by WHO as possible treatments for COVID-19 and should be tested for efficacy and adverse side effects. Furthermore, medicinal herbs have become an essential purpose to determine, isolate and purify the natural compounds for treatment of viral diseases. Most recent in silico studies revealed that natural compounds like myricitrin, methyl rosmarinate, calceolarioside B, myricetin3-O-β-D-glucopyranoside, licoleafol, and amaranthin could be potential leads to develop novel anti-SARS-CoV-2 drugs. WHO recognises that traditional, complementary and alternative medicine has many benefits. Medicinal plants have great prospect in the ultimate search for the cure against the dreaded coronavirus [2, 11-20].

The traditional medicinal system based on herbal therapies has always played a pivotal role in the health systems [20]. This review presents herbal remedies as a potential drug solution against COVID-19.

2. Plants with Antiviral and Immunomodulatory Properties

To date, medical professionals and researchers all over the globe are in pursuit for the discovery of prophylactic or anaphylactic remedy against COVID-19. One of the strategies employed is the exploration of traditional medicine as a potential source of an effective anti-COVID-19 drug. Plant extracts have long been used in the treatment of viral infections and their efficacy has been the subject of numerous scientific publications. Indeed, plant extracts can via several mechanisms inhibit viral growth and their effectiveness has been demonstrated on many viruses encountered in human pathology including SARS-CoV-1, poliovirus, varicella-zoster virus, HIV, human papillomavirus, HSV-1, HSV-2, influenza virus, cytomegalovirus and many others. By their antiviral properties, these plant extracts could also act on SARS-CoV-2, the viral agent responsible for COVID-19. It has also been shown that plant extracts can act at several levels of the body and regulate various mechanisms including the expression of the immune system. As with any other microbial infection, the immune system plays an important role in controlling COVID-19 infection. The immunocompromised are the most at risk. By boosting the immune system, plant extracts with immunostimulating properties make the body able to prevent the establishment of infection or to fight against its deleterious effects. Plant extracts can enhance immune reactions via the stimulation of non-specific systems, such as granulocytes, macrophages, complement, certain T-lymphocytes and various effector substances. The selection of plant extracts proven to be safe and possessing anti-SARS-CoV-2 and immunostimulatory properties could be exploitable in the development of an effective anti-COVID-19 drug. Plant extracts provide a rich resource for novel antiviral drug development and can improve the immunity against virsuses or other pathogen. In several countries around the world, drug formulations made from medicinal plants are used to prevent and fight COVID-19. This is the case with Qing FeiPai Du Tang (QFPDT), a Chinese medicine formula which has been reported to be efficacious on COVID-19 in China. The main herbs of QFPDT have been shown to have antiviral effects via different mechanisms. It can direct effect on virus replication and autophagy, and promotes the human defense system via T and B cell functions [21-23]. Table 1 below presents some plants with antiviral which can also act on immune system.

Table 1. *Plants with antiviral and immunomodulatory properties.*

Medicinal plants/family	Susceptible viral species	Effect on the immune system	References
Acacia nilotica (L.) Willd. ex Delile / Fabaceae	Influenza A virus, hepatitis C Virus	Modulates splenocyte proliferation and IL-10 secretion	[24-26]
Aloe vera (L.) Burm. F. / Aloeaceae	Coronavirus SARS-CoV-1, poliovirus, varicella-zoster virus, HIV, human papillomavirus, haemorrhagic viral rhobdavirus septicaemia, Herpes simplex virus type 1, Herpes simplex virus type 2, influenza virus, cytomegalovirus	Stimulates humoral immunity, activates macrophages and cytokine release, stimulates cellular immune response and prevents immune suppression, stimulates antibody production	[27-33]
Andrographispaniculata (Burm. f.) Wall. ex Nees / Acanthaceae	HIV, flaviviruses, pestiviruses, herpes simplex virus, Epstein-Barr virus	Induces lymphocyte proliferation, inhibits the production of TNF-α and IL-12 by macrophages, stimulates the production of antibodies, improves the tolerogenic properties of immature dendritic cells, stimulates the innate immune response, increases the production of IL-2, reduces the secretion of IFN-γ and IL-2 in murine T cells	[34-39]
Annonamuricata L. / Annonaceae	Dengue virus type 2	Induces transcriptional expression of TNF-α and IL-1β via MAP kinase pathways, enhances the immune activity of the RAW 264.7 macrophage, increases white blood cells, T lymphocytes and natural killer cells, promotes the production of 'nitric oxide, IL-6 and TNF-α, modulates effector functions of human macrophages	[40-43]
Artemisia annua L. / Asteraceae	Herpes simplex virus type 1, bovine viral diarrhoea virus	Stimulates the production of Th1 cytokines (IFN-γ) and inhibits that of the Th2 pathway (IL-4 and IL-10), increases the levels of CD4+ and CD8+ T cells, stimulates lymphoproliferation, increases co-stimulating molecules CD80 and CD86 on APCs, stimulates the generation of NO and enhances the Th1 immune response	[44-47]
Azadirachtaindica A. Juss. / Meliaceae	Group B Coxsackie viruses, duck plague virus	Increases serum IL-2 level and induces proliferation of T lymphocytes in thymus, increases IgM and IgG level, improves phagocytic activity of immune cells, increases red blood cells, white blood cells, lymphocytes, monocytes and neutrophils, decreases IgE and IL-4 expression, has anticomplement activity, activates cell-mediated immune mechanisms, stimulates PMNs, activates macrophages, increases phagocytosis and reduction of NBT, promotes proliferative responses of T lymphocytes, stimulates the secretion of IFN-γ by T cells	[48-54]
Boerhaviadiffusa L. / Nyctaginaceae	Potato virus X, mung bean yellow mosaic virus	Stimulates cell-mediated immune response by upregulating IL-2 and downregulating pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, enhances NK cell activity, antibody-dependent cell cytotoxicity and antibody-dependent complement-mediated cytotoxicity, enhances leukocyte production, enhances phagocytic activity of macrophages	[55-57]
Carissa edulis (Forssk.) Vahl / Apocynaceae	Herpes simplex virus	Induces an increase in red blood cells, lymphocytes, monocytes, neutrophils, eosinophils and basophils	[58, 59]
Echinacea purpurea (L.) Moench / Asteraceae	Coronavirus, Herpes simplex virus type 1, respiratory syncytial virus, influenza A virus, influenza B virus	Improves NK cell activity and B cell response, increases T cell proliferation and cytokine production, increases IgG, interferon γ and cytokine expression, increases hemoglobin level, red blood cells, white blood cells, lymphocytes, IgM and stimulates phagocytosis, increases the functions of NK cells, p38 MAPK, NF-kB, JNK, differentiation of DC and phagocytic and bactericidal activity intracellular, stimulates production IL-1, IL-6, IL-12p70, TNF-α, NO, CD80, CD86 and MHCII, activates macrophages, CCR7, IL-10, PPAR-γ, IL-2, IFN-γ, reduces number and function of regulatory T cells	[60-70]
Eclipta alba Hassk / Asteraceae	Hepatitis C Virus, HIV	Increases the phagocytic index of PMNs, antibodies and white blood cells	[71, 72]
Jatrophacurcas L. / Euphorbiaceae	HIV, Newcastle disease challenge virus	Stimulates both humoral and cell-mediated seroresponse, increases antibody, lymphocyte and macrophage cells	[73, 74]
Kigelia Africana (Lam.) Benth. / Bignonaceae	Herpes Simplex Virus, HIV	Increases both humoral immunity and cell mediated immunity, increases antibody level	[75, 76]
Emilia sonchifolia (L.) DC /Asteraceae	White spot syndrome virus, yellow head virus, japanese encephalitis virus,	Increases white blood cell count, bone marrow cellularity, α-esterase activity and lymphoid organ weight, increases antibody titer, increases cell-mediated immune response by enhancing the activity of destruction of CTL, improves production of IL-2 and IFN-γ	[77-79]
Mangiferaindica L. / Anacardiaceae	Herpes simplex virus type 2, poliovirus type-1, influenza virus.	Increases humoral antibody (HA) titer, neutrophil adhesion, PMN phagocytic index, improves innate and adaptive immune response via increased blood cell count, spleen index and titer 'hemagglutination (HA)	[80-84]
Moringaoleifera Lam. / Moringaceae	HIV, herpes simplex virus type, HBV, EBV, FMDV, NDV	Stimulates both cellular and humoral immunity, increases WBC, neutrophils, neutrophil adhesion, antibody, lymphocytes, eosinophils, monocytes, weight of thymus and spleen, phagocytic index, increase the cell number of CD4+ and CD8+	[85-88]
Ocimumbasilicum L. / Lamiaceae	Adenoviruses, hepatitis B virus, coxsackievirus B1,	Stimulates lymphoproliferation, increases WBC	[89-91]

Medicinal plants/family	Susceptible viral species	Effect on the immune system	References
	herpes viruses, enterovirus 71, HIV-1		
Phyllanthusniruri L. / Phyllanthaceae	Hepatis B virus, herpes simplex viruses, dengue virus, HIV	Increasespolymorphonuclear neutrophils and leucocytes mobilization, leucocytes count, humoral antibody titre, induces proliferation of peripheral blood mononuclear cells, increases NO release, and improves macrophages phagocytic activity, increases WBC and lymphocytes	[92-95]
Phyllanthusreticulatus Poir. / Euphrobiaceae	Herpes simplex virus type 1, Herpes simplex virus type 2	Increases the phagocytic activity of mononuclear macrophage, neutrophil adhesion, and white blood cell, acts on NK cells by promoting NFκBsignaling enhancement	[96-98]
Psidiumguajava Linn. / Myrtaceae	Influenza viruses, dengue virus	stimulates both humoral and cell mediated immunity, increases the WBC, RBC, platelet, monocyte, neutrophil, eosinophil, lymphocyte, antibody and hemoglobinlevels	[99-101]
Solanumnigrum L. / Solanaceae	Hepatitis C Virus	Increases the antibody response, IgG level, neutrophil activity, induces phagocytosis activity and stimulated the production of TNF-α and IL-6, activates macrophages, increases IFN-α, IL-2 and IFN-γ production	[102-105]
Tinosporacordifolia (Thunb.) Miers / Menispermaceae	HIV virus, hepatitis-A Virus	Increases the phagocytic activity of macrophages, the production of reactive oxygen species (ROS) in human neutrophils, improves the production of nitric oxide (NO) by stimulation of splenocytes and macrophages, stimulates the production of cytokines, mitogenicity, the activity of immune effector cells, regulates the activity of IL-6 cytokines, activates cytotoxic T lymphocytes and B lymphocyte differentiation, induces IL-1 secretion, activates lymphocytes and synthesis of pro and anti-inflammatory cytokines	[106]
Vernoniaamygdalina Del./Asteraceae	HIV, hepatitis B virus	Increase CD4+ T cell, IgM, IgG1 and IgA antibody responses, white blood cell, neutrophil and lymphocyte counts, decreases IL-6 level	[107-109]
Zingiberofficinalis L. / Zingiberaceae	Chikungunya virus, human respiratory syncytial virus, hepatitis C virus	Stimulates phagocytic activity of white blood cells, humoral immune response, increases hematocrit, red blood cells and white blood cells	[110-113]

3. Conclusion

The advent of the COVID-19 pandemic has totally changed global habits both economically and socially. To date, no antiviral drug has been approved to fight this disease. Traditional medicine once held pride of place as the premier treatment for emerging diseases. Several plant species are known there for their therapeutic and anti-infectious properties in particular. Since the advent of COVID-19 many potions made from herbal remedies have been proposed as drugs to fight this infection. However, no scientific studies demonstrating the efficacy and safety of these drugs for approval have been performed. Clinical studies on these drug potions and an exploration of other therapeutic possibilities offered by traditional medicine would help to overcome this pandemic.

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