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Whole Plant Herbal Formulations based on a Review: Potential Therapeutics for SARS CoV-2 (COVID-19)

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Abstract

SARS CoV-2 (COVID-19) is a global health concern with global mortality increasing daily. There is a race by researchers and medical practitioners to find new therapeutic agents but success has so far been elusive. Thus, it is worth examining the offerings of whole plant medicines. In this paper, whole-plant herbal formulations created after a thorough review of the literature are proposed as potential therapeutic options that are more readily available, more easily deployed, and possibly more efficacious than synthetic pharmaceuticals.

Keywords: COVID-19; Plant medicines; Synthetic pharmaceuticals

Introduction

Traditional herbal medicines consisting of plant-derived substances with minimal or no industrial processing are getting significant attention in global health debates. During the SARS outbreaks in China, traditional herbal medicine played a prominent role in the strategy to contain and treat the disease. There are hopes that traditional herbal medicine research will play a critical role in global health with China, India, Nigeria, the United States, and WHO all making substantial research investments in these traditional plant medicines. While the application of reductionism in modern biomedical research and practice has resulted in some utterly amazing feats, reductionism alone is not only inadequate but has created some collateral damage [1]. Reducing complex biological or medical phenomena into their individual components, improves the chances of identifying a single cause in order to devise a cure. However, this eliminates the value of the complexities of whole plants and the entourage effect. "The entourage effect refers to the synergistic effects of the multiple compounds present in whole organisms, which may potentiate clinical efficacy while attenuating side effects [2]. In opposition to this view, mainstream pharmacology is adamant about the need to use purified substances, presumably more specific and safe."

This reductionist approach is also inappropriate for rapidly mutating organisms and oftentimes results in antimicrobial resistance [3]. The classic example is bacterial resistance to β-lactams *via* the mechanism of β-lactamase production by penicillin-resistant S. aureus which became clinically relevant after penicillin became widely distributed. "Bacteria have a remarkable genetic plasticity that allows them to respond to a wide array of environmental threats, including the presence of antibiotic molecules that may jeopardize their existence." Like bacteria, RNA viruses share this genetic plasticity, mutating faster than DNA viruses, with single-stranded viruses mutating faster than double-strand viruses [4].

This faster mutation rate match makes it nearly impossible to create a highly effective vaccine for RNA viruses. Influenza vaccines are an excellent example [5,6]. According to the CDC, "flu vaccination reduces the risk of flu illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine."

Likewise, the issue of resistance to antiviral drugs is endemic. Hussain, et al reported that rapidly acquired resistance against both adamantes and Neuraminidase Inhibitors (NAIs) mutation targeting the viral components M2 ion channel and NA, respectively. Resistance is conferred by viral mutation of these components [7]. A majority of the Influenza A Virus (IAV) subtypes, especially the most common H1N1 and H3N2, circulating globally are resistant to adamantanes, making these drugs essentially obsolete. NAIs target the NA surface protein of IAV NA which, through enzymatic activity, prevents infected cells from infecting naive cells and the spread of the infection [8-10]. In the 2008-2009 flu season, 90% of globally circulating IAV H1N1 subtypes were resistant to the NAI, oseltamivir. However, the H1N1 strain that emerged, causing the 2009 "swine flu" pandemic, was found to be sensitive [11].

Despite this, by the 2018-2019 flu season, a French cohort revealed a 23% resistance rate to oseltamivir in patients infected with the H275Y mutant strain of H1N1, the most common mutation conferring oseltamivir resistance, revealing the re-emergence of these resistant strains. These patients also had a higher day 28 mortality [12]. It is reasonable, therefore, to believe that this novel coronavirus, a single-stranded RNA enveloped virus, will share similar characteristics and, indeed, that is what is being seen. As of this writing, molecular

epidemiologists are tracking the global spread and properties such as transmissibility and virulence of SARS CoV-2 *via* its genetic mutations [13]. The triad of vaccines, antiviral drugs, and surveillance is the mainstay for dealing with viral infections and the current global pandemic is no exception. However, given the lack of truly effective therapeutics after more than 6 months after the onset of the pandemic, the argument can be made that the current approach to antiviral medications is insufficient [14]. An alternative, and potentially more effective, approach to medical treatments that can shorten the course and lessen the severity of viral infections is phytomedicine, inclusive of Traditional or Indigenous forms of medicine [15,16].

Phytomedicine utilizes the synergistic interactions of multiple herbs, explaining the efficacy of low doses of active constituents in combined herbal formulations. The supporting evidence of these synergies is accumulating in the medical and scientific literature. Additionally, using whole plant extracts, in combination, can help address antimicrobial resistance as different plants have different compounds that impact different pathways of microbial binding and replication, 'attacking' the microbe in a multi-faceted way [17]. This creates therapeutic options in the face of novel microbial infections as well as known and endemic antimicrobial resistant infections. In order to identify herbs, and therefore herbal combinations, that might have such an effect, a thorough review of the medical and scientific literature was undertaken. This review led the authors to develop two multi-herbal tinctures with the theoretical potential to treat SARS CoV-2 [18-20].

Literature Review

This herbal tincture recipe is a combination of equal parts of the tinctures (60% ethanol/40% water v/v extraction menstruum with a 5:1 w/v percolation) of 7 herbs with known antiviral properties. Information about each herb and why it was chosen follows. This work is based on a study of the scientific and medical literature and inspired by the herbalist Stephan Harrod Buhner, author of "Herbal Antivirals" [21].

Scutellaria baicalensis (Chinese skullcap)

Scutellaria baicalensis is a traditional Chinese medicinal herb that has been used for centuries with demonstrated antiviral activity and low toxicity. Its extracts and compounds exert broad-spectrum antiviral activities against HIV, influenza virus (H1N1), DENV, HBV, and HTLV-I [22]. Baicalein is a flavonoid and the primary Chinese skullcap extract studied. In a study of mice infected with Influenza A (H1N1 strain), 480 mg/kg of baicalein orally for 4 days prevented death, prolonged survival time, inhibited lung consolidation, and reduced pulmonary viral titers [23,24]. These effects were comparable to the neuraminidase inhibitor, lamivudine, indicating one possible mechanism of action. Modulation of the immune system is another potential mechanism of action. When baicalein (400 mg/kg for 5 d, p.o.) was used in combination with ribavirin (50 mg/kg) superior survival rates than any single treatment alone [25]. It has also been found that a decoction containing *S. baicalensis*, was effective in the treatment of severe pneumonia, when combined with ulinastatin. When 15 grams of each therapeutic was given twice daily for 10 days, the effect was statistically significantly better than ulinastatin alone (93.4% *vs.* 83.5%, P=0.037). The likely mechanism is *via* an increase in serum TNF-alpha and Procalcitonin (PCT) expression. The group receiving both therapeutics also had a lower adverse event rate (4.4 (4/91 *vs.* 13.2 (12/91) P=0.036) [26-30].

Because of its broad spectrum antiviral activity, *S. baicalensis* has been used to treat severe HFMD (Hand, Foot, and Mouth Disease) in patients older than one year of age. In these conditions rapid fever reduction and attenuation of oral lesions and rashes has been noted along with an improvement of nervous system symptoms [31]. Additionally, baicalein- and wogonin (another *S. baicalensis* component molecule) containing extracts have also been found to modulate cytokine production, inhibiting IFN-alpha and IFN-gamma while stimulating TNF-alpha and IL (IL-12, IL-10) production. These extracts have also been identified as augmenting the natural resistance of human leukocytes to viral infection, another important mechanism of innate immunity. Another *in vitro* study evaluating the inhibiting effect of baicalin on influenza type A and B, herpes simplex type I and II and Cox B3 virus infections revealed that baicalin can inhibit the cytopathic effect of influenza type A virus and Coxsackievirus B3 in already infected cells. Baicalin was also found *in vitro* and *in vivo* to induce IFN, attenuating viral replication [32,33].

In an *in vitro* study of the impact of baicalin on Enter Virus 71 (EV71), baicalin exhibited a strong antiviral effect in a dose-dependent fashion with a low IC50 (the half maximal inhibitory concentration) of 4.96 μg/mL, indicating high efficiency with low toxicity. Despite this, there appears to be no direct virucidal or prophylactic effect for baicalin against EV71 however baicalin does significantly suppress EV71 replication indicating that the antiviral impacts occur during the early stages of infection [34]. Additionally, most viral infections eventually result in apoptosis of a variety of host cells, as is the case with EV71. Baicalin appears to inhibit the apoptosis of EV71-infected cells through the activation of the Fas/FasL signaling pathways. Baicalin also decreases the secretion of cytokines by downregulating NF-κB signaling pathways.

Safety profile: No known contraindications or other precautions. Chinese skullcap may decrease plasma levels of cyclosporine and rosuvastatin and has been found to induce the drug metabolizing isoenzyme CYP2B6 [35]. Allergic reactions have been reported. Diarrhea and stomach discomfort have been reported after ingestion. In Traditional Chinese Medicine, Chinese skullcap is used commonly during pregnancy. Very large doses (25 g/kg) produced some developmental abnormalities in offspring of pregnant mice. Lower doses (0.25 g/kg and 12.5 g/kg) did not. No information on the safety in lactation has been identified in the scientific or traditional literature.

Isatis indigotica (Woad root)

Woad root has been used for the prevention of influenza for hundreds of years in many Asian countries [36]. A study of the anti-IVA properties of various woad root extracts (clemastanin B, a phenylpropanoid and epigoitrin, an alkaloid) found that their anti-influenza activity included inhibition of viral replication,

prophylaxis, and preventing virus attachment. However, no direct virucidal properties were noted. In another study, five major compounds of *I. indigotica* root were tested for anti-SARS activity, particularly the 3C-Like protease (3CLpro) of SARS-coronavirus which mediates replication and functional proteins. The researchers found significantly inhibitory effects on SARS-CoV 3CLpro, making *I. indigotica* root an important plant in the development of therapeutics for SARS-CoV-2 [37].

Safety profile: No known contraindications. Use with caution in persons with allergy to sulfonylureas or sulfonamide drugs. No information on its use in pregnancy or lactation has been identified in the scientific or traditional literature.

Glycyrrhiza glabra (Licorice)

Ancient Chinese, Indian and Grecian manuscripts all report the use of *Glycyrrhiza* species for use in viral respiratory tract infections and hepatitis. Randomized controlled trials confirm a reduction in hepatocellular damage in those with chronic hepatitis B and C and animal studies demonstrate a reduction of mortality and viral activity in IVA pneumonia. *In vitro* studies also reveal antiviral activity against HIV-1, SARS-related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus [41]. *Glycyrrhiza glabra* (licorice) constituents that show structural similarities to known influenza NA Inhibitors (NAIs), that are important in inhibiting viral replication. *In vitro* studies have confirmed that 11 of 12 phytochemical constituents of licorice showed significant influenza virus NA inhibition as well as general antiviral activity [42].

Safety profile: Not for use in pregnancy except under the supervision of a qualified healthcare professional as heavy consumption has been associated with early births. No case reports of adverse effects have been reported in persons using licorice within the recommended dose (less than 50 g daily) and treatment period less than 6 weeks. Licorice may cause reversible potassium depletion and sodium retention when consumed in therapeutic doses over a prolonged period. Therefore caution should be taken in those with hypertension, liver disorders, edema, severe kidney insufficiency, hypokalemia, and congestive heart failure (AHPA, 2013).

Houttuynia cordata

Houttuynia Cordata (HC) is conventionally used to treat pneumonia in the Traditional Chinese Medicine (TCM) tradition and has direct inhibitory activity against Herpes Simplex Virus type 1 (HSV-1), influenza virus, and Human Immunodeficiency Virus type 1 (HIV-1) [43]. During the SARS-CoV epidemic in late 2002 to mid-2003, Chinese scientists shortlisted HC to help address the SARS problem. One study found that HC water extract could significantly stimulate the proliferation of mouse splenic lymphocytes in a dose-dependent fashion [38]. It was also revealed that HC increased the proportion of $CD4^+$ and $CD8^+$ T cells and caused a significant increase in the secretion of IL-2 and IL-10 by mouse splenic lymphocytes. With respect to antiviral activity, HC, like woad root, significantly inhibits the effects on SARS-CoV 3C-Like protease (3CLpro) impacting replication. HC was also noted to inhibit RNA-dependent RNA polymerase (RdRp), a replication catalyzing enzyme. No toxicity was noted to the mice even at levels as high as 16 g/kg.

Safety profile: It does have emmenagogue actions so should be avoided in pregnancy. No other interactions, contraindications, or precautions have been identified in the scientific or traditional literature.

Ceanothus americanus (Red root)

Betulinic acid, the primary constituent extract of red root, is a natural triterpene also found in birch trees. Betulinic acid and its derivatives have known anti-HIV-1 activity *via* several known mechanisms including inhibition of HIV-1 maturation, blocking viral infection at a post-binding stage, inhibition of an envelope-dependent step during fusion of the virus to the cell membrane, and inhibition of HIV-1 protease. Additionally, betulinic acid and two of its ionic derivatives were found to inhibit Herpes Simplex type 2 (HSV-2) replication at concentrations similar to those reported for acyclovir. In another *in vitro* study betulin, betulinic and betulonic acids inhibited ECHO 6 virus reproduction with the antiviral activity parameters of betulinic acid being higher than those of pleconaril, an inhibitor of enteroviruses and rhinoviruses also developed for treatment of diseases caused by picornaviruses. These constituents also had a pronounced antiviral activity against HSV-1, but were less effective in comparison with acyclovir. However, because they remain efficacious against acyclovir-resistant HSV-1, their value as a therapeutic remains. Betulonic acid also has been identified as having a weak antiviral activity against influenza virus [39].

Safety profile: No interactions, contraindications, precautions, side effects or adverse effects have been identified in the scientific or traditional literature. No information on the safety of red root in pregnancy has been identified in the scientific or traditional literature. Early human, animal and *in vitro* studies indicated that red root causes an increase in the speed of blood coagulation.

Lingusticum porteri (Osha)

Osha is primarily added for taste however doses of 20 mg/kg/day of Z-ligustilide, osha's primary constituent, has significant anti-inflammatory properties. In a study of mice infected with endotoxin, Z-ligustilide reduced pro-inflammatory cytokines including Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), vascular endothelial growth factor-α, and IL-17 within 24 hours of infection.

Safety profile: No interactions, contraindications, precautions, side effects or adverse effects have been identified in the scientific or traditional literature. Osha has been used as an emmenagogue and sho should be avoided in pregnancy. No information on the safety of osha in lactation has been identified.

Cinchona officinalis (Cinchona bark)

Cinchona or Peruvian bark contains several alkaloid compounds. The most well-known, quinine, has been used for

centuries in the treatment of malaria. However, in an attempt to identify novel drug therapeutics for Dengue Virus (DENV) infection, quinine and three other FDA approved drugs (aminolevullic acid, azelaic acid, mitoxantrone hydrochloride) were evaluated for their ability to inhibit DENV replication. Quinine was found to have the most pronounced anti-DENV activity of the four evaluated, inhibiting DENV replication by approximately 80% compared to untreated controls. This inhibition occurred with all four serotypes of DENV *in vitro*. Additionally, quinine improved the expression innate immune response-related genes. Chloroquine, a synthetic quinine analog, was discovered in 1934. Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Chloroquine has been shown to inhibit different viruses requiring a pH-dependent step for entry, such as the Borna disease virus, the minute virus of mice MVMp, the avian leukosis virus, and SARS CoV. Chloroquine also has immunomodulatory effects, suppressing the production/release of TNF-α and IL-6. It's speculated that, because of their effects on several enveloped viruses and on immune activation, chloroquine/hydroxychloroquine might be of some use for the clinical management of SARS [40].

Current recommendations from the FDA caution against use of hydroxychloroquine or chloroquine outside the hospital setting given the cardiac complications that have arisen in trials evaluating their use in SARS CoV-2 (COVID-19). A Brazilian trial was halted due to deaths related to cardiac dysrhythmias in patients receiving the higher dose of the drug (12 grams over 10 days *vs* 2.7 grams over 5 days). It's important to note that the amount of quinine in this tincture is small in comparison. Cinchona bark is approximately 5% quinine by weight. In the course of a viral illness, a patient would consume approximately 120 ml of tincture containing a total of 170 mg of quinine administered over 3-4 days orally [41].

Safety profile: Quinine has been used as an abortifacient, although some sources indicate the compound is generally ineffective for this purpose and toxic to the mother. Based on this and related information, use during pregnancy is not recommended except under the supervision of a qualified health care practitioner. Quinine may cause serious and potentially life-threatening hypersensitivity reactions in some individuals. Cinchona may cause gastrointestinal irritation in persons with gastric or intestinal ulcers. Symptoms of "cinchonism" due to overdose of the compound quinine include headache, nausea, disturbed vision, tinnitus, delirium, abdominal pain and diarrhea. The compound quinine can cause thrombotic thrombocytopenic purpura in sensitive individuals. Do not exceed the standard dose of 1 g-4 g daily.

For use during an active viral infection:

- For moderate infection: 60 drops (2 droppers) or 3 ml (1/2 tsp) every hour at onset of symptoms for 3-4 days.
- For severe infection: 1-2 tsp every hour for 3-4 days.

Cytokine reduction

Research has shown that, like SARS-CoV, SARS-CoV-2 uses the ACE-2 receptor to gain entry into ACE-2-expressing cells, which include cells of the lung, lymph and spleen epithelial cells. As noted earlier, licorice and Chinese skullcap block this attachment to varying degrees. However once attachment occurs, there can be increased vascular permeability, pulmonary edema and neutrophil accumulation. After viral entry to the cells (active infection) inflammatory cytokines are upregulated. Dysregulation or an excessive inflammatory response can be deemed a "cytokine storm" which begins locally and spreads corporally *via* the systemic circulation [42]. The cytokine storm, seen in SARS-CoV-2 infections, is best exemplified by severe lung infections, in which local inflammation spills over into the systemic circulation, producing systemic sepsis, as defined by persistent hypotension, hyper or hypothermia, leukocytosis or leukopenia, and often thrombocytopenia.

A common consequence is Acute Lung Injury (ALI) which can progress into its more severe form, Acute Respiratory Distress Syndrome (ARDS), as seen with SARS-CoV and influenza virus infections, with a 9%-20% mortality rate. IL-1β is a key cytokine driving proinflammatory activity in bronchoalveolar lavage fluid of patients with lung injury. Intense inflammation in the lungs also can have other systemic effects such as renal dysfunction. Fourteen cytokines have been confirmed in Severe Acute Respiratory Syndrome (SARS) patients. IFN-gamma, IL-18, TGF-beta, IL-6, IP-10, MCP-1, MIG, and IL-8, were highly elevated in the acute phase sera of Taiwan SARS patients. IFN-gamma was significantly higher in those with antibodies to the virus compared to those without. Furthermore, levels of IL-18, IP-10, MIG, and MCP-1 were significantly higher in those who died from the infection than in those who survived [43].

High Mobility Group Box 1 (HMGB1), a DNA binding protein, has also been proposed as a mediator of ALI and ARDS. HMGB1 is a late-acting cytokine, first appearing 8-12 hours after the initial macrophage response to a pro-inflammatory stimulus and is a marker of late stage sepsis. This has been verified in animal studies and it's been noted that administration of exogenous HMGB1 to mice induces fever, derangement of intestinal barrier function, and tissue injury [44]. However it's been observed that treatment of HMGB1 blockade up to 24 h after the onset of sepsis offers a window of opportunity to allow rescue from lethal sepsis. Additionally, secondary Hemophagocytic Lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome often triggered by viral infections. It's hallmarks are fulminant and fatal hypercytokinemia with multiorgan failure and occurs in approximately 4% of sepsis cases. Pulmonary involvement, including ARDS, develops in approximately 50% of patients. Severe cases of COVID-19 share a similar cytokine profile that includes increased Interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α. In a recent study of 150 confirmed COVID-19 cases in Wuhan, China, hyperferritinemia (a marker of inflammation) in non-survivors as compared to survivors also suggests that mortality may be related to hyperinflammation [45].

Corticosteroids may be of some benefit in controlling the inflammatory response within the lung but may also cause uncontrolled immunosuppression resulting in pulmonary superinfection. Thus, a more nuanced approach to modulating the immune response is required. Likewise, the pneumonia associated with COVID-19 is insidiou [46]. Front-line physician are reporting that infected patients are presenting to emergency departments with advanced radiographic pneumonia and dangerous hypoxia (oxygen saturation as low as 50%) with no feelings of shortness of breath. These patients decompensate quickly but have had viral symptoms such as cough and fever for as long as a week before seeking treatment. Therefore, it's critical that treatment begin at the onset of viral symptoms to avoid this treacherous course. This herbal tincture recipe was created with these ideas in mind. It is a combination of equal parts of the tinctures (60% ethanol/40% water v/v extraction menstruum with a 5:1 w/v percolation) of 3 herbs and a cannabinoid extract with properties that have the potential to dampen a cytokine hyper-response. Information about each herb and why it was chosen follows [47,48].

Salvia miltiorrhiza (Danshen)

Salvia Miltiorrhiza (SM) or Danshen, is used in treatment of various systemic and surgical infections in Chinese hospitals. It's been shown to block the lethal toxicity of lipopolysaccharide, the major structural component of the outer membrane of Gram-negative bacteria that is used to induce sepsis in mouse models, and prevent liver injury. The ability of SM to suppress LPS-induced TNF-alpha was confirmed by *in vitro* experiments on human Peripheral Blood Leukocytes (PBL). Additionally, after infection with *Listeria Monocytogenes* (LM), a 2% Danshen solution was found to inhibit the production of the inflammatory cytokine IL-1β in the liver and spleen [49].

Pueraria montana var. *Lobata* or *Pueraria thunbergiana* Benth. (Kudzu)

Kudzu, or Japanese arrowroot, is a perennial leguminous vine. Both its root and flower have been used for herbal medicine in Asia for centuries. Kudzu roots have been shown to contain large amounts of isoflavones (an average 1.8% to 12% dry matter), including puerarin, daidzin, daidzein, rutin, caffeic acid, epigallocatechin gallate (gallic acid), chlorogenic acid, quercetin, quercitrin, hyperosidem, rhamnetin, kaempferol, myricetin, p-coumaric acid, ferulic acid, sinapic acid, and p-hydroxybenzoic acid. One of its major constituents, robinin (kaempferol), possesses anti-inflammatory activity, inhibiting the production of Nitric Oxide Synthase (iNOS), cyclooxygenase-2, TNF-α, and IL-6 [50].

A study of 18 bioactive dietary molecules for potential antiviral and anti- SARS included several kudzu leaf extracts including epigallocatechin gallate (gallic acid), genistein, quercetin and daidzein. Molecular docking study against proteins of SARS-CoV-2 was assessed and compared to remdesvir and chloroquine. All of the four kudzu leaf extracts evaluated, all were found to have active activity against COVID-19 with gallic acid exhibiting the strongest molecular interactions. Gallic acid was also far more active than the standard drugs remdesvir and chloroquine.

Cannabidiol (CBD)

While whole plant extracts are preferred, federal and state regulations make utilization of whole plant cannabis (hemp) extracts difficult. As such, utilizing non-psychotropic isolates is more practical. Effects of both stimulation and inhibition of the immune system by cannabinoids have been reported with contradictory evidence for the specific effects of cannabinoids on biosynethesis of T-cell derived cytokines. The literature houses studies that reveal both an inhibition of Th1 and Th2 cytokine production, and stimulation. However, there is now recent and consistent proof that cannabinoids are responsible for a decrease in the expression of certain pro-inflammatory cytokines such as IL-6, IL-12, IL-1, IL-2, and TNF-α. Therefore proving their role in the reduction of the inflammatory profile in certain pathologies. Recently it was also shown that cannabinoids have the ability to reduce the expression of IL-6 and NO-induced by LPS.

Several important interactions between the endocannabinoid signaling system and the immune and inflammatory changes in the context of sepsis, have been observed. There are increased interactions between CBD receptors and multiple immune cells such as monocytes, leukocytes, polymorphonuclear cells, natural killer cells, and $CD4^+$ and the $CD8^+$ lymphocytes. Recent studies have also shown a series of anti-inflammatory, antioxidant, and antiapoptotic properties of cannabinoids in sepsis. For the sake of simplicity, the link between the cannabinoid system and sepsis can be explained by the effects of cannabinoids on inflammation, on the immune system, and on the redox activity [51]. At a molecular level, CBD and THC are involved in most of the biological processes impacting microRNAs expression and blocking the excessive production of pro-inflammatory cytokines. The result is modulation of immune response leading to an enhanced molecular response during a sepsis event. In a mouse model of LPS induced sepsis-related encephalitis CBD prevented arteriolar and venular vasodilation as well as leukocyte margination and abolished increases in TNF-alpha and COX-2 expression. CBD also reduced the expression of inducible-nitric oxide synthase and preserved the integrity of the blood-brian barrier.

Conclusion

The COVID-19 global pandemic has exposed the weaknesses of our current approach to dealing with communicable viral diseases, especially those that are novel and rapidly mutating. It's likely that a vaccine is many months on the horizon and quality surveillance and testing has been, in many places, lackluster. Given the lack of effective therapeutic agents and the safety profile of whole plant extracts used in combination, it is the opinion of the authors that examination of the efficacy of these medicinals should occur in a clinical setting.

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