Botanical Drugs and Supplements Affecting the Immune Response in the Time of COVID-19: Implications for Research and Clinical Practice

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Abstract

In times of health crisis, including the current COVID-19 pandemic, the potential benefit of botanical drugs and supplements emerges as a focus of attention, although controversial efficacy claims are rightly a concern. Phytotherapy has an established role in everyday selfcare and health care, but since botanical preparations contain many chemical constituents rather than single compounds, challenges arise in demonstrating efficacy and safety. However, there is ample traditional, empirical, and clinical evidence that botanicals can offer some protection and alleviation of disease symptoms as well as promoting general well-being. Newly emerging viral infections, specifically COVID-19, represent a unique challenge in their novelty and absence of established antiviral treatment or immunization. We discuss here the **roles and limitations** of phytotherapy **in helping to prevent and address viral infections**, and specifically regarding their effects on immune response. Botanicals with a documented immunomodulatory, immunostimulatory, and anti-inflammatory effect include adaptogens, *Boswellia* spp., *Curcuma longa*, *Echinacea* spp., *Glycyrrhiza* spp., medicinal fungi, *Pelargonium sidoides*, salicylate-yielding herbs, and *Sambucus* spp. We further provide a clinical perspective on applications and safety of these herbs in prevention, onset, progression, and convalescence from respiratory viral infections.

Keywords: adaptogens, *Boswellia,* herbal medicine, COVID-19, *Curcuma, Echinacea, Glycyrrhiza,* medicinal fungi, *Pelargonium,* phytotherapy, salicylate, *Sambucus*

Introduction

In December 2019, a novel beta-coronavirus identified in China, was found to cause respiratory disease and pneumonia (Zhu et al., 2020). The infection developed quickly into a pandemic involving every continent except Antarctica, with over 73 million cases and 1.6 million deaths reported globally (16 December 2020) (https://covid19.who.int/; Zhu et al., 2020). The virus was initially referred to as novel coronavirus 2019 (nCoV-2019), but is now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

(Coronaviridae Study Group of the International Committee on Taxonomy of, 2020) causing Coronavirus disease 2019 (COVID-19) (https://covid19.who.int/).

The complexity of the disease suggests potential need for a range of therapies, including antiviral agents, immunostimulants, immunosuppressants, and anticoagulants (Al-Horani, Kar, & Aliter, 2020; Drozdzal et al., 2020; Fierabracci, Arena, & Rossi, 2020; Schijns & Lavelle, 2020; Sethi & Bach, 2020; van Haren et al., 2020). Although basic scientific information regarding the virus has accumulated quickly over the past year, no definitive cure is available and approved drugs such (as the antiviral drug remdesivir and the corticosteroid dexamethasone show only moderate benefit (Beigel et al., 2020; Horby et al., 2020; https://covid19.who.int/). Vaccines are now receiving regulatory approvals but will take time to reach the general public.

Sepsis, cardiovascular, and/or respiratory diseases are among the most serious complications in COVID-19 patients, especially the elderly and those with underlying health problems (F. Zhou et al., 2020). Use of NSAIDs for COVID-19 patients has been a matter of debate (Little, 2020), but strong evidence is lacking to advise against their use. Some reports indicate the harm of NSAIDs including ibuprofen, naproxen, and diclofenac due to their relationship with high rates of cardiovascular diseases, including myocardial infarction, heart failure, and stroke (Bhala et al., 2013). However, other reports support their intermittent use if paracetamol (acetaminophen) proved insufficient (Besedovsky, Lange, & Haack, 2019; Ye, Wang, & Mao, 2020).

Botanical drugs and supplements have been recommended for prevention (Boozari & Hosseinzadeh, 2020), as adjuvant therapy (Silveira et al., 2020), or after exposure to SARS-CoV-2 (Ang, Lee, Kim, & Lee, 2020). Traditional Chinese Herbal Medicine (TCM) is used in conjunction with conventional Western medicine to reportedly good effect (Fan, Gu, & Alemi, 2020). Natural extracts and compounds of potential clinical interest have been identified based on observed mechanisms of action and in-silico studies, but no clinical studies have yet been performed (Fuzimoto & Isidoro, 2020; Zhang, Wu, Zhang, Deng, & Peng, 2020).

Concerns over use of botanical drugs and supplements include being 'unproven', with insufficient evidence to endorse widespread use (Y. Yang, 2020), and the theoretical possibility that immune-stimulating herbs' may initiate a cytokine storm (Alschuler et al., 2020). There is an urgent need for authoritative information. This review addresses misapprehensions regarding the safety and efficacy of herbal ingredients, to highlight research targets and to guide clinical use.

SARS-CoV-2 and Immune Response to Infection

SARS-CoV-2 is the seventh coronavirus known to infect and cause disease in humans, alongside human coronaviruses 229E (HCoV-229E, alphacoronavirus), OC43 (HCoV-OC43, betacoronavirus), NL63 (HCoV-NL63, New Haven, (alphacoronavirus), HKU1 (HCoV-HKU1, betacoronavirus), SARS-CoV (betacoronavirus), and Middle East respiratory syndrome coronavirus (MERS-CoV, betacoronavirus) (Corman, Muth, Niemeyer, & Drosten, 2018; Cui, Li, & Shi, 2019; F. Wu et al., 2020; Yin & Wunderink, 2018). HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are endemic in humans and typically cause mild-to-moderate common cold-like respiratory disease (Channappanavar & Perlman, 2017; Corman et al., 2018).

Since 2002, SARS-CoV-2 is the third coronavirus causing a substantial outbreak associated with significant mortality (F. Wu et al., 2020). SARS-CoV outbreak in 2002/2003 resulted in 8,098 confirmed and suspected cases and 774 deaths (mortality rate: 9.6%) (https://www.who.int/publications/m/item/summary-of-probable-sars-cases-with-onset-of-illness-from-1-november-2002-to-31-july-2003). For MERS-CoV, WHO reports 2,562 laboratory-confirmed cases and 881 deaths (mortality rate: 34.4%) (https://www.who.int/emergencies/mers-cov/en/). However, human-to-human spread of MERS-CoV remains very limited. SARS-CoV-2 disease is associated with a mortality rate below 1% (Gudbjartsson et al., 2020; Perez-Saez et al., 2020; Poletti et al., 2020). Unlike SARS-CoV, SARS-CoV-2 can be transmitted by asymptomatic individuals (S. Lee, Meyler, Mozel, Tauh, & Merchant, 2020; Petersen et al., 2020; Pollán et al., 2020).

SARS-CoV-2 has a single-stranded positive sense RNA (+ssRNA) genome of approximately 29.8 kilobases and was annotated to contain 14 ORFs and 27 proteins (A. Wu et al., 2020). Two ORFs at the 5'-terminus (ORF1a, ORF1ab) encode the polyproteins pp1a and pp1b, which comprise 15 non-structural proteins (NSPs), the NSPs 1 to 10 and 12-16 (A. Wu et al., 2020). Additionally, SARS-CoV-2 encodes four structural proteins (S, E, M, N) and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, orf14) (A. Wu et al., 2020).

The spike (S) protein mediates coronavirus entry into host cells (Y. Chen, Liu, & Guo, 2020; Cui et al., 2019). ACE2 has been identified as cellular receptors for SARS-CoV-2 S, the same receptors as for SARS-CoV (Cui et al., 2019; Hoffmann et al., 2020; Letko, Marzi, & Munster, 2020; H. Zhou et al., 2020). To interact with ACE2, SARS-CoV-2 S requires cleavage by cellular serine proteases such as TMPRSS2 (Hoffmann et al., 2020; Shang et al., 2020). ACE2 is widely expressed in cells from multiple tissues (Ni et al., 2020). Accordingly, COVID-19 symptoms can range from mild respiratory to life-threatening multi-organ disease.

The immune system is a complex network, uniting cells, tissues and organs with biochemical processes and interactions, aimed at maintaining the integrity and function of an organism exposed to environmental insults. When triggered by a specific provocation, the immune system exhibits a response. Immune responses can be grouped into two general types, innate and adaptive immunity, both of which contain humoral and cellular components. If a pathogen overcomes the physical barriers of the human body, (skin or mucous membranes) it is immediately addressed by the innate immune system, comprising physical epithelial barriers, phagocytic leukocytes, dendritic cells, natural killer (NK) cells, circulating plasma molecules (e.g., antimicrobial peptides, reactive oxygen species), the complement system, innate antibodies, and related cytokines. While rapid, innate immune responses are not specific to the type of microorganism, i.e., different provocations trigger similar reactions and response patterns. Thus, innate immunity does not provide continuous protection from a specific pathogen (Carrillo, García, Coronado, García, & Cordero, 2017; D. H. Lee & Kim, 2014; J. M. Wu et al., 2016).

The control of adaptive immunity by the innate immune system follows a well-established paradigm (S. P. Wasser, 2017; Zmitrovich, Belova, Balandaykin, Bondartseva, & Wasser, 2019). Recognition of a pathogen by the innate immune system is mediated by pattern-recognition receptors (PRRs) detecting conserved pathogen-associated molecular patterns (PAMPs). These molecular patterns may represent viral nucleic acids, bacterial or fungal cell-wall components. There are several families of PRRs, e.g., members of the Toll-like receptor (TLR), nuclear oligomerization domain (NOD) or NOD-like receptor, C-type lectin receptor, complement receptor, and mannose receptor families (Coll & O'Neill, 2010), which can detect foreign materials, e.g., polysaccharides, glycolipids, lipoproteins, nucleotides, and nucleic acids. When PRR identifies PAMP, it initiates inflammatory responses and innate host defences. While mechanisms underlying the sensing of microbial organisms by different PRR receptors are still being investigated, PRR-mediated sensing determines the origin of the antigen and type of infection, leading to the activation of adaptive immune responses (Zmitrovich et al., 2019).

Adaptive immune responses are slower to manifest, but highly specific to the triggering pathogen. There are two categories of adaptive immune responses – humoral immunity (mediated by antibodies produced by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes). The adaptive immune system can provide long-lasting protection from specific pathogens by creating immunological memory following an encounter and response, allowing for enhanced response to the same pathogen in the future (D. H. Lee & Kim, 2014; J. M. Wu et al., 2016).

In an uncompromised immune system, the inflammatory response initiated by a viral infection is moderated and ultimately resolved following clearance of the presenting antigen. Inflammation early in infection facilitates the arousal of the immune response and assists the delivery of response cells to the site of infection. However, there is potential harm in unregulated inflammation and excess stimulatory cytokine production. Anti-inflammatory cytokines, e.g., Il-10, are released. regulating the pro-inflammatory response (Tay, Poh, Renia, MacAry, & Ng, 2020).

Severe COVID-19 disease appears driven by an excessive immune response and hyperinflammation ('cytokine storm'), resulting in acute respiratory distress syndrome (ARDS), systemic coagulation and thrombus formation (coagulopathy), and sepsis-related multiple-organ failure (Domingo et al., 2020; Iba, Levy, Levi, & Thachil, 2020; Morris et al., 2020; Nowill & de Campos-Lima, 2020). A broad range of proinflammatory cytokines has been associated with severe COVID-19 disease including IL-1b, IL-17, IFN-γ, TNF-α and IL-6. Elevated levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP1, MIP1A, and TNF-α were found in COVID-19 patients, who required intensive care (Cao, 2020; Nowill & de Campos-Lima, 2020), and IL-6 was found to be particularly high in patients who died from COVID-19 (Ruan, Yang, Wang, Jiang, & Song, 2020).

Echinacea (*Echinacea* spp.)

Preparations made from aerial and root parts of various species of *Echinacea* (mainly *E. angustifolia* and *E. purpurea*) are popular self-medications for the prevention and treatment of the common cold.

Immunomodulatory effects on macrophages and NK cells have been demonstrated by echinacea extracts (Hudson, 2012; S. Park et al., 2018; Pleschka, Stein, Schoop, & Hudson, 2009; Sharma, Anderson, Schoop, & Hudson, 2009; Sharma, Arnason, & Hudson, 2006), including decreasing the rhinovirus-induced expression of over 30 transcription factors essential to inflammatory cytokine production (Sharma et al., 2006). In human bronchial epithelial cells (BEAS-2B), echinacea inhibited induction of inflammatory cytokines and chemokines by a variety of respiratory viruses (Sharma et al., 2009). Echinacea protected against stress-mediated immune suppression in BALB/c mice by increasing CD^{4+} and CD^{8+} T lymphocytes, up-regulating cytokines and increasing NK cell activity (S. Park et al., 2018). Echinacea extracts contain a mixture of compounds with cytokine-suppressing, but also cytokine-inducing, effects (Todd et al., 2015). 8,11-Dihydroxy-dodeca-2E,4E,9E-trienoic acid isobutylamide was found to suppress production of TNF-α by RAW 264.7 cells (Leyte-Lugo et al., 2015), suggesting that echinacea extracts and alkamides may be useful for treating allergic and inflammatory responses mediated by mast cells (Gulledge et al., 2018).

Extracts and alkamides from *E. purpurea* may alleviate the inflammatory response that accompanies infection with H1N1 influenza (Cech et al., 2010). Alkamides are readily bioavailable and bind to cannabinoid receptors (CB2R), which are key modulators of the immune system (Ardjomand-Woelkart & Bauer, 2016). Selective stimulation of CB2R may reduce the inflammatory response in SARS-CoV-2 patients (Rossi, Tortora, Argenziano, Di Paola, & Punzo, 2020). There are no commercially available CB2R agonists approved for human use (Rossi et al., 2020), although alkamides of echinacea have such an effect (Raduner et al., 2006; Woelkart & Bauer, 2007). CB2 receptor stimulation has also a well-documented immunosuppressive effect by reducing immune cell proliferation (Rockwell, Raman, Kaplan, & Kaminski, 2008), and production of antibodies (Carayon et al., 1998), which may be beneficial in the exacerbated inflammatory response in COVID-19 patients.

Echinacea extracts have shown direct antiviral effects *in vitro,* preventing binding and cell entry of highly pathogenic avian (H5N1, H7N7) and swine origin H1N1 influenza (Pleschka et al., 2009). Despite sequential passage in cell culture with H1N1 present, no resistance to the protective effects of echinacea were seen. In a recent in vitro study, a standardized preparation from fresh *E. purpurea* herb and root (Echinaforce®, A. Vogel, Switzerland) showed antiviral activity against human coronaviridae HCoV-229E, SARS-CoV-1, SARS-CoV-2, and MERS-CoV upon direct contact (Signer et al., 2020).

Meta-analysis of human clinical trials has demonstrated efficacy for prevention and treatment of common cold viral infections (David & Cunningham, 2019). A further meta-analysis, focused on recurrent upper respiratory tract infections, showed that ethanolic extracts of echinacea decreased risk of developing subsequent infections in the same cold season as well as lowering the risk of infectious complications (A. Schapowal, Klein, & Johnston, 2015).

Analysis of the adverse events reported in multiple clinical trials do not show occurrence of serious adverse events (David & Cunningham, 2019; A. Schapowal et al., 2015). The largest human echinacea trial involved >700 patients treated for four months; occurrence of adverse events was 9% in the treatment group and

10% in the placebo group (Jawad, Schoop, Suter, Klein, & Eccles, 2012). Theoretical concerns that inflammatory symptoms of autoimmune diseases, and HIV infection may be exacerbated by immunostimulatory effects of echinacea, and that these may stimulate the onset of cytokine storm have been raised (Alschuler et al., 2020). Pharmacological data suggest that echinacea exerts a modulation of the immune response, balancing stimulatory and suppressive effects (Matthias, Banbury, Bone, Leach, & Lehmann, 2008), resulting in a biphasic effect (Gertsch, Schoop, Kuenzle, & Suter, 2004). A comprehensive review of the safety of echinacea preparations did not substantiate such a risk (Ardjomand-Woelkart & Bauer, 2016). A low rate of acute hypersensitivity reactions in children (5% of almost 15,000 adverse event reports) using echinacea (Meincke et al., 2017).

Echinacea shows no significant inhibition of cytochrome P450 enzymes 2D6 or 1A2 and weak induction of 3AA4, with induction of the drug transporter p-glycoprotein (Ardjomand-Woelkart & Bauer, 2016). Several adverse events have been reported with drugs with a narrow therapeutic index but the clinical evidence does not consistently demonstrate a significant effect (Fasinu & Rapp, 2019). In general, the risk of clinically significant herb-drug interactions with echinacea is deemed low (Izzo, 2012).

Elderberry (*Sambucus nigra*)

The juice of the ripe berries of *Sambucus nigra* (SN) has long been used as a diaphoretic in the treatment of common colds (Teuscher, Willuhn, & Loew, 2016). SN contains characteristic anthocyanins (mainly cyanidin-3-*O*-glucoside, cyanidin-3-*O*-sambubuioside, cyanidin-3-*O*-sambubioside-5-*O*-glucoside and – depending on the cultivar -their coumaroyl-derivatives). Other constituents include flavonol-glycosides (e.g., rutin, kaempferol-, and isorhamnetin-3-*O*-rutinoside), caffeoylquinic acid derivatives, and organic acids such as citric, malic, and tartaric acid (Porter & Bode, 2017; Teuscher et al., 2016).

Elderberry has immunomodulatory properties. In monocytes of healthy donors, a commercial formulation (Sambucol®, Razei Bar Industries, Ltd., Jerusalem, Israel) containing elderberry juice, stimulated production of the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, and TNF-α (Barak, Halperin, & Kalickman, 2001; Waknine-Grinberg, El-On, Barak, Barenholz, & Golenser, 2009). Enhanced release of IL-6, IL-8 and TNF-α was also seen in the human alveolar carcinoma cell line A549 exposed to SN juice concentrate (Torabian, Valtchev, Adil, & Dehghani, 2019). SN juice and methanolic extracts also produced a decrease in LPS-stimulated NF-κB activation, a key transcription factor involved in the immune response (Voldvik, 2015). A reduction of LPS-induced proinflammatory cytokines (IL-1β, IL-6, TNF-α) and COX-2 gene expression was reported in a murine macrophage model where the SN extract (1 mg/mL) had been exposed to a simulated gastrointestinal digestion process prior to the bioassay (Olejnik et al., 2015). Elderberry juice concentrate (10 mg/day) increases influenza A-specific neutralizing antibodies in bronchioalveolar lavage fluid of female BALB/c mice (Kinoshita, Hayashi, Katayama, Hayashi, & Obata, 2012).

SN extracts have shown in vitro antiviral effects against influenza virus A and B. Three studies used proprietary products containing SN extracts (Sambucol® or Rubini®, Iprona SpA, Lana, Italy) showed a reduction in infectious virus titre at dilutions ranging from 1:8 to 1:100 (Krawitz et al., 2011; Zakay-Rones et al., 1995). Sambucol-treated influenza A H9N2 virus-inoculated embryonic chicken eggs (95 mg/mL) resulted in a neutralizing index of >7.7, considered an effective antiviral treatment (Karimi, Mohammadi, & Dadras, 2014). Antiviral effects of elderberry juice concentrate were reported in four publications; concentrations between 150-1000 µg/mL showed impact on influenza A H1N1 (Kinoshita et al., 2012; Roschek Jr, Fink, McMichael, Li, & Alberte, 2009), HIV (Fink, Roschek, & Alberte, 2009), and IBV viruses (C. Chen et al., 2013).

Evidence from four human clinical trials demonstrate the effectiveness of SN in the treatment of upper respiratory infections by influenza or the common cold. A meta-analysis of these trials concluded that "supplementation with standardized elderberry extract is significantly effective at reducing the total duration and severity of upper respiratory symptoms, as compared to a placebo group" (Hawkins, Baker, Cherry, & Dunne, 2019).

A double-blind, placebo-controlled trial on healthy volunteers assessed elderberry consumption on pro-inflammatory cytokine levels. Subjects (n=26) received elderberry extract (500 mg anthocyanins per day) whereas the control group (n=26) received an equal amount of placebo capsules. After 12 weeks there was no statistical difference in measures of immunological parameters, e.g., IL-6, TNF- α, RANTES, or C-reactive protein (CRP) (Curtis et al., 2009). Overall, the data on the immunomodulatory effects of elderberry extracts are inconsistent but based on the limited data on elderberry from this study, it appears the there is a low risk that elderberry intake would have a negative impact on the immune response during the course of COVID-19.

Safety data from human studies and literature searches revealed no reports of significant adverse effects for short-term use of commercially available extracts (Ulbricht et al., 2014). Elderberry has no reported herb-drug interactions.

Despite the promising results reported in human clinical trials for the treatment of viral infections, any efficacy against the influenza virus cannot be used as an indication for a positive effect of elderberry in patients with COVID-19 as there are no scientific data supporting a positive outcome of elderberry in COVID-19 patients. However, elderberry has an excellent safety profile, the available information suggesting a low risk of adverse effects when using elderberry prior to or at early stages of COVID-19.

Umckaloabo (*Pelargonium sidoides*)

Pelargonium sidoides (PS) is endemic to South Africa and Lesotho and the roots and rhizomes are important traditional medicine Preparations of PS, specifically EPs® 7630 (Umckaloabo®, Schwabe Group, Karlsruhe, Germany), have undergone extensive clinical testing (Brendler & Van Wyk, 2008).

Characteristic active constituents of PS are oxygenated coumarins, including 5,6,7-trimethoxycoumarin (umckalin), 6,8-dihydroxy-7-methoxycoumarin (fraxetin), 6,8-dihydoxy-5,7-dimethoxycoumarin (artelin), umckalin-7-β-glucoside, and 5,6-dimethoxycoumarin-7-sulfate (Brendler & Van Wyk, 2008; Kolodziej, 2007; Schnitzler, Schneider, Stintzing, Carle, & Reichling, 2008; Schötz & Nöldner, 2007).

Immunostimulant activity of PS and its constituents has been assessed in several in-vitro models: infection with *Leishmania*, fibroblast-virus protection (for IFN activity) and fibroblast-lysis assays (for TNF-α activity), and biochemical and gene expression analyses. Interference with adhesion of microorganisms to cells, and stimulation of immune responses such as phagocytosis, oxidative burst, and intracellular killing of *Candida albicans* yeast by human peripheral blood phagocytes were demonstrated for PS in-vitro (Kolodziej, 2011; Kolodziej & Kiderlen, 2007; Thale, Kiderlen, & Kolodziej, 2011; K. Witte, Koch, Volk, Wolk, & Sabat, 2015). EPs® 7630 affected immune response in athletes during strenuous exercise by increasing of immunoglobulin α production in saliva, decreasing levels of interleukin (IL)-15 and IL-6 in serum, and IL-15 in the nasal mucosa (Luna et al., 2011). EPs® 7630 increased IL-22 production, leading to increased antimicrobial proteins (AMPs) in airway epithelium, thus protecting against airway infection (Katrin Witte, Koch, Volk, Wolk, & Sabat, 2020).

The antiviral activity of PS has shown for EPs® 7630, which inhibited virus replication for influenza virus H1N1 and H3N2, respiratory syncytial virus, human coronavirus (HCo-229E), parainfluenza virus type 3, and coxsackie virus A9, but not for non-enveloped adenovirus or rhinovirus (RV) (Michaelis, Doerr, & Cinatl, 2011). EPs® 7630 increased human bronchial epithelial cell survival in RV infections by down-regulating cell membrane docking proteins and up-regulating host defence proteins β-defensin-1 and SOCS-1 (Roth, Fang, Stolz, & Tamm, 2019). EPs® 7630 was found prevented asthma attacks provoked by RV in children, likely by decreasing inflammation caused by an increase in IL-6, IL-8, and IL-16 expression (Tahan & Yaman, 2013).

More than 30 clinical trials have been conducted with EPs® 7630 over the last 25 years (total study population >10,500) in the treatment of acute respiratory tract infections. It is well tolerated, from ~304 million daily doses sold between 1994 and 2006 only 257 minor AEs were reported (Careddu & Pettenazzo,

2018; Matthys, Lehmacher, Zimmermann, Brandes, & Kamin, 2016; Tahan & Yaman, 2013; Timmer et al., 2013). Promising antiviral effects and an excellent safety profile warrant further clinical investigation (Kamin, Funk, Seifert, Zimmermann, & Lehmacher, 2018; Andreas Schapowal et al., 2019).

Medicinal Mushrooms and Fungal Preparations

Medicinal fungi (commonly referred to as mushrooms, although fungi include underground mycelium whereas mushrooms are above-ground fruiting body) are of increasing research and clinical interest, with *Pleurotus ostreatus* (PO), *Ganoderma* spp. (GS), *Inonotus obliquus* (IO), *Ophiocordyceps sinensis* (OS), and *Grifola frondosa* (GF) being the most popular. Medicinal fungi are used in medicinal foods and dietary supplements, and in cosmeceuticals. Clinical studies on medicinal fungi preparations have been published in over 1,000 papers and reports. Approximately 300 clinical studies have been conducted on GS alone. Other mushrooms which have undergone clinical trials are *Lentinula edodes*, *Trametes versicolor, Schizophyllum commune*, *Phellinus linteus,* and *Agaricus subrufescens.* Most of this research focuses on treatment of cancers, immunological diseases, and immune-adjuvant therapy (S. P. Wasser, 2017).

Active compounds occur in fruiting bodies, cultured mycelium, and cultured broth. Medicinal fungi present a rich source of large molecular weight polysaccharides (especially β-glucans) and polysaccharide-protein complexes with anticancer and immunomodulating properties. Low-molecular-weight compounds (triterpenes, lectins, steroids, phenols, polyphenols, lactones, statins, and alkaloids) are also present and are similarly biologically active (Benson et al., 2019; Boh, 2013; Chang & Wasser, 2012, 2018; Lindequist, 2013; Solomon P Wasser, 2010). Their effects on chronic blood-borne infections with influenza viruses A (subtype H5N1) and B (Teplyakova & Kosogova, 2016) and SARS-CoV-2 (Murphy et al., 2020) are most relevant to COVID-19 issues.

Medicinal fungi have long been used to prevent immune disorders and maintain quality of life, especially in immunodeficient and immuno-depressed patients, and those being treated with chemotherapy or radiotherapy (Chang & Wasser, 2012, 2018; Lindequist, 2013; Solomon P Wasser, 2010). Bioactive polysaccharides or polysaccharide-protein complexes from medicinal fungi appear to enhance innate and cell-mediated immune responses and exhibit antitumor activities in animals and humans. Clinical studies have clarified the basic mechanisms involved in the immunomodulatory activity of β-D-glucans, which bind to dectin-1 and complement receptor 3 (CR3) receptors (D. H. Lee & Kim, 2014). CR3 and dectin-1 located on the surface of innate immune cells which can induce cytokine responses. Dectin-1 is expressed on macrophages, neutrophils, dendritic cells, and T lymphocytes. In clinical trials, medicinal fungi were shown to activate cytotoxic macrophages, monocytes, neutrophils, NK cells, dendritic cells, and cytokines, such as interleukins, interferons, and colony-stimulating factors, triggering complementary and acute phase responses. Medicinal fungi can be considered as multi-cytokine inducers, able to induce gene expression of immunomodulatory cytokines and cytokine receptors (Zmitrovich et al., 2019).

Results from clinical studies in cancer therapy cannot be transferred viral infections, but human studies have reported a stimulation of the innate immune system while not affecting, or slightly reducing, markers of inflammation. Multiple myeloma patients receiving a combination of extracts of AB, GF, and *Hericium erinaceus* exhibited an increase in regulatory T cells and plasmacytoid dendritic cells, while concentrations of pro-inflammatory cytokines (IL-6, TNF-α) did not change significantly when compared to placebo (Tangen et al., 2015). Healthy children receiving β-glucan (isolated from GL) in yoghurt showed significantly higher levels of circulating CD8+ T cells without a significant increase in cytokines IL-1β, IL-6, IL-10, IL-12, and TNF-α (Henao, Urrego, Cano, & Higuita, 2018). A small study evaluating immune cell function in patients with myelodysplastic syndromes showed improved neutrophil and monocyte function in those patients receiving a GF extract compared to placebo group, although cytokine concentrations were not assessed (Wesa et al., 2015).

The effects of an α-glucan obtained from basidiomycetes mushrooms were assessed in healthy volunteers receiving the influenza B vaccine and showed higher concentrations of CD8+ T and NKT cells in those

individuals receiving the mushroom preparation compared to the control group. No significant differences in cytokines IL-4, IL-6, IL-10 and IFN-γ levels were reported, although the number of patients with measurable amounts of cytokines was low and results may not be reliable (Roman, Beli, Duriancik, & Gardner, 2013).

The combination of immune cell activation combined with a moderate impact on inflammatory cytokines could be beneficial in patients with COVID-19. β-glucan-rich extracts from LE could be beneficial for COVID-19 patients as cell-based studies show a reduction in pro-inflammatory cytokines (Murphy et al., 2020). The authors pointed out that there were substantial differences in the immunomodulatory effects depending on the extract composition, illustrating the difficulties inherent when assessing mushrooms as an entire category: there are distinct differences in the chemical compositions of the various species tested in in vitro, animal, and human studies. While glucans generally appear to be most closely linked to immunomodulatory effects, it is not clear how the glucan composition affects the clinical outcome.

Data with chemically well-defined fungal ingredients in COVID-19 patients are necessary to further evaluate if specific fungi indeed could be beneficial at certain stages of the disease. Clinical studies have reported mild gastrointestinal side effects (Klupp et al., 2015; Wesa et al., 2015), but generally the intake of fungal dietary supplements has a history of safe use in food and is not considered problematic.

Adaptogens

Adaptogens are natural compounds or mixtures thereof that increase adaptability, resilience, and survival of organisms (Alexander G. Panossian et al., 2020); they increase "the state of nonspecific resistance" of organisms (Lazarev, 1959) to harmful factors (Wagner, Norr, & Winterhoff, 1994), including bacterial and viral pathogens. Nonspecific defence responses depend on the body's ability to recognize conserved features of pathogens by the innate immune system, which is activated at the onset of infection (Alberts et al., 2002). More than 100 medicinal plants have been attributed with adaptogenic activity; however, only few, *Andrographis paniculata* (AP), *Eleutherococcus senticosus* (ES), *Panax* spp. (ginseng, Psp), *Rhodiola rosea* (RR), *Schisandra chinensis* (SC), and *Withania somnifera (*ashwagandha, WS), have been shown to exhibit multitarget effects on the neuroendocrine-immune system, by triggering adaptive stress response, and increasing of non-specific resistance and adaptation in stress (A. Panossian, Seo, & Efferth, 2018).

Specific antiviral, non-specific antiviral, anti-inflammatory, and detoxifying and cytoprotective effects have been demonstrated for active ingredients of these species: andrographolides in AP; eleutherosides in ES; ginsenosides in Psp; salidroside, rosavin, ellagic and gallic acids in RR; schisandrins and anwulignan in SC; and withanolides in WS, – in vitro and in vivo, and multiple molecular targets identified. Table 1 summarizes activities elucidated in pre-clinical investigations (Alexander Panossian & Brendler, 2020).

Table 1. Direct and indirect effects (preclinical) of adaptogens on the immune response to a viral infection

	AP	**ES**	**Psp**	**RR**	**SC**	**WS**
Influenza, rhino-, and syncytial viruses						
Human Rhinovirus (HRV)		+				
Respiratory Syncytial Virus (RSV)		+	+			
H1N1 influenza A virus	++	++	++	+		
H3N2 influenza virus			++			
H5N1 avian influenza virus	+		++	+		
H7N9 influenza			+			
H9N2 avian influenza virus				+		
SARS structural and non-structural proteins involved in docking, RNA synthesis, and replication						
NSP_1	+					
NSP_3	+	++	++	++	++	
NSP_5 (M_{pro})	++	++	++	++	++	
NSP_{12}	+					

Spike protein S2	+					
Mediators of adaptive immune response						
Defensins	++					
TLRs	++	++	++	++	++	++
Interferons	+	++	++	++	+	++
Natural killer cells		++		+	+	+
Interleukins	++	++	++	++	++	++
Melatonin signalling pathways		+		+	+	+
Components of adaptive immune response						
T cells and MHC proteins		++			+	++
B cells and antibodies	+	+				++
Mediators of inflammatory response, antioxidant and detoxifying systems involved in cell- and tissue repair						
PLA2s	+		++	++	+	++
COX-2	++	+	++	++		+
Leukotrienes, lipoxins, resolvins		+		+		++
PAF	++		++		++	+
NOC	++	+	++	+	++	+
NFκB	++	++	++	++	++	++
PI3K, PKB (Akt), KEAP1, Nrf2-ARE	++	+	++	++	++	++
SOD, GST, NQO1, HO1	++	+	++	++	++	++
Hsp72		++		++	++	
RORα		+		+	+	+

(+) - evidence from one primary source, (++) - evidence from multiple primary sources.

In a systematic review of 33 randomized clinical trials (RCTs) with AP (monotherapy and fixed combinations) in >7,000 patients, AP was shown to significantly improve overall symptoms of respiratory tract infections (RTIs) compared to placebo, usual care, and other herbal therapies. None of the studies reported major adverse events (AEs), minor AEs were mostly gastrointestinal (Hu et al., 2017).

More than 70 observational trials with ES, carried out in the 1970s and 80s in >4,500 subjects, reported an improvement of performance under stress, or stress related, cardiovascular, and pulmonary disorders. While all these studies would not meet modern standards, the sheer volume of favourable evidence cannot be ignored, and many results have been corroborated in more recent, well-conducted studies. Several studies investigating ES as a prophylactic agent found a reduction in overall disease incidence (up to 35%), and a controlled and double-blinded study on influenza and RTIs in 1,376 subjects, found that which complications were found to be significantly lower with ES. Studies investigating the effect on morbidity caused by respiratory viral infections in >900 children receiving prophylactic ES treatment, found reduced morbidity rates of 30-40% (EMA, 2014).

Five RCTs with a fixed combination of AP and ES (KanJang®, KJ, Swedish Herbal Institute, Goteborg, Sweden) in >1,000 subjects confirmed relief of symptoms of uncomplicated RTIs caused by common cold (Caceres, Hancke, Burgos, & Wikman, 1997; Gabrielian et al., 2002; Kulichenko, Kireyeva, Malyshkina, & Wikman, 2003; Melchior, Spasov, Ostrovskij, Bulanov, & Wikman, 2000; Spasov, Ostrovskij, Chernikov, & Wikman, 2004). None of the studies reported any serious AEs, and a Periodic Safety Update Report for KJ (Anon., 2010), reported only 37 AEs (mainly allergic reactions) over 23 years out of 20 million daily doses sold.

Clinical evidence for efficacy and safety of Psp has been obtained primarily with two proprietary extracts, G115 (60+ trials) and COLD-fX (15+ trials) with >12,000 participants. Of relevance are 20 investigations with focus on immune response to RTI with a total study population >3,400 (Bilia & Bergonzi, 2020; Iqbal & Rhee, 2020), which produced significant evidence for immunomodulatory activity. A reduction in cytokine levels and oxidative stress decreased severity, duration, and symptom frequency, but also demonstrated potential for prevention of respiratory infections. All tested products were generally well tolerated, with only minor AEs reported.

Systematic reviews of clinical trials and case reports involving RR with a combined study population >3,500 corroborate multiple pre-clinical findings of efficacy in areas of relief of stress and fatigue, viral infection, inflammation, and cardiovascular disease. All studies report a low incidence of minor AEs only (Anghelescu, Edwards, Seifritz, & Kasper, 2018; EMA, 2012; A. Panossian, Wikman, & Sarris, 2010; Pu et al., 2020; Tao et al., 2019; L. Yu et al., 2014).

Beneficial effects of SC as a mono-product and in combinations was postulated from clinical assessments conducted between 1950 and 1990 in a total study population >7,000 for a broad variety of indications (2,800 in infectious diseases like influenza, chronic sinusitis, otitis, neuritis, otosclerosis, and pneumonia). Although these studies showed methodological weaknesses (A. Panossian & Wikman, 2008), many outcomes were corroborated in 29 more recent investigations (Aslanyan et al., 2010; Narimanian et al., 2005). Positive outcomes were observed in chemotherapy-induced immunosuppression (Kormosh, Laktionov, & Antoshechkina, 2006), COPD (X. Yu, Zheng, Qian, Jiang, & Wang, 2019), and fatigue (J. Park, Han, & Park, 2020). SC was overall well tolerated with no or only mild AEs reported.

WS has recently been reviewed (Pratte, Nanavati, Young, & Morley, 2014; Tandon & Yadav, 2020), 33 clinical investigations with a total study population of >2,500 were identified. Outcomes included impact on stress, anxiety, cognitive improvement, and adaptogenic effects, which in most cases were deemed significant. No trial reported more than mild and transient AEs.

Next to immunity, the ability of adaptogens to alleviate stress-induced mental and behavioural disorders (A. G. Panossian, 2013) is relevant as these conditions have increased significantly since the onset of the COVID-19 pandemic due to self-isolation (Stanton et al., 2020) and chronic exposure to stress and low-grade inflammation (Meftahi, Jangravi, Sahraei, & Bahari, 2020).

Liquorice (*Glycyrrhiza* spp.)

Liquorice spp. (primarily *Glycyrrhiza glabra, G. inflata,* and *G. uralensis*) are native to the Europe and south-western Asia, and widely cultivated. The root contains triterpenoid saponins (mostly glycyrrhizin), flavonoids, coumarins, and other phenolics (Asl & Hosseinzadeh, 2008; Hosseinzadeh & Nassiri-Asl, 2015). Glycyrrhizin is a potent anti-inflammatory agent, acting via suppression of NFκB translocation and decreasing the production of multiple pro-inflammatory mediators such as COX 2, iNOS, TNF-α, IL-6, and levels of inflammatory modulators IL-10 and TGF-β (R. Yang, Wang, Yuan, & Liu, 2015).

The antiviral effects of glycyrrhizin and glycyrrhetinic acid have been reported in several studies (Fiore et al., 2008; H. Li et al., 2020; Wang et al., 2006). Glycyrrhizin inhibited replication of SARS-associated coronavirus (FFM-1 and FFM-2) isolated from patients in Vero cell cultures, possibly by inducing nitric oxide synthase. The highest activity of glycyrrhizin was observed during and after the adsorption time of the virus (Cinatl et al., 2003) and a derivative of glycyrrhizin, 2-acetamido-β-D-glucopyranosylamine was more effective against SARS-CoV Adding N-acetylglucosamine residues to the glycyrrhizin molecule would increase hydrophilic properties, and perhaps binding to the carbohydrates of the S-proteins, thus inhibiting the entry of coronaviruses (Hoever et al., 2005).

The S-protein of SARS-CoV-2 binds to ACE2 with a higher affinity than SARS-CoV-1 (Wrapp et al., 2020). Docking studies show that glycyrrhizin may target the ACE2 receptor and prevent SARS-CoV-2 entry (H. Chen & Du, 2020). A further molecular docking study confirmed that glycyrrhizin has lower binding energy and could be active against SARS-CoV-2 (Li, Ma, Shen, & Zhang, 2020), but research is needed investigate whether glycyrrhizin can prevent SARS-CoV-2 from entry to cells *in vivo*.

Glycyrrhizin inhibits PLA2 activity in *in vitro* (Matsumoto et al., 2013; Okimasu et al., 1983; Shiki et al., 1992; T. Y. Wu et al., 2011). Glycyrrhizin has anti-inflammatory effects in acute lung injury (ALI)-induced by lipopolysaccharide (LPS) in mice, inhibiting release of pro-inflammatory cytokines TNF-α, IL-1α, and IL-6 and the infiltration of neutrophils via decreasing C-X-C chemokine receptor type 4/1 (CXCR4/CXCR1) expression, and expression of COX-2, iNOS, and NF-κB in bronchoalveolar lavage fluid, possibly via inhibition

of the TLR-4/NF-κB signal pathway (S. A. Lee, Lee, Kim, & Lee, 2019). The flavonoids of liquorice have anti-inflammatory effects in an acute pulmonary inflammation model by LPS, reducing the infiltration of inflammatory cells (esp. neutrophils), oxidative stress, and pro-inflammatory mediator expression (TNF-α, IL-1β) in the lung (Xie, Dong, Wu, Yan, & Xie, 2009). These effects are similar to those of drugs that mitigate the effects of cytokines released in response to the COVID-19 and limit lung damage in patients with severe disease (Rameshrad, Ghafoori, Mohammadpour, Nayeri, & Hosseinzadeh, 2020).

β-Glycyrrhetinic acid, the major metabolite of glycyrrhizin, is a potent inhibitor of 11β-hydroxysteroid dehydrogenase (11β-HSD) which causes an accumulation of glucocorticoids with anti-inflammatory properties (Asl & Hosseinzadeh, 2008). β-Glycyrrhetinic acid also has an inhibitory effect on the 11β-HSD enzyme in human lung tissue and enhances the activity of hydrocortisone, suggesting that coadministration of β-glycyrrhetinic acid with hydrocortisone may have a therapeutic effect in lung inflammatory diseases (Schleimer, 1991). In COVID-19 infection, neutrophils have a pivotal role in the development of lung oedema in ALI/ARDS and there are increasing pro-inflammatory cytokines in cytokine storms (Azkur et al., 2020), and glycyrrhizin may play a role in overcoming these two events. Glycyrrhizic acid was identified to be effective against SARS-CoV-2 target proteins in an in silico ADMET study (Vardhan & Sahoo, 2020).

The most common herbal use of liquorice is in multi-ingredient TCM formulae. A meta-analysis of 18 clinical trials involving liquorice (at least 100 mg of glycyrrhizic acid) showed a significant correlation between even moderate doses of liquorice and increases in systolic and diastolic blood pressure (Penninkilampi, Eslick, & Eslick, 2017). Serum potassium, renin, and aldosterone are likewise significantly reduced, resulting in pseudo-hyperaldosteronism, which recently caused fatal cardiac arrythmia (Edelman, Butala, Avery, Lundquist, & Dighe, 2020). Glycyrrhizic acid inhibits the activity of 11-beta-hydroxysteroid dehydrogenase, leading to an increase in the activity of endogenous glucocorticoids, and causes a subsequent loss of potassium, retention of sodium and water, and suppression of renin and aldosterone (Omar et al., 2012; R. Yang et al., 2015). Doses of 60 g of liquorice candy, or 100 mg of glycyrrhizic acid, daily for two weeks can result in adverse events.

More studies are required to access new insights into the potential role of liquorice in the treatment of COVID-19. However, the potential benefits of liquorice are balanced against its adverse event profile (Nazari, Rameshrad, & Hosseinzadeh, 2017).

Turmeric (*Curcuma longa*)

Curcuma longa, a rhizomatous herb growing in India, contains curcumin, which exerts a plethora of pharmacological actions of therapeutic interest. Standardized turmeric extracts with high levels of curcumin (up to 95%) have been subjected to clinical research. Oral bioavailability of curcuminoids is generally poor, and methods used to improve bioavailability include the addition of piperine, binding to more soluble agents, or as nanoparticles (W. Liu et al., 2016).

An overview of systematic reviews provided evidence that curcumin-containing dietary supplements can exert systemic antioxidant actions which may alleviate inflammatory conditions and reduce cardiovascular risk factors (Pagano, Romano, Izzo, & Borrelli, 2018).

Curcumin has demonstrated activity against a wide variety of viruses, by interfering with pathways controlling penetration and cellular signalling. It has been shown to interact with over 30 viral proteins including DNA polymerase and protein kinase and has been suggested as a potential agent for SARS-CoV-2 (Zahedipour et al., 2020). Curcumin may affect some of the pathophysiological and clinical features of COVID-19, including virus penetration, cytokine storm-associated pulmonary fibrosis, and vascular coagulopathy (Zahedipour et al., 2020). Curcumin may potentially target critical steps of the viral replication cycle, including penetration and replication (Mathew & Hsu, 2018). Curcumin inhibits ACE2 receptors and may thus prevent SARS-CoV-2 entry into the cell (Shanmugarajan, Prabitha, Kumar, & Suresh, 2020). An in-silico investigation of potentially useful drugs found that curcumin, formed the most stable complex with SARS-

CoV-2 main protease among those tested (Huynh, Wang, & Luan, 2020). SARS-CoV-2 main protease activity is fundamental in viral maturation and it is a well-recognized drug target.

Responses are being evaluated in inflammation-induced alveolar damage and cytokine storms in COVID-19 patients (Schijns & Lavelle, 2020). Curcumin blocks cytokine release, most importantly the pro-inflammatory interleukins IL-1, IL-6, and TNF-α. This suppression by curcumin correlates with clinical improvement in animal models of diseases where a cytokine storm plays a prominent role in morbidity and mortality (Sordillo & Helson, 2015). Curcumin has been shown to inhibit the release of IL-6 in rheumatoid synovial fibroblasts (Kloesch, Becker, Dietersdorfer, Kiener, & Steiner, 2013), IL-8 in human oesophageal epithelial cells (Rafiee et al., 2009), and in alveolar epithelial cells (Biswas, McClure, Jimenez, Megson, & Rahman, 2005). These properties are relevant to pulmonary diseases characterized by abnormal inflammatory responses, including pulmonary fibrosis (Lelli, Sahebkar, Johnston, & Pedone, 2017). Curcumin modulated the inflammatory response inhibited fibrosis in a mouse model of viral-induced acute respiratory distress syndrome (Avasarala et al., 2013); the effect was associated with a reduction in the expression of key cytokines, including IL-6, in both the inflammatory infiltrate and whole lung tissue. Curcumin, in combination with an antibiotic therapy, protected mice against pulmonary inflammation and acute injury induced by *Klebsiella pneumoniae* (Bansal & Chhibber, 2010).

Impaired coagulation is common in COVID-19, with disseminated intravascular coagulation present in most deceased patients (Boccia et al., 2020). Experimental evidence supports the positive actions of curcumin in haemostasis, anticoagulation, and fibrinolysis (Keihanian, Saeidinia, Bagheri, Johnston, & Sahebkar, 2018). In a rodent model of disseminated intravascular coagulation induced by LPS, curcumin attenuated coagulopathy, renal injury, and mortality rate (H. W. Chen, Kuo, Chai, Ou, & Yang, 2007). The effect was associated with a decrease of circulating TNF-α levels, the consumption of peripheral platelets and plasma fibrinogen (H. W. Chen et al., 2007).

Curcumin has been given in human trials up to a dose of 6 g/d for 4-7 weeks without significant toxicity (Soleimani, Sahebkar, & Hosseinzadeh, 2018). No serious adverse events were reported in meta-analysis of 22 clinical trials of curcumin for treatment of osteoarthritis, Alzheimer's, inflammatory bowel diseases, depression, and serum lipid reduction (Pagano et al., 2018).

In summary, curcumin has been shown to possess properties that may theoretically be of benefit in COVID-19 pathophysiology and clinical manifestations.

Frankincense (*Boswellia* spp.)

The genus *Boswellia* comprises several species traditionally used for their medicinal properties, the most prominent being South Arabian and African *B. sacra* (syn. *B. carteri*), *B. frereana, B. rivae*, *B. papyrifera*, and Indian *B. serrata*. Research on frankincense exceeds 700 publications, mainly describing its role in treating anti-inflammatory chronic diseases such as osteoarthritis, inflammatory bowel disease, arthritis, and asthma (Abdel-Tawab, Werz, & Schubert-Zsilavecz, 2011; A. Al-Harrasi, Csuk, Khan, & Hussain, 2019; Ahmed Al-Harrasi, Hussain, Csuk, & Khan, 2018; H. Ammon, 2016).

The anti-inflammatory activity of frankincense extracts and its molecular targets and mechanism of action are well established. Boswellia extracts inhibit the synthesis of 6-keto-prostaglandin (PG) F1α, a product of cyclooxygenase 1 (COX-1) (H. P. Ammon, Mack, Singh, & Safayhi, 1991) and suppress the synthesis of cytokine IL-1A-induced PGE2, COX-2, and synthesis of prostaglandin E synthase (Blain, Ali, & Duance, 2010; Ranjbarnejad, Saidijam, Moradkhani, & Najafi, 2017). Boswellic acids are COX-1 and prostaglandin E 2 synthase-1 inhibitors (Ulf Siemoneit et al., 2008; U Siemoneit et al., 2011) and both Boswellia extracts and boswellic acids inhibit leukotriene B4 (LTB4) and 5-hydroxyeicosatetraenoic acid (5-HETE) production via inhibition of 5-lipoxygenase (5-LOX) (Koeberle et al., 2018; Safayhi et al., 1992; Safayhi, Sailer, & Ammon, 1995). Acetyl-11-keto-β-boswellic acid (AKBA) inhibits membrane-binding with catalytic domains of 5-LOX (Gilbert et al., 2020). A reduction in inflammatory mediators (IL-1ß, IL-6, TNF-α, IFN-γ, and PGE2) and downregulation of IFN-γ and IL-12 have been shown by Boswellia extracts and several boswellic acids, in

particular AKBA (Gayathri, Manjula, Vinaykumar, Lakshmi, & Balakrishnan, 2007; Morsy et al., 2019; Syrovets, Buchele, Krauss, Laumonnier, & Simmet, 2005; Umar et al., 2014). *Boswellia sacra* and its triterpenoic compounds inhibited the proliferation, degranulation, and secretion of inflammatory mediators of anti-CD3 and anti-CD28 activated human T cells (Zimmermann-Klemd et al., 2020).

Most clinical data result from over 40 clinical trials with *B. serrata* preparations. Investigations have tested the effects of Boswellia and boswellic acids as mono-products and in combinations with other herbs in a study population >2,000 on various inflammation-related disease states (Cameron & Chrubasik, 2014; Kafil et al., 2017; X. Liu, Machado, Eyles, Ravi, & Hunter, 2018; Rajabian, Sadeghnia, Fanoudi, & Hosseini, 2020). Most studies reported moderate efficacy, and no reports of serious AEs could be found.

There is insufficient evidence to advise against use of anti-inflammatory therapies in patients with COVID-19. However, Boswellia extracts and their active components represent a promising approach for treatment of COVID-19-related inflammatory complications,

Salicylate Drugs of Botanical Origin

A range of herbs contain salicylic acid derivatives, including:

- Willow species *Salix alba*., S. *daphnoides, S.* x *fragilis*, *S. purpurea* and other spp.
- Meadowsweet, *Filipendula ulmaria*
- Birch (*Betula* spp., esp. *Betula lenta*)
- Wintergreen oil (*Gaultheria procumbens*)

These herbs contain NSAIDs and are inhibitors of COX-1 and / or COX-2. In April 2020, preliminary evidence assessment by the UK's National Institute for Clinical and Health Care Evidence (NICE) concluded that there is 'no evidence to determine if there is any increased risk of developing COVID-19 due to acute use of NSAIDs with people having an increased risk of contracting the disease' (https://www.nice.org.uk/advice/es23/resources/covid19-rapid-evidence-summary-acute-use-of-nonsteroidal-antiinflammatory-drugs-nsaids-for-people-with-or-at-risk-of-covid19-pdf-1158174128581).

NSAIDs remain a treatment option where indicated (https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19), and while there is no specific guidance for herbal substances containing salicylic acid derivatives, the same applies provided that the preparations are generally considered safe.

Willow bark preparations are used in many European countries for fever, rheumatoid diseases, chronic pain, and headache. Salicin, the β-glucoside of salicylic alcohol, is metabolized to salicylic acid and was the lead molecule for the development of acetylsalicylic acid (aspirin). Widely used willow bark dry extracts contain a salicin content of 15–18%. The special extract STW33-1 (Steigerwald, Germany) has shown strong inhibition of TNF-α and NFκB in activated monocytes (Bonaterra et al., 2010). A Cochrane review has concluded that there is low-to-moderate quality evidence that willow bark reduces acute and chronic lower back pain and has few adverse effects (Gagnier et al., 2016). It was superior to placebo for osteoarthritis and lower back pain with fewer adverse effects than aspirin (Oltean et al., 2014). While there are no safety assessments, the evidence points to willow preparations not posing a specific risk in the current COVID-19 pandemic.

Meadowsweet is indicated for the 'supportive treatment of common cold' and also 'for the relief of minor articular pain (EMA, 2011). Evidence is available for anti-inflammatory effects (Katanić et al., 2016), but overall, there are limited data supporting specific therapeutic benefits.

Preparations derived from birch are mostly used externally, for the alleviation of rheumatic pain and for eczema, but evidence for efficacy is weak. Topical preparations of wintergreen oil are used for sprains, rheumatism, sciatica, neuralgia, and muscular pain. With no immediate therapeutic benefits apparent, neither are relevant with reference to COVID-19 symptoms.

Preparations containing salicylic acid derivatives are often used externally, and there is no evidence for any negative effects in the context of COVID-19. With internal use, there is no evidence that high-quality products pose a specific risk in patients with Covid-19

Potential Drug Interactions of Herbal Medicines in Patients with COVID-19

There is no evidence that immunomodulating herbs discussed here would cause excess immune stimulation, exacerbating a cytokine storm. Likewise, concerns raised over potential adverse effects of NSAI drugs on SARS-CoV-2 do not apply to herbs discussed above. Herb-drug interactions are not expected, especially with drugs used in mild-to-moderate disease or for symptom relief. When compared directly to drugs with similar actions, the AE profile of herbs is favourable. In fact, to date there are no case reports of relevant herbal interactions regarding COVID-19 treatment.

Remdesivir, initially developed to combat Ebola virus, has now been administered to >1,800 COVID-19 patients worldwide via clinical trials, compassionate use, and expanded access, and has shown mixed efficacy (Y. Yang, 2020). The U.S. Food and Drug Administration issued an Emergency Use Authorization for use of remdesivir for the treatment of hospitalized patients with COVID-19 on May 1, 2020. The potential for drug interactions involving remdesivir is a complex topic with varying conclusions from different studies. CYP inhibitors do not pose a significant risk of pharmacokinetic drug interaction, but strong CYP inducers may do so, reducing blood levels of remdesivir and resulting in treatment failure (Y. Yang, 2020). In the light of this possibility and because other antiviral agents have been shown to interact with *Hypericum perforatum* (St John's wort), concurrent use should be avoided. Other commonly used herbal medicines do not appear to pose a similar risk.

Hydroxychloroquine has famously been promoted as a COVID-19 treatment, and chloroquine to a lesser extent, but evidence for the benefits and harms of using either is conflicting (Hernandez, Roman, Pasupuleti, Barboza, & White, 2020). Both have been used for many years for other indications and generally their drug interaction potential is low. A report from 2008 describes a patient suffering from acute hepatitis, prolonged cholestasis, and loss of interlobular bile ducts. taking hydroxychloroquine with tibolone and *H. perforatum*, concluding that the interaction was between tibolone and St John's wort, with hydroxychloroquine not playing a part (Etogo-Asse, Boemer, Sempoux, & Geubel, 2008).

Discussion / Conclusion

The immunomodulatory botanicals discussed above demonstrated properties that improve parameters of the immune response, without evidence of risk of overstimulation, and may have the potential to decrease the risk of a cytokine storm. Adaptogens mitigate the adverse effects of physical and psychological stress and improve immune function and could provide real benefits. They are useful for the prevention and convalescence from viral infections. While no studies have yet been conducted on the impact of adaptogens on SARS-CoV-2 specifically, their effects on innate immunity, non-specific antiviral, anti-inflammatory, detoxifying and cytoprotective activities may apply here. Vaccines are becoming available but may not provide complete protection. Some botanicals have been shown to increase sero-conversion and thus vaccine efficacy.

Botanical drugs and supplements as sources of potential therapeutic agents for SARS-CoV-2 drug development are increasingly reported in the literature. Research is needed on mechanisms of action and effectiveness of phytotherapeutic interventions, in the context of SARS-CoV-2 exposure, with or without a vaccine, as adjunctive agents during onset or recovery.

Botanicals discussed here represent an option for use in the appropriate phase of COVID-19. Data are not strong enough to support active recommendation, but the balance of the evidence suggests that they are safe enough to permit use by members of the public, with appropriate caution.

Author Contributions

Brendler – concept, team and project lead, pelargonium, adaptogens, editing; Al-Harrasi – frankincense; Bauer – echinacea; Gafner – elderberry, editing; Hardy – introduction and discussion, editing; Heinrich – salicylate drugs; Hosseinzadeh, Nassiri-Asl – liquorice; Izzo – turmeric; Michaelis – SARS-CoV-2; Panossian – adaptogens; Wasser – introduction, medicinal mushrooms; Williamson – herb drug interactions, safety, editing.

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Competing Interests

None declared.

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