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Review article

Can *Echinacea* be a potential candidate to target immunity, inflammation, and infection - The trinity of coronavirus disease 2019

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ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing public health emergency. The pathogenesis and complications advanced with infection mainly involve immune-inflammatory cascade. Therefore, the therapeutic strategy relies on immune modulation, reducing infectivity and inflammation. Given the interplay of infection and immune-inflammatory axis, the natural products received attention for preventive and therapeutic usage in COVID-19 due to their potent antiviral and anti-immunomodulatory activities. Recently, *Echinacea* preparations, particularly *E. purpurea,* have been suggested to be an important antiviral agent to be useful in COVID-19 by modulating virus entry, internalization and replication. In principle, the immune response and the resultant inflammatory process are important for the elimination of the infection, but may have a significant impact on SARS-CoV-2 pathogenesis and may play a role in the clinical spectrum of COVID-19. Considering the pharmacological effects, therapeutic potential, and molecular mechanisms of *Echinacea*, we hypothesize that it could be a reasonably possible candidate for targeting infection, immunity, and inflammation in COVID-19 with recent recognition of cannabinoid-2 (CB2) receptors and peroxisome proliferator-activated receptor gamma (PPARγ) mediated mechanisms of bioactive components that make them notable immunomodulatory, anti-inflammatory and antiviral agent. The plausible reason for our hypothesis is that the presence of numerous bioactive agents in different parts of plants that may synergistically exert polypharmacological actions in regulating immune-inflammatory axis in COVID-19. Our proposition is to scientifically contemplate the therapeutic perspective and prospect of *Echinacea* on infection, immunity, and inflammation with a potential in COVID-19 to limit the severity and progression of the disease. Based on the clinical usage for respiratory infections, and relative safety in humans, further studies for the evidence-based approach to COVID-19 are needed. We do hope that *Echinacea* could be a candidate agent for immunomodulation in the prevention and treatment of COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing public health emergency that affects millions worldwide and continues to affect people in the due course of time, until an effective drug or vaccine becomes available [1, 2]. Most deaths occur due to complications such as severe pneumonia, acute respiratory distress syndrome, shock, sepsis, and resultant multiorgan failure [3]. The pathogenesis of COVID-19 has emerged as a multifaceted, multi-system, multi-organ disorder including viremia due to overt activation of immune responses and inflammatory processes [4]. This results in

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dysregulated immune patterns manifested by an exorbitant rise in the levels of proinflammatory cytokines, chemokines, and adhesion molecules, causing the onset of a "cytokine storm" or "cytokine release syndrome" [5]. This process primarily affects the lungs and produces pathogenic effects through a ubiquitous target at the level of multiple organs [6].

The infection of SARS-CoV-2 spread through microdroplets containing exhalates of infected persons or by close contact with fomites contaminated with viral particles. The entry of virus through nasal routes spreads to the bronchioles and alveolar spaces [7]. The main targets of SARS-CoV-2 are bronchial epithelial cells and angiotensin-converting enzyme-2 (ACE2) pneumocytes of the alveolar epithelium [7, 8]. Autophagy [9, 10], basal membrane disconnection, and diminished expression of ACE2 [11,12] are induced by SARS-CoV infection, therefore permitting angiotensin II to bind the AT1aR receptor, which consequently causes acute lung injury [13]. Importantly, type-I and type –III interferons (IFN) are produced by infected cells in response to an early defense mechanism, and SARS-CoV-2 is responsive to the antiviral effects of IFN, due to their ability to inhibit the induction of SARS-CoV-2 [9,14, 15]. Massive quantity of virions is produced, which causes infection of other target neighboring cells and viremia, due to the wide distribution of ACE2 in various tissues, viremia also causes systemic infection [16, 17].

The early phases of SARS-CoV-2 infection are highlighted in recent publications [7, 14, 18]. Chu et al. [18] reported that *in vitro* SARS-CoV-2 infection in human lung explants causes type-I and –II pneumocytes infection, in addition to alveolar macrophages, besides there is an extraordinary capacity of this virus to replicate well in pulmonary tissues. The transcriptional response of SARS-CoV-2 was studied along with other viruses, e.g., middle east respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, influenza A virus (IAV), parainfluenza virus 3 (HPIV3), and respiratory syncytial virus (RSV) infections in the respiratory cell lines; *in vitro* studies, infection of ferrets; *in vivo* experiments and post-mortem samples of lung tissues from patients of COVID-19 [14]. SARS-CoV-2 showed to cause reduced responses of IFN-I and IFN-III and significant increased levels of various proinflammatory cytokines and chemokines. These results were further supported with the findings of other reports which showed enhanced serum levels of inflammatory cytokines and molecules in COVID-19 patients [19]. Collectively, these studies strongly suggest that SARS-CoV-2 has an outstanding ability to replicate within the pulmonary tissues, escape from the antiviral environment afforded by IFN-I and IFN-III and activate innate responses along with induction of the production of cytokines required for the recruitment of adaptive immune cells [7].

The transitions between innate and adaptive immune responses are critical for the clinical progress of SARS-CoV-2 infection. At this vital situation, while the immune regulation process is still poorly understood, it will lead to the onset of either a defensive immune response or a deleterious inflammatory response [20, 21, 22]. The defensive immune response is mediated by T cell, along with CD4 helping B cells, which produce specific neutralizing antibodies, and infected cells are eliminated by cytotoxic CD8 cells. It is noteworthy to mention that almost 80% of the infiltrating cells in COVID-19 are CD8 cells [15]. On the contrary, a deleterious response, incapable to hinder the replication of the virus and elimination of infected cells, could cause an event of inflammatory response, which eventually leads to a cytokine storm, clinically recognized by severe acute respiratory distress syndrome (ARDS) and systemic effects, such as disseminated intravascular coagulation. Recently, an aminopeptidase, CD26, plays a key role in the activation of T cell, which probably binds to the S protein of SARS-CoV-2, causing a nonproductive T cell infection [23]. Recently, an immunoglobulin, CD147, induces extracellular matrix metalloproteinases that bound to S1 domain and ease the viral entry into host cells [24]. The S protein binding to CD26 and CD147, which contribute to the activation of T cell, would advocate a nonproductive T cell infection that eventually leads to activation-induced cell death (AICD). It has been previously observed that MERS-CoV induces apoptosis of T cells [25, 26], and in severe COVID-19 patients functionally exhausted T cells were observed [27].

The blockade of virus attachment to ACE2 expressing cells are achieved by mainly antibodies (humoral response) against the S protein as shown by various studies [28, 29, 30]. Although, the importance of antibodies against different viral proteins are still a matter of great concern, and antibodies cross-reactivity against other extremely widespread α- and β-coronavirus, while it is observed that antibody cross-reactivity was found mainly within the β-coronaviridae [31], predominantly between SARS-CoV-2 and SARS-CoV that showed 90% homology in their amino acid sequence of S1 protein [29]. At present, few antiviral or immunomodulator agents are available, which include primarily repurposed drugs selected based on their antiviral, antibiotic, anti-inflammatory, or immunomodulatory activities against MERS-CoV, SARS-CoV, human immunodeficiency virus (HIV), and Ebola viruses [32]. Since the appearance of COVID-19, several drugs, including antivirals (remdesivir, lopinavir, ritonavir, interferon-β, ribavirin), and immunomodulators (chloroquine, hydroxychloroquine, azithromycin, tocilizumab, and ivermectin) have emerged as promising alternatives on an empirical basis with a pharmacological rationale [33]. The pathogenesis and related complications of COVID-19 mainly involve the immune-inflammatory cascade; thus, the available therapeutic strategies focus on immune modulation, reducing inflammation, viral entry and replication [34, 35].

Despite availability of the novel vaccines for COVID-19, the importance of finding drugs which could be useful in COVID-19 is crucial until the vaccine become available for the entire population and may be proven successful to provide long term immunity against the virus. Given the mortality and morbidity of COVID-19, drugs are urgently needed to check the virus, reduce hospital stays and enhance prognosis [32]. The drugs should be pharmacologically able to block the entry of the virus, prevent its replication, and/or ameliorate the hyperimmune and hyperinflammatory state to prevent disease progression and worsening [32]. In SARS-CoV infections, the use of antiviral drugs alone is insufficient for preventing the cytokine storm and related complications in critically ill patients because immune dysregulation in combination with hyperinflammatory conditions leads to complications, worsening the prognosis, rather than addressing viremia [36]. To reduce COVID-19-related complications and mortality, it is important to identify agents capable of attenuating the cytokine storm, as well as exerting antiviral effects [37]. In principle, immune responses and the resultant inflammatory process are important for the elimination of the infection; however, they may significantly impact pathogenesis and manifest the clinical spectrum of COVID-19 [35]. Considering the interplay between the immune-inflammatory axis and viral infection, natural products that are reputed as sources of antimicrobials, especially antivirals; anti-inflammatory agents; and immunomodulatory agents are suggested to be explored for preventive and therapeutic use in COVID-19 [38]. The immunomodulators suggested useful in COVID-19 are presented in Table 1.

In this context, *Echinacea* species particularly *Echinacea purpurea (E. purpurea)*, one of the most clinically studied herbal medicines, have been suggested to be an important and useful antiviral agents that modulate virus entry, internalization, and replication [38]. Among numerous herbal drugs, *Echinacea* has been suggested as a potential herbal drug candidate for novel coronaviruses [38, 39, 40, 41, 42]. In a very recent *in vitro* study, the virucidal and antiviral activity of Echinaforce® (an extract of *E. purpurea* containing caftaric acid, chlorogenic acid, cichoric acid, echinacoside and alkamide, adodeca 2E,4E,8Z, 10E/Z tetraenoic acid-isobutylamide) has been showed against human coronavirus (HCoV) 229E, MERS- and SARS coronaviruses including SARS-CoV-2 [43]. The formulation reported to exhibit virucidal activity and a protective effect in an organotypic respiratory cell culture system against RNA viruses with envelope; HCoV-229E, MERS-CoV, and SARS-coronaviruses including SARS-CoV-2. The preparations were also found virucidal against yellow fever virus. However, it did not show any activity against vaccinia virus and minute virus of mice, the DNA viruses, with and without an envelope, respectively [43]. Recently, in another study,

Table 1. Immunomodulatory agents for the management of SARS-CoV-2 infection.

Immunomodulatory agents	Mechanism of action	References
Remdesivir (GS-5734)	• inhibits enzyme RNA-dependent RNA polymerase • delays chain-termination	[208, 209]
Lopinavir and Ritonavir	• protease inhibitor and inhibits the production of mature virions	[208]
Favipiravir	• inhibits enzyme RNA-dependent RNA polymerase	[210]
Ruxolitinib	• inhibits JAK1 and JAK2	[211]
Eculizumab	• prevents immune mediated death being anti-C5 monoclonal antibody	[212]
Meplazumab	• inhibits CD147 receptor mediated binding of viral spike protein	[213]
Tocilizumab	• IL-6 receptor antagonist	[214]
Sarilumab	• IL-6 receptor antagonist	[215]
Anakinra	• anti-cytokine, IL-1 receptor antagonist	[216]
Adalimumab	• anti-cytokine, anti-TNFα	[217]
Chloroquine/Hydroxychloroquine	• inhibits synthesis of proinflammatory cytokines • interferes with glycosylation of ACE2 and interaction of spike protein	[208]
Ivermectin	• inhibits importin α/β, which mediates nuclear transport of viruses • blocks the nuclear trafficking of RNA viral proteins	[218]
Azithromycin	• antiviral, anti-inflammatory and immunomodulatory • limits viral entry and replication • decreases mucus production and recovers the lung infections • inhibits interaction of ACE2 with SARS-CoV-2 spike protein	[219]
Dexamethasone	• reduces cytokine responses and exerts anti-inflammatory effects • exerts anti-fibrotic effects	[220]
Type I, III interferon, interferon β-1a and interferon α-2b	• exerts antiviral effects by inhibiting viral replication • interacts with toll like receptors (TLRs) to mediate the antiviral effects	[221]
Convalescent plasma	• neutralizing antibodies provide short-term passive immunity	[222]
Intravenous immunoglobulin	• exerts immunomodulating and anti-inflammatory effects	[223]
Statins	• improves endothelial and vascular function • augments ACE2 expression • inhibition of TLR-MYD88-NF-κB signaling pathway	[224]
Darunavir	• protease inhibitor and inhibits the production of mature virions	[187]

thirty-nine herbal medicines were evaluated based on its benefits/risk assessment following many qualitative or semiquantitative guidelines and suggested that *Echinacea* could be a promising agent [39]. Additionally, a report emphasized that the immunomodulatory effects of *Echinacea* are immunosuppressive in nature rather than immunostimulant ascribed to the inhibitory actions on the release of various cytokines [44].

Interestingly, in addition to antiviral properties, *Echinacea* possesses notable immunomodulatory, anti-inflammatory, antioxidant, and antibacterial properties [45, 46]. Considering the pharmacological effects, molecular mechanisms, and therapeutic potential of *Echinacea*, we hypothesize that *Echinacea* could be a potential candidate for COVID-19 treatment. We hypothesize to scientifically contemplate the therapeutic prospect of using *Echinacea* for infection, immunity, and inflammation and speculate its potential for reducing the severity and complications and improving the prognosis of COVID-19. The rationale for our hypothesis is the presence of numerous bioactive agents in different parts of the plant, which have shown multiple pharmacological properties, including receptor-mediated regulation of the immune-inflammatory axis, an important therapeutic target for COVID-19. Herein, we discuss the possibilities of preventive and therapeutic potential of *Echinacea* in COVID-19 based on its relevant pharmacological properties and therapeutic effects. Much of the information presented in the hypothesis is based on data derived from previously published studies that report the immunomodulatory, anti-inflammatory, and antimicrobial properties of *Echinacea*.

Echinacea belongs to the family *Asteraceae or Compositae*, a flowering or daisy family known by various names such as coneflower, red sunflower, and rudbeckia. The species of *Echinacea* include *E. purpurea*, *E. angustifolia*, *E. pallida*, *E. atrorubens*, *E. laevigata*, *E. paradoxa*, *E. sanguinea*, *E. simulate*, and *E. tennesseensis*. Among them, after *E. angustifolia* (black sampson) and *E. pallida* (pale purple coneflower), *E. purpurea*, commonly referred to as purple coneflower, is the most abundant, extensively studied, and popularly used for therapeutic benefits [47]. *Echinacea* preparations containing either one from different species or a mix of *E. angustifolia* and *E. purpurea* are among the top-selling herbal medicines worldwide, including in North America and Europe [48]. Because of their potent antiviral and immunomodulatory properties, they are extensively studied in experimental and clinical studies and reviewed, including in metanalyses that have reported the efficacy and safety of *Echinacea* preparations in cough, cold, seasonal flu, and upper respiratory infections [46, 49, 50, 51, 52, 53, 54, 55]. Clinical studies assessing the effect of *Echinacea* on the common cold have used various *Echinacea* preparations and study designs [45, 49, 50]. Recently, a meta-analysis analyzed 24 double-blind randomized clinical trials with 4631 participants, including comparison of a total of 33 *Echinacea* preparations and placebo; it indicated that *Echinacea* preparations exhibit a moderate benefit [49].

2. Importance of phytochemical diversity of *Echinacea* for different therapeutic effects

The aerial part of *E. purpurea* mainly contain caffeic and ferulic acid derivatives, caftaric acid, chicoric acid, and chlorogenic acid as the major phenolic compounds; polysaccharides; and glycoproteins [56]. Caftaric acid is highly abundant in aqueous extracts of flowers, and chicoric acid is highly present in ethanolic extracts of flowers and roots [57]. The roots contain pyrrolizidine alkaloids, namely, tussilagine, isotussilagine, and essential oils [58]. The flowers and roots of *E. purpurea* additionally contain cynarin and echinacoside [59]. In addition, the plant contains water-soluble sucrose-derived fructans, alkaloids, proline, hydroxyproline, and flavonoids (quercetin, kaempferol, isorhamnetin, and their free phenolic acids, including p-coumaric, p-hydroxybenzoic, and protocatechuic acids) [60]. High amounts of sesquiterpene and monoterpene hydrocarbons were identified in *Echinacea* species, including *E. purpurea* [46]. The essential oils of *Echinacea* contain germacrene D, borneol, bornyl acetate, pentadeca-8z-en-2-one, naphthalene, caryophyllene

oxide, cedrol α-phellandrene, α-cadinol, and caryophyllene [61]. The essential oils from the roots of *E. purpurea* primarily contains α-phellandrene, whereas the flowers, leaves, and stem contains β-myrcene [46].

Various *Echinacea* preparations based on different species and plant parts have been evaluated in preclinical and clinical studies. Evidence from seven trials is available for preparations mainly containing the aerial components of *E. purpurea*. The phenolics in the plant, including echinacoside, cynarin, chicoric acid, caftaric acid, and chlorogenic acid, and volatile terpenes, such as germacrene D and polyacetylene, possess antimicrobial and antioxidant activities. Ascorbic acid, known as vitamin C, is abundantly present in the leaves; it aids in immune augmentation. The polysaccharides/glycoproteins in the plant including inulin, arabinogalactans, and heteroxylans, which exhibit immunostimulatory and anti-inflammatory activities [50, 60]. The polysaccharide fraction of *E. purpurea* has been shown to attenuate leukopenia [45] and adjuvant effects on T-cell cytokine responses characterized by enhancing and suppressive effects that are regulated by T-cell density [62]. Phylloxanthobilins present in the leaf extracts of *E. purpurea* have exhibited free-radical scavenging activity and have restored glutathione levels to counter oxidative stress [63]. Fructans in the plant showed potent immunomodulatory, antioxidant, free-radical scavenging, and antiviral effects through inhibition of reactive oxygen species (ROS) production, activation of regulatory T-cells following binding to toll-like receptor 2 (TLR2), and enhancement of anti-inflammatory cytokines [64].

The roots and flower heads of *E. purpurea* and *E. angustifolia* are used in most of the *Echinacea* formulations because they exhibit an abundance of bioactive compounds, whereas the leaves and stems contain low amounts of bioactive compounds [65, 66, 67]. The bioactive constituents of *Echinacea* exhibit a substantial variability because of numerous factors including genotype, species, weather, and climate, parts/components used for extraction (leaves, flowers, stem, or roots), extraction procedure, harvest period, processing, and storage conditions [65, 66, 67]. Because of these variations, a standardized extract has been suggested for therapeutic applications, preferably the extract of the whole plant, including flowers, leaves, and roots [65, 66, 67, 68]. Additionally, the inclusion of both aqueous and ethanolic extracts in the preparation could be beneficial, due to the presence of polar compounds (caffeic acid derivatives, chlorogenic acid, and chicoric acid); nonpolar compounds (alkamides, acetylenic secondary metabolites, and essential oil); and constituents with high molecular weight, such as polysaccharides and glycoproteins [65, 66, 67]. Most dosage forms available for use contain aqueous or ethanolic extracts of the aerial parts, including flowers, roots, and rhizomes. The minimum suggested standard levels are >3 mg/g for alkamides and >5 mg/g for chicoric acid [69]. Considering the variation in constituents, their activities, and concentrations of different components, it is beneficial to use a hydroalcoholic extraction that will provide a mixture of both polar and nonpolar constituents for achieving synergistic immunomodulatory, anti-inflammatory, antioxidant, and antiviral actions [70].

In addition to phenolics, polysaccharides, and terpenes, a major and important group of compounds in *Echinacea* are fatty acid compounds, popularly known as alkylamides or alkamides, with more than thirty compounds identified till date [71]. Studies have detected a high concentration of alkylamides in the aerial parts; a high amount of alkamides in the petals, disc, flowers, and seeds (mainly in the outer surface), and a moderate amount of alkamides in the flower head receptacles [72]. Alkamides (undeca-2*E*/*Z*,4*E*-diene-8,10-diynoic acid isobutylamides and dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides, and N-isobutyldodeca-2E,4E,8Z,10Z-tetraenamide) are among the most abundant compounds in the roots of *E. angustifolia* and in the aerial parts and roots of *E. purpurea* [72, 73]. Alkamides are structurally similar to anandamide, an endogenous ligand of cannabinoid (CB) receptors and an integral component of the endocannabinoid system that plays a key role in immune-inflammatory responses [71, 74]. Alkamides exert potent anti-inflammatory and immunomodulatory effects by inhibiting inflammatory signaling pathways, including cytokines, cyclooxygenase (COX), and lipoxygenases, that mediate the activation of CB receptors [75, 76]. Alkamides, including a compound isolated from *E. angustifolia* roots, showed affinity for the CB2 receptor (CB2R), as determined through bioassays using [3H] CP-55,940 as a radioligand; they are believed to be responsible for the immunomodulating property of *E. angustifolia* extracts [74]. In addition to alkamides, polysaccharides also exhibit potent immunomodulating properties [77, 78].

3. Immunomodulatory effects of *Echinacea*

Immunomodulators can activate or suppress both the innate and adaptive immune mechanisms by positively affecting the host's defense mechanisms and the capability to tolerate injuries caused by pathogens. Cumulative evidence demonstrates that *Echinacea* promotes immune function in healthy as well as immunocompromised animals [79]. Studies have concluded that several purified compounds from *Echinacea* species (e.g., glycoproteins, soluble polysaccharides, caffeic acid derivatives, phenolic compounds, and alkamides) could induce transcriptional changes that activate immunomodulatory pathways [76, 79, 80]. *E. purpurea* exhibited immunosuppressive effects by restoring splenic natural killer (NK) cell activity and splenocyte proliferation and improving the blood levels of CD4+ and CD8+ T lymphocytes and cytokines, including interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-17 (IL-17) [81]. *E. purpurea* essential oil has been reported to suppress inflammation by inhibiting interleukin-2 (IL-2), IL-6, and tumor necrosis factor (TNF-α) in the blood [82]. Aqueous and alcoholic extract of *E. purpurea,* which contain glycoproteins, polysaccharides, caffeic acid compounds, alkamides, and sesquiterpenes, have been shown to exert immunomodulatory activity by influencing both adaptive and innate immunity-regulating immune cells [83, 84, 85, 86, 87, 88].

The effects of *Echinacea* on immune cells such as monocytes, macrophages, NK cells, T cells, and dendritic cells are well demonstrated [89]. It has been reported to regulate antibody production by augmenting the production of both Th1 and Th2 cytokines [85]. Immune cells possess pattern recognition receptors (PRRs), which recognize microbe-associated molecular patterns and damage-associated molecular patterns (DAMPs) and maintain the immune-inflammatory homeostasis, thereby maintaining host health. *Echinacea* as an immunomodulator modulates both innate and adaptive immune responses and contributes to the anti-inflammatory effects [84]. The immunomodulatory activities of *Echinacea* are primarily attributed to alkamides, which bind significantly to CB2R, exert cannabimimetic responses, and influence both pro- and anti-inflammatory pathways [82, 90]. Modulation of CB2R is devoid of psychotropic effects, which are commonly observed with CB1 receptors. CB2R activation was shown to exert potent immunomodulation *via* cell death induction, cytokine suppression, inhibition of cell proliferation, and stimulation of regulatory T cells and anti-inflammatory cytokines [91, 92].

Activation of CB2R showed potent anti-inflammatory, immunomodulatory, and organoprotective properties in acute myocardial infarction (AMI), acute neuronal injury, acute liver injury, acute renal injury, neuropathic pain, anxiety, depression, interstitial cystitis, autoimmune encephalomyelitis, hyperglycemia, atherosclerosis, cardiomyopathy, vascular inflammation, intestinal inflammation, liver inflammation and fibrosis, pulmonary inflammation, and fibrosis [93, 94]. For patients with COVID-19, the use of immunomodulators is receiving attention and is regarded as “sub-etiological treatment” in the absence of an effective antiviral drug. In a convincing number of studies, *Echinacea* has been shown to modulate systemic and local immunity [84]. Its immunomodulatory effect has been attributed to the ability of *Echinacea* to inhibit CD4+ and CD8+ T lymphocytes and proinflammatory cytokines and enhance phagocytosis following increased lysosomal activity and nitric oxide production in macrophages. In a recent study, *Echinacea* was found to inhibit ACE activity, which may play an important role in virus entry, viremia onset, and further complications [95]. In most experimental models involving inflammatory states akin to COVID-19, the principal

pharmacological and molecular mechanisms underlying CB2R activation were inhibition of proinflammatory cytokines, nuclear factor NF-κB, adhesion molecules, and chemokines; subsequent modulation of signaling pathways, primarily TLRs, sirtuin-1 (SIRT1)/PPARγ coactivator (PGC-1α), AMP-activated protein kinase (AMPK)/cAMP-response element binding protein (CREB), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and nuclear respiratory factor 2 (Nrf2)/Kelch-like associated protein 1 (Keap1)/Heme oxygenase-1 (HO-1), and activation of nuclear PPARs [94, 96].

Mice deficient in CB2R showed increased susceptibility and vulnerability to influenza infection, demonstrating that CB2R is important for immunoregulation in respiratory viral infections [97]. CB2R activation has been reported to suppress lung pathology in infants infected with acute RSV *via* reducing cytokines and chemokines [98]. Because *Echinacea* has been recognized to contain a CB2R agonist, it is speculated that the therapeutic benefits of *Echinacea* are mediated by CB2R-dependent suppression of the immune-inflammatory cascades. In HIV patients, CB2R activation has been shown to impair productive infection and viral transmission involving the crosstalk/interaction between CB2R [99] and PPAR family and inhibit replication of the virus in monocytes and macrophages [100]. Furthermore, ligands activating CB receptors interact or exhibit crosstalk with the PPAR family, which consists of three subtypes, PPARα, PPARβ/δ, and PPARγ; these receptors are encoded by distinct genes and regulated by steroids and lipid metabolites [101]. The PPAR subtypes exhibit a specific tissue distribution and interact with a unique ligand to mediate their effects, primarily maintaining energy homeostasis and influencing inflammatory processes. Among these subtypes, PPARγ, which is mainly expressed in adipocytes and macrophages upon upregulation, exerts anti-inflammatory responses; this effect has renewed the interest in using PPARγ agonists, thiazolidinediones such as pioglitazone and rosiglitazone, for their anti-inflammatory potential. Recently, thiazolidinediones have been suggested for repurposing in COVID-19 treatment and as candidate drugs for cytokine storm owing to their potent anti-inflammatory action [102]. This effect is attributed to the inhibition of proinflammatory cytokines, chemokines, adhesion molecules, and other inflammatory mediators and induction of inducible nitric oxide synthase, COX-2, and proteases following PPARγ activation in macrophages [102].

Additionally, PPARγ agonists have been shown to inhibit the replication of numerous viruses including HIV, RSV, hepatitis B, and hepatitis C [103, 104]. Furthermore, PPARγ agonists have been shown to reduce morbidity and mortality in infections with influenza A virus [105]. PPARγ activation in macrophages residing in the alveolae suggested to ameliorate acute pulmonary inflammation along with enhancement in host responses to respiratory viral infections recovery from, severe viral infections, including respiratory influenza virus A and RSV [106]. The extract of *E. purpurea* has been shown to stimulate PPARγ activity in a dose-dependent manner [107]. A dichloromethane root extract of *E. purpurea* has been reported to contain isomeric dodeca-2E,4E,8Z, 10E/Z-tetraenoic acid 2-methylbutylamides, C_{12}-alkamides, which activated PPARγ-promoted glucose uptake in adipocytes [108]. An ethanolic extract of *E. purpurea* and its constituents, dodeca-2(*E*),4(*E*)-dienoic acid, isobutylamide, and hexadeca-2E,9Z,12Z,14E-tetraenoic acid isobutylamide, have exhibited PPARγ activation [109, 110]. The alkamide undeca-2E-ene-8,10-diynoic acid isolated from *E. angustifolia* showed no affinity for CB2R but inhibited IL-2 and stimulated PPARγ [70]. Activation of CB2R showed subsequent activation of PPARγ thus, the property of *Echinacea* to activate CB2R may attribute to further induce PPARγ activation. Thus, it is highly possible that *Echinacea* may have the potential to diminish the cytokine storm and ameliorate tissue damage.

PPARγ is highly expressed in the gut and is known to play a role in intestinal homeostasis in response to both diet- and microbiota-derived signals [111]. The polysaccharides in *Echinacea*, which are prebiotics, improve health by maintaining physiological function, enhancing protection against pathogens, and favorably modifying immune responses [30, 31]. Additionally, the fructan components in *Echinacea* influence the microbiota *via* increasing *Lactobacilli* and *Bifidobacteria* growth and produce short-chain fatty acids, which stimulate AMPK signaling [77]. PPARγ activation has been considered a nutritional as well as therapeutic strategy for preventing intestinal inflammation through improving redox balance, restoring antimicrobial immunity, and attenuating inflammatory mediators [112]. Intestinal inflammation and diarrhea are common in COVID-19 patients; thus, *Echinacea* could be a useful candidate for use as a therapeutic agent or adjuvant for reducing inflammation and restoring homeostasis *via* favorably modulating microbiota-derived signaling pathways.

Certain COVID-19 patients, after recovery, have been reported to develop postinfection sequelae with persistent lung dysfunction and fibrosis [113]. Recently, PPARγ activation has been shown to exert beneficial effects in pulmonary edema through regulation of alveolar fluid clearance and influencing epithelial sodium channels, a rate-limiting factor for alveolar fluid clearance [114]. The role of PPARγ activation in the attenuation of pulmonary inflammation and lung tissue injury has been demonstrated in models of endotoxemia, sepsis, allergic airway inflammation, and acute lung injury, which mimic acute respiratory distress syndrome; it inhibits the generation of proinflammatory cytokines, collagen secretion, and apoptosis of alveolar type II epithelial cells and promotes the expression of surfactant-associated protein A [115, 116, 117]. PPARγ agonism by *Echinacea* may represent a promising therapeutic approach. On the basis of available studies demonstrating the affinity of *Echinacea* to CB2R and PPARγ, it is apparent that *Echinacea* could produce a synergistic effect and prevent late-onset lung fibrosis. *Echinacea* can serve as an alternative to synthetic thiazolidinediones, which are known to possess numerous adverse effects such as weight gain, osteoporosis, heart failure, stroke, and increased risk of urinary cancer.

4. Antiviral potential of *Echinacea*

SARS-CoV-2 enters into the host cells through interaction and binding with ACE2 receptors, and the virus pathogen-associated molecular pattern (PAMP) signals induce innate immune cells, antiviral effectors such as T CD8+ cells, NK cells, neutrophils, monocytes, and macrophages in the presence of the invading virus. The innate immune cells, which possess PRRs such as TLRs, retinoic acid-inducible gene I RIG-I-like receptors (RLRs), and nucleotide-binding and oligomerization domain NOD-like receptors (NLRs), detect PAMPs and induce a suitable immune response against the invading pathogen [118, 119, 120]. The interaction between the PRR and PAMP triggers phagocytosis and elicits the synthesis of proinflammatory cytokines, such as type I interferon (IFNα/β) and type II interferon (IFN-γ), and chemokines, such as CXCL-10 and CCL-2, producing an antiviral response [34]. The immunomodulatory activity of *Echinacea* induces an antiviral response by influencing PRR, PAMP, and DAMPs. *Echinacea* have been shown to be effective against rhinoviruses [121], influenza virus [122], RSV [44], herpes virus [44], adenoviruses [44], and coronaviruses [43, 123]. Another compound, chicoric acid, has also shown potent antiviral effects against herpes simplex, influenza, enterovirus, hepatitis B virus, HIV, vaccinia virus, and vesicular stomatitis virus (VSV)-Ebola [124]. In HIV-1, chicoric acid and its derivatives inhibit the enzyme integrase, the function of which is the integration of the viral DNA into the host genome, leading to the replication of virus [125]. Treatment with *Echinacea* has been shown to retain the activity of NK cells and monocytes, which provides nonspecific immunity and eliminates virus-containing cells [126].

E. purpurea roots showed antiviral activity against influenza, herpes virus, and VSV in resistant mouse L929 cells [127]. In a recent review, the antiviral properties have been presented and many possible targets of antiviral actions are suggested that include membrane components, cellular attachment or entry of the virus, enzymes involved in replication and egress of progeny virus from infected cells [123]. In a recent study, *E. purpurea* reduced influenza virus A infection-induced enhanced adhesion of *Haemophilus influenzae* and *Staphylococcus aureus* to

bronchial epithelial cells. The extract has been demonstrated to inhibit the expression of intercellular adhesion molecule 1 (ICAM-1), fibronectin, and platelet-activating factor receptor, and inflammatory responses through reducing the expression of IL-6, IL-8, NF-κB-p65, and TLR-4. The study is suggestive of the potential benefits of *E. purpurea* for inhibiting the cytokine storm and preventing the risk of respiratory complications associated with viral infections [128]. The constituents of *Echinacea*, such as isoprinosine have exhibited immunostimulant properties through enhancing the reactivity of the human defense system against lymphotropic human herpesvirus-6 latent infection in lymphoid cells [129].

5. Therapeutic potential of *Echinacea* in the respiratory system

Patients with COVID-19 may develop acute respiratory distress, which causes lung injury characterized by parenchymal injury, neutrophil infiltration, bilateral pulmonary infiltrates, and vasculitis, following the massive release of proinflammatory cytokines, particularly, raised levels of IL-6, that often correlates with the severity, prognosis, and mortality [130, 131]. Similarly, enhanced levels of IL-6 in experimental models have been demonstrated to play role in the onset and severity of acute lung injury [132], which resembles in patients with SARS and COVID-19. Various studies postulated that IL-6 inhibition may potentially alleviate the lung damage induced by virus [132, 133]. Tocilizumab has demonstrated therapeutic effectiveness in mitigating cytokine storm associated with COVID-19 by particular inhibition of IL-6. However, it exhibits many adverse effects such as hematologic, liver and gastrointestinal abnormalities as well as high blood pressure and dermatological reactions [133]. In line with these observations, the lozenges of *E. purpurea* has been reported to decrease IL-6 and TNF-α levels in humans [134].

During acute viral respiratory infections, the chances of secondary bacterial infections are high because of the compromised host immune response, which worsens the condition. The immune system, primarily macrophages and granulocytes, produces antibacterial nonspecific immune responses. COVID-19 patients have also exhibited secondary bacterial infections [135]. *E. purpurea* has been shown to inhibit respiratory pathogens and several viruses, fungi, bacteria, and parasites including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Legionella pneumophila*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Propionibacterium acnes*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Moraxella catarrhalis*, *Bordetella pertussis*, *Mycoplasma pneumoniae*, *Clostridium difficile*, *Candida albicans*, *Leishmania donovani*, and *Trypanosoma brucei*; and lipopolysaccharides (LPS), which are bacterial endotoxins, in experimental studies and isolates from humans [123, 136]. *Echinacea* increases the activation of granulocytes and lymphocyte response in resistant strains [137]. The antibacterial activities of *Echinacea* are primarily attributed to phenolic components, rather than alkylamides or polysaccharides [136]. *Echinacea* has also reported to ameliorate mucosal immune suppression which usually occurs during intense exercise and may decrease the duration of upper respiratory tract infections [138].

6. Organprotective effects *of Echinacea*

In addition to severely affecting lungs, the clinical manifestations of COVID-19 including acute injuries to the liver, heart, intestine, and brain that may progresses to sepsis and multiorgan failure, resulting in death [139, 140]. The probability of mortalities is significantly high in aged people with co-morbid conditions including diabetes, cancer, diseases of heart, and respiratory problems. SARS-CoV-2 infection may lead to sepsis and subsequent multiorgan failure [141]. Sepsis involves both an inflammatory response and immune suppression simultaneously in response to an infection [142]. CB2R plays an important regulatory role in the immune response to sepsis. Mice lacking CB2R exhibited enhanced levels of IL-6 in the serum, neutrophil recruitment, reduced neutrophil activation, and reduced p38 activity at the site of infection and bacteremia [143]. Reduced survival and acute lung injury have been correlated with CB2R deficiency. Activation of CB2R has been shown to reduce the recruitment of neutrophils, enhance neutrophil activation and p38 activity, and improve survival [143]. CB2R plays a vital role in neutrophil/leukocyte recruitment, thereby suppressing infection and inflammation during sepsis [144]. CB2R agonists have been reported to ameliorate leukocyte adhesion to the endothelium, oxidative stress, systemic inflammatory mediators, microcirculatory dysfunction, bacteremia, and lung injury, along with improving survival in experimental models of sepsis [145, 146]. CB2R activation specifically mitigated septic lung injury by suppressing inflammatory mediators and augmenting autophagy [147, 148].

In an experimental model of polymicrobial sepsis, CB2R activation decreased histopathological damage in the brain, heart, lungs, and liver by reducing caspase-3, p–NF–κB, TNF-α, IL-1β, and IL-6 levels in these tissues, as well as in the serum, and improved the levels of the anti-inflammatory cytokine IL-10 [149]. Several experimental models of sepsis rely on LPS-induced macrophages, which involve activation and release of inflammatory mediators including cytokines [150]. *Echinacea* has been reported to suppress inflammatory mediators and inhibit macrophages [151]. Considering the association of SARS-CoV-2 with sepsis-induced life-threatening organ dysfunction and the beneficial role of CB2R in attenuating sepsis [149], *Echinacea* constituents may serve as a promising candidate for sepsis associated with SARS-Cointerferon α-2bV-2.

E. purpurea and the alkamide dodeca-2E,4E,8Z,10Z(E)-tetraenoic acid isobutylamide, showed hepatoprotective effects in experimental model by restoring liver enzymes, attenuating inflammation, inhibiting inflammatory cytokines, and activating the c-Jun N-terminal kinase (JNK)/HO-1 pathway [152]. *E. purpurea* has been reported to enhance the utilization and homing of CD34(+) stem cells to myocardial tissue cytokines in rats with AMI, demonstrating its usefulness in stem-cell-based regeneration of acute myocardial injury [153]. *E. purpurea* showed protective effects in intestinal inflammation [154], drug-induced liver injury, and hematologic toxicity [155], and radioprotective effects mediating antioxidant activity and reduction in DNA fragmentation in gamma-irradiated mice [156].

Additionally, COVID-19 significantly impacts mental health and may adversely impact immune functioning [157]. It has been reported that there is an increased susceptibility to viral upper respiratory infections following rise in psychosocial problems such as stress, anxiety, and depression which commonly occurring in health workers or in general populations due to this pandemic [158]. It has been suggested that psychoneuroimmunity can be important in COVID-19 infection due to the association of psychosocial distress with immune-inflammatory processes. *Echinacea* appears useful to modulate psychoneuroimmunity by relieving stress, anxiety, and depression. Stress exposure causes excitotoxicity and neuroinflammation, which contribute to stress-related neuropathologies such as depression. *Echinacea* has been demonstrated to have antidepressant, antistress, and antianxiety effects in experimental models regulating excitatory synaptic transmission in the hippocampus by improving antioxidant levels, inhibiting proinflammatory cytokines and inflammatory mediators, and interacting with the dopaminergic system [159]. Considering the impact of COVID-19 on organ function, it is speculated that the organoprotective effect of *E. purpurea* might aid in reducing complications and multiorgan failure in COVID-19.

7. Antioxidant activity of *Echinacea*

In addition to immunoinflammatory changes, macrophages and neutrophils can produce numerous ROS including hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet -}$) and hydroxyl ($OH^{\bullet}$) radicals, which further activate several signaling pathways and institute inflammation and cell death in multiple organs, including the lungs [160]. Oxidative stress and subsequent activation of NF-κB/TLR signaling pathways, triggered by

viral pathogens such as SARS-CoV, are believed to amplify the host inflammatory response, which results in acute lung injury [161]. Additionally, the hyperinflammatory/oxidative state may lead to dysfunction of the mitochondria, the hub of cellular oxidative homeostasis, and causes platelet damage, which upon interaction with coagulation cascades aggravate clotting events and thrombus formation. Mitochondrial oxidative stress may contribute to microbiota dysbiosis, altered coagulation pathways, and fuel the inflammatory/oxidative response, leading to a vicious cycle of events [161]. Oxidative stress may further primes endothelial cells to acquire a pro-thrombotic and pro-inflammatory phenotype, predisposing patients to thromboembolic and vasculitis events and disseminated intravascular coagulopathy [162]. Nrf2, a transcription factor that regulates the redox balance and the expression of genes involved in immunity and inflammation, is believed to provide defense against SARS-CoV-2 [163]. Reduced redox status of a cell increases susceptibility to oxidative stress, which may lead to cell death and viral release [164]. SARS-CoV-2 infection can lead to alterations in redox balance in infected cells through modulation of NAD^+ biosynthesis, poly (ADP-ribose) polymerase (PARP) function, and alteration of proteasome and mitochondrial function in the cells, thereby leading to enhanced cell stress responses that further exacerbate inflammation. ROS production can increase IL-6 production and lipid peroxidation, resulting in cell damage [165]. Virus-induced inflammation and oxidative stress can act as common mechanisms responsible for cardiovascular, pulmonary, renal, and neurological symptoms in COVID-19 patients [166].

Free-radical scavenging and antioxidant activities of *Echinacea* extracts have been ascribed to phenolic constituents, including chicoric acid; moreover, the alkamides present in these extracts lacked free radical scavenging activity [167]. Although alkamides did not exhibit antioxidant activity, they augment the antioxidant power of chicoric acid by providing better surface access by preventing lipid oxidation in the lipophilic component of the emulsion and facilitating the revival of chicoric acid by providing allylic hydrogen to the one-electron oxidized chicoric acid [167]. *E. purpurea* has been shown to augment endogenous antioxidants, exert ferric reducing properties, Fe^{2+} chelation, and radical-scavenging activity in numerous *in vitro* assays and *in vivo* models, resulting in mitigation of oxidative stress through counteraction of ROS generation, inhibition of lipid peroxidation, and glutathione modulation [46, 168]. Additionally, *E. purpurea* enhances tolerance against stress and improves antioxidant power in different tissues of the heart, brain, intestine, liver, stomach, kidney, pancreas, and blood, which may aid in the protective and adaptive responses against viral infections and drugs [46]. *Echinacea* has been shown to exert protective effects by suppressing ROS generation and NADPH oxidase 2/4 expression and control cell proliferation and inflammation by inhibiting proinflammatory cytokines and the Nrf2/HO-1 and NF-κB/Nrf2 signaling pathways [46, 169].

8. Pharmaceutical preparation and drug interactions of *Echinacea*

Echinacea preparations are available in multiple dosage forms including elixirs, tinctures, tea, juice, lozenges, tablets, soft gel capsules, and topical formulations. The active constituents of *Echinacea* are important ingredients of several polyherbal formulations, including SAMITAL® (IndenaSpA, Milan, Italy), which contains *E. angustifolia* [170], Echniforce® (Bioforce, Switzerland), which contains *E. purpurea* [171], and Viracea®, a topical formulation from Destiny BioMediX Corp [172]. In respiratory diseases, *E. purpurea* has exhibited synergistic or additive immunomodulatory effects with multiple natural supplements including licorice (a major source of glycyrrhizin) [173], black seed (a major source of thymoquinone) [174], curcumin [175], garlic [176], ginseng [177], vitamin D [79], vitamin C [79, 178], and zinc [79, 178]. A preparation, Immunal® containing *E. purpurea* extract showed to enhance the antibody production and specific cellular immunity [179].

Recently, studies have suggested the repurposing of curcumin [180], glycyrrhizin [181], thymoquinone [182], and polyphenolic flavonoids [183] for COVID-19 owing to their potential to exert synergistic or additive effects including antiviral, anti-inflammatory, immunomodulatory, and antioxidant activities, with no systemic toxicity. Although, the interaction and risks appear to have negligible therapeutic concern [184]. *Echinacea* did not affect the pharmacokinetics of lopinavir/ritonavir (protease inhibitors) in healthy volunteers [185] and etravirine (a non-nucleoside reverse transcriptase inhibitor of HIV) and darunavir (protease inhibitor) in HIV patients [186]. Both these drugs are used in the management of COVID-19 [187] worldwide, and no interaction with these drugs is further suggestive of the possible safety of *Echinacea* for therapeutic use. Figure 1 presents a scheme that depicts the plausible effect of *Echinacea* on the inhibition of inflammatory cytokines and activation of CB2/PPAR in the context of the triad of infection, immunity, and inflammation in COVID-19.

One of the preparations, Immulant® (containing *Echinacea* and *Nigella sativa*), promoted the immune response following avian influenza virus (AI-H9N2) vaccination and suppressed pathogenicity by improving antioxidant, hematology, immunology and histopathology parameters in dexamethasone-induced stress in animals [174]. Additionally, in recent studies, the early use of immunomodulators including corticosteroids and intravenous immunoglobulin has been suggested to be helpful in reducing the morbidity and mortality rates of older patients with underlying conditions [188]. The *Echinacea* extract, as well as the active components chicoric acid, caftaric acid, and alkamides, are well absorbed through the esophageal, buccal, and intestinal membranes [189] and are bioavailable in all major organs including the liver, kidney, heart, brain, intestine, and spleen; additionally, the components may rapidly cross the blood-brain barrier [190] following oral administration [71].

9. Safety and adverse effects of *Echinacea*

Echinacea has been reported relatively safe and tolerable in adults, children, and infants and beneficial in reducing pain and inflammation with a positive risk-to-benefit ratio with few minor adverse effects [60]. A systematic review has presented adverse events of *Echinacea* in humans and suggested short-term safe use [191]. Most herbal medicines are perceived for their preventive ability and are used for their protective effects. However, *Echinacea* is well considered for therapeutic purposes and often indicated for the prevention of common cold during winter climate. *Echinacea* preparations have been suggested for a week or ten days (e.g., EMA/HMPC/48 704/2014) and the *Echinacea* based products used for the short term were found to have a relatively low risk to consumers [191, 192]. Various regulatory agencies, including the European Scientific Cooperative on Phytotherapy, World Health Organization, and German Commission E, suggest that it should not exceed 8 weeks. In human studies, the oral doses of *Echinacea* were usually in the range of 800–1500 mg per day. The consequences of long-term use (years) of *Echinacea* are unknown. There have been negligible toxic effects associated with continuous ingestion of different *Echinacea* preparations for up to 6 months. Some adverse effects were reported by the UK Committee on Safety of Medicines and the Medicines and Healthcare Products Regulatory Agency's spontaneous reporting scheme (the "yellow card" scheme), commonly including abdominal pain, angioedema, dyspnea, nausea, pruritus, rash, erythema, and urticarial [60]. In animal studies, *Echinacea* showed to cause early termination of pregnancies [193], although does not cause teratogenicity or malformations in fetus [194]. Whereas, another reports suggest that *Echinacea* may interfere with embryonal angiogenesis and affect fetal development, thus should be avoided in pregnancy [195].

10. Contraindications on the use of *Echinacea* as an immunomodulator

The *Echinacea* preparations are also contraindicated in patients, suffering from progressive systemic diseases, e.g., leukemia, leukemia-like diseases, tuberculosis, multiple sclerosis, collagen disorders, and

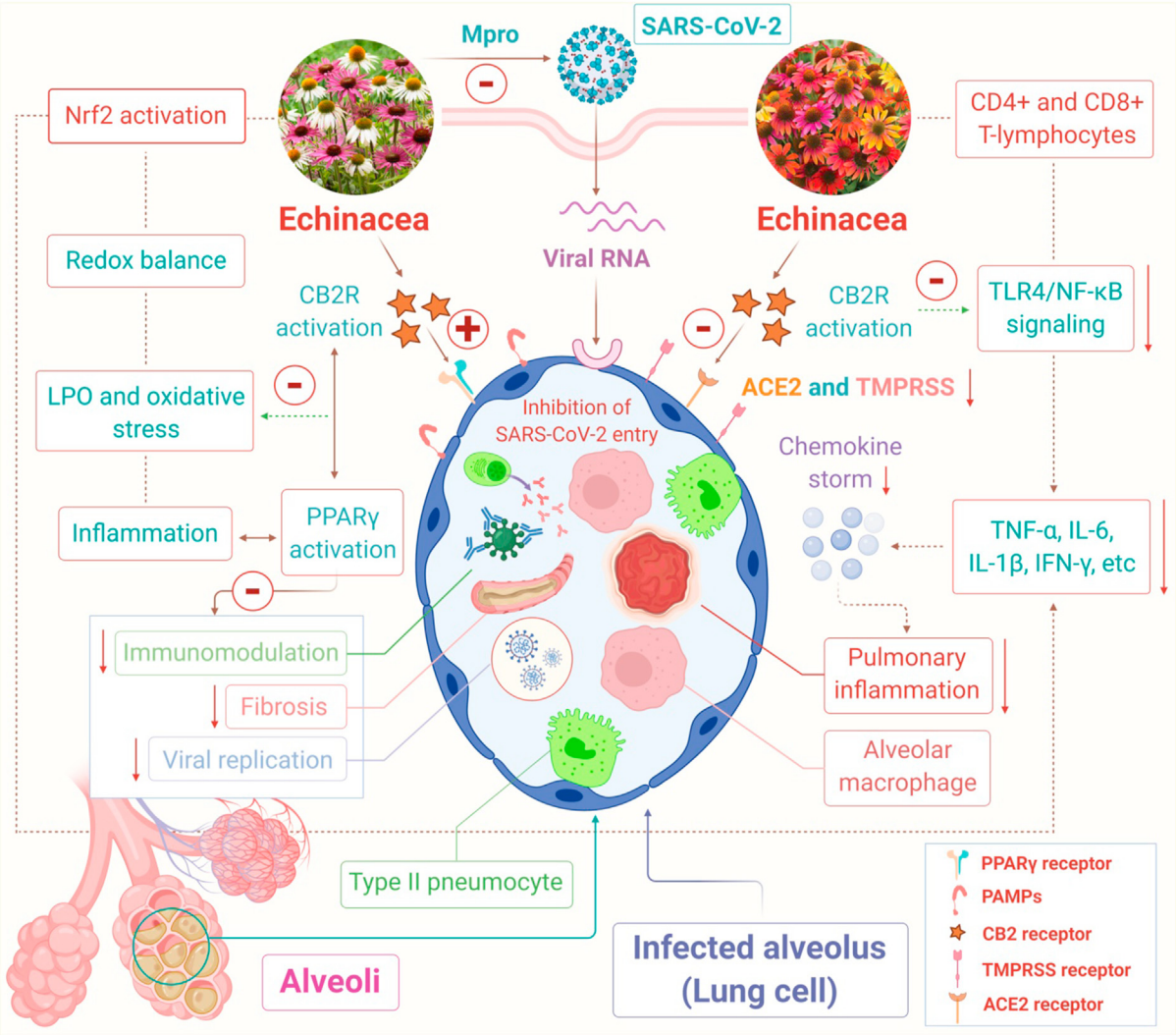

Figure 1. A scheme to depict the plausible mechanisms and effect of *Echinacea* on the inhibition of inflammatory cytokines and activation of CB2/PPAR in the context of infection, inflammation, and immunity in COVID-19.

other autoimmune diseases [60]. *Echinacea* products are also contraindicated in AIDS and HIV infections. The contraindications are based on the theory of immunomodulatory activity of *Echinacea*, although there is a differing idea that these products are not harmful in patients with autoimmune diseases [60]. Though, with the available limited safety data, *Echinacea* appears well tolerated, but the safety profiles of different *Echinacea* preparations still need to be set up through further investigation and surveillance. Safety issues include the possibility of allergic reactions, the use of *Echinacea* by patients with autoimmune diseases, and the potential for *Echinacea* preparations to interact with conventional medicines.

Immunostimulants are used cautiously as they may worsen or exacerbate autoimmunity in genetically sensitive people [196]. *Echinacea* has the potential to enhance immune function, therefore it cannot be ruled out that there may be a risk of activation of the immune system during a cytokine storm. However, in many clinical studies, *Echinacea* preparations have been shown to reduce pro-inflammatory cytokines and promote anti-inflammatory cytokines [44, 197, 198, 199, 200]. Based on human studies, *Echinacea* may have a prophylactic value once given at the onset of symptoms, rather than using at later stages. The majority of the clinical studies carried out in healthy humans had normal immune status, thus the change in immune function cannot be well inferred from the studies. The available preclinical studies on *Echinacea* showed a reduction in proinflammatory cytokines along with improving survival of infected animals with influenza [201] and SARS-CoV [202] that demonstrated the co-administration of *E. purpurea* with other drugs metabolized by CYP3A or CYP1A2 may affect the elimination of the latter [203].

11. Limitations on the use of *Echinacea*

Echinacea preparations are one of the extensively studied herbal drugs and reputed for their therapeutic benefits since many years in respiratory infections. It is well-studied, extensively used, widely accessible reputed herbal immunomodulator and antiviral which is gaining importance due to its therapeutic benefits along with preclinical and clinical studies. Among numerous herbal drugs, *Echinacea* has been proposed as a potential herbal drug candidate for novel coronaviruses [38, 39, 40, 41, 42] and a recent experimental (*in vitro*) study, showed that *Echinacea* has inhibitory activity against SARS-CoV-2 [43]. It is also considered as a functional food ingredient [60]. The dietary nature, availability as a functional food ingredient, pleiotropic effects and immune boosting properties make *Echinacea* as an attractive candidate for potential use as a preventive agent or therapeutic adjuvant in COVID-19. The use of *Echinacea* in COVID-19 is still inconclusive because the *in vitro* antiviral effects need to be established in the *in vivo* as well as human studies.

However, the potential of *Echinacea* in SARS-CoV-2 infections cannot be overlooked provided the experimental data on antiviral, immunomodulatory, anti-inflammatory, and tissue protective effects.

The SARS-CoV occurred in 2003, since then many natural products have shown potential in experimental studies to be developed as a candidate drug until recent years, but still there is very less focus on drug development from natural products due to numerous reasons ranging from lack of pharmacokinetic and drug formulation studies [204, 205, 206]. Recently, it has been suggested that a meticulous, focused and integrated approach may have the potential to develop the drugs from traditional drugs to modern medicines following the scientific standards of drug development [207]. Provided the potent pharmacological effects against infection, inflammation and immunity in experimental models and in clinical studies, the potential role of *Echinacea* may be possible and thus speculated to be beneficial. Before recommendations on the potential application of *Echinacea* in COVID-19, further studies are encouraged to evaluate in the preclinical and clinical studies. Nevertheless, *Echinacea* can be one of the most suitable agents for potential usage in COVID-19, in context to dysregulated immune-inflammatory homeostasis. Provided the oragnprotective effects attributed to inhibition of proinflammatory cytokines and chemokines and salvage of tissues, *Echinacea* may be a vital agent for potential in improving prognosis and curbing complications appears after recovery. Recent availability of animal models of SARS-CoV-2 pathogenesis may be valuable in assessing efficacy, mechanisms, and safety. Further, the drug interaction studies can be carried out to determine the use of *Echinacea* with currently used drugs in prevention and treatment.

12. Conclusion and future remarks

The available literature suggests the potential candidature of *Echinacea* for evaluation in COVID-19 management on the basis of its plausible effects on infection, inflammation, and immunity. However, till date, no comprehensive and conclusive data is available on the preclinical or clinical benefits of *Echinacea* in COVID-19. Therefore, preclinical and clinical studies are recommended further to demonstrate *Echinacea* as a preventive agent or therapeutic adjuvant in COVID-19. *Echinacea* preparations comprise unique blend of numerous phytochemicals, including phenolics, alkaloids, alkamides, polysaccharides, terpenoids, vitamins, and fructans, which activate or regulate the immune system through direct or indirect mechanisms by modulating T-cells, macrophages, lymphocytes, cytokines. Considering the pharmacological and molecular mechanisms of *Echinacea*, including cannabimimetic property-mediated anti-inflammatory and immunomodulatory effects and integration of antiviral and antibacterial activities along with antioxidant and organoprotective effects, they may be beneficial for controlling symptoms, disease worsening, secondary infections, complications, progression, and resultant death in COVID-19. Future studies should investigate *Echinacea* as preventive agent or therapeutic adjuvant in COVID-19 and as an immune-boosting agent in people at risk or with comorbidities.

Declarations

Author contribution statement

M.F. Nagoor Meeran; H. Javed: Performed the experiments; Wrote the paper.

C. Sharma: Wrote the paper.

S. N. Goyal: Conceived and designed the experiments.

S. Kumar: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

N. K. Jha: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

S. Ojha: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in the article are appropriately cited. The authors hypothesized based on the available reports and does not promote the use of *Echinacea* in any forms until the mechanisms investigated and efficacy proven in the *in vivo* and human studies.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] H. O, L. K, M. B, N.E. D, H. I, N. B, et al., The pathogenesis of coronavirus disease 2019 (COVID-19): evaluation and prevention, J. Immunol. Res. 2020 (2020) 1357983.
[2] X. H, F. W, L. H, L. W, K. C, Epidemiology and clinical characteristics of COVID-19, Arch. Iran. Med. 23 (4) (2020) 268–271.
[3] C. H, Y. W, X. L, L. R, J. Z, Y. H, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[4] Q. Y, B. W, J. M, The pathogenesis and treatment of the `Cytokine Storm' in COVID-19, J. Infect. 80 (6) (2020) 607–613.
[5] Y. T, J. L, D. Z, Z. X, J. J, C. W, Cytokine storm in COVID-19: the current evidence and treatment strategies, Front. Immunol. 11 (2020) 1708.
[6] M. V, S. R, K. F, A. DB, E. G, Atherosclerosis as pathogenetic substrate for sars-cov2 cytokine storm, J. Clin. Med. 9 (7) (2020) 2095.
[7] M. Gentzsch, B.C. Rossier, A pathophysiological model for COVID-19: critical importance of transepithelial sodium transport upon airway infection, Function (Oxf) 1 (2) (2020) zqaa024.
[8] R. Y, Y. Z, Y. L, L. X, Y. G, Q. Z, Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2, Science 367 (6485) (2020) 1444–1448.
[9] C.S. S, H.Y. Q, C. B, N.N. H, M. A-A, J.H. S, et al., SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome, J. Immunol. 193 (6) (2014) 3080–3089.
[10] T.S. F, D.X. L, The ER stress sensor IRE1 and MAP kinase ERK modulate autophagy induction in cells infected with coronavirus infectious bronchitis virus, Virology 533 (2019) 34–44.
[11] K. K, Y. I, S. R, H. G, F. G, B. G, et al., A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (8) (2005) 875–879.
[12] S. P, A.A. D, Immunopathogenesis of coronavirus infections: implications for SARS, Nat. Rev. Immunol. 5 (12) (2005) 917–927.
[13] Y. I, K. K, S. R, Y. H, F. G, B. G, et al., Angiotensin-converting enzyme 2 protects from severe acute lung failure, Nature 436 (7047) (2005) 112–116.
[14] D. B-M, B.E. N-P, W.C. L, S. U, D. H, R. M, et al., Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181 (5) (2020) 1036–1045, e9.
[15] G. L, Y. F, Y. L, T. H, Z. L, P. Z, et al., Coronavirus infections and immune responses, J. Med. Virol. 92 (4) (2020) 424–432.
[16] I. H, W. T, M.L. B, A.T. L, G. N, H. vG, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2) (2004) 631–637.
[17] X. Z, K. C, J. Z, P. H, J. H, Z. H, Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection, Front. Med. 14 (2) (2020) 185–192.
[18] H. C, J.F. C, Y. W, T.T. Y, Y. C, Y. H, et al., Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19, Clin. Infect. Dis. 71 (6) (2020) 1400–1409.
[19] D.M. DV, S. K-S, H.H. H, N.D. B, S. N, B. W, et al., An inflammatory cytokine signature predicts COVID-19 severity and survival, Nat. Med. 26 (10) (2020) 1636–1643.
[20] M.Z. T, C.M. P, L. R, P.A. M, L.F.P. N, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (6) (2020) 363–374.

[21] R.H. M, M. Z, M. H, M.H. M, COVID-19 as an acute inflammatory disease, J. Immunol. 205 (1) (2020) 12–19, 1.
[22] X. C, COVID-19: immunopathology and its implications for therapy, Nat. Rev. Immunol. 20 (5) (2020) 269–270.
[23] N. V, J.A. W, Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26, Emerg. Microb. Infect. 9 (1) (2020) 601–604.
[24] H. U, M.M. P, CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement, Stem Cell Rev. Rep. 16 (3) (2020) 434–440.
[25] I.C. H, C.C. B, J.L. W, S.R. R, M.M. B, J.J. C, et al., Distinct patterns of IFITM-mediated restriction of filoviruses, SARS coronavirus, and influenza A virus, PLoS Pathog. 7 (1) (2011), e1001258.
[26] T.S. F, D.X. L, Human coronavirus: host-pathogen interaction, Annu. Rev. Microbiol. 73 (2019) 529–557.
[27] M. Z, Y. G, G. W, G. S, S. L, D. S, et al., Functional exhaustion of antiviral lymphocytes in COVID-19 patients, Cell. Mol. Immunol. 17 (5) (2020) 533–535.
[28] A. B, B.D. Z, D.E. W, P.J. T, K.V. H, Identification of a receptor-binding domain of the spike glycoprotein of human coronavirus HCoV-229E, J. Virol. 89 (17) (2015) 8816–8827.
[29] A.C. W, Y.J. P, M.A. T, A. W, A.T. M, D. V, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (2) (2020) 281–292, e6.
[30] X. O, Y. L, X. L, P. L, D. M, L. R, et al., Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV, Nat. Commun. 11 (1) (2020) 1620.
[31] L. G, L. R, S. Y, M. X, D. C, F. Y, et al., Profiling early humoral response to diagnose novel coronavirus disease (COVID-19), Clin. Infect. Dis. 71 (15) (2020) 778–785.
[32] S. F, D. X, Y. W, L. L, X. Z, W. Z, Research progress on repositioning drugs and specific therapeutic drugs for SARS-CoV-2, Future Med. Chem. 12 (17) (2020) 1565–1578.
[33] R. Wu, L. Wang, H.-C.D. Kuo, A. Shannar, R. Peter, P.J. Chou, et al., An update on current therapeutic drugs treating COVID-19, Curr. Pharmacol. Rep. 11 (2020) 1–15.
[34] A. A, M. DG, A. T, C. M, S. G, Immunopathology of SARS-CoV-2 infection: immune cells and mediators, prognostic factors, and immune-therapeutic implications, Int. J. Mol. Sci. 21 (13) (2020) 4782.
[35] J.W. S, C. Z, X. F, F.P. M, Z. X, P. X, et al., Immunological and inflammatory profiles in mild and severe cases of COVID-19, Nat. Commun. 11 (1) (2020) 3410.
[36] R. C, A.R. F, R. V, M. M, J. Z, D.K. M, et al., Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice, Cell Host Microbe 19 (2) (2016) 181–193.
[37] J. Z, J. H, Current findings regarding natural components with potential anti-2019-nCoV activity, Front Cell Dev. Biol. 8 (2020) 589.
[38] A. H, R. B, M. H, V. S, O. K, G. H, et al., Challenges at the time of COVID-19: opportunities and innovations in antivirals from nature, Planta Med. 86 (10) (2020) 659–664.
[39] D. S, J.M. P-G, F. B, O. E, Y.M. F-B, C.M. J, et al., COVID-19: is there evidence for the use of herbal medicines as adjuvant symptomatic therapy? Front. Pharmacol. 11 (2020) 581840.
[40] M. A, K. C, P.R. S, J. C, D. A, D.N. M, et al., The effect of Echinacea spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: a rapid review, Adv. Integr. Med. 7 (4) (2020) 203–217.
[41] M. B, H. H, Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies, Phytother Res. (2020).
[42] R.V. N, H. R, M. G, A.F. K, N. A, Traditional herbal medicine candidates as complementary treatments for COVID-19: a review of their mechanisms, pros and cons, Evid. Based Compl. Alternat. Med. 2020 (2020) 2560645.
[43] J. S, H.R. J, W.C. A, M. S, R. Z, S. R, et al., In vitro virucidal activity of Echinaforce®, an Echinacea purpurea preparation, against coronaviruses, including common cold coronavirus 229E and SARS-CoV-2, Virol. J. 17 (1) (2020) 136.
[44] M. S, S.A. A, R. S, J.B. H, Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract, Antivir. Res. 83 (2) (2009) 165–170.
[45] D. M, K. L, F. W, R. B, H. W, Immunomodulation with echinacea - a systematic review of controlled clinical trials, Phytomedicine 1 (3) (1994) 245–254.
[46] M. S-R, D. M, M.F.B. M-B, J.N.P. C, C.F. B, H.D.M. C, et al., Echinacea plants as antioxidant and antibacterial agents: from traditional medicine to biotechnological applications, Phytother Res. 32 (9) (2018) 1653–1663.
[47] A. G-F, Medicinal plants: traditions of yesterday and drugs of tomorrow, Mol. Aspect. Med. 27 (1) (2006) 1–93.
[48] J.L. P, S.I. C, C.S. H, M.L. S, Echinacea biotechnology: advances, commercialization and future considerations, Pharm. Biol. 56 (1) (2018) 485–494.
[49] M. K-V, B. B, D. K, R. B, K. A-W, K. L, Echinacea for preventing and treating the common cold, Cochrane Database Syst. Rev. 2 (2) (2014) CD000530.
[50] A. M, M. V, S. S, Echinacea purpurea: pharmacology, phytochemistry and analysis methods, Pharmacogn. Rev. 9 (17) (2015) 63–72.
[51] K. A-W, R. B, Review and assessment of medicinal safety data of orally used echinacea preparations, Planta Med. 82 (1-2) (2016) 17–31.
[52] S.M. R, Echinacea purpurea: a proprietary extract of echinacea purpurea is shown to be safe and effective in the prevention of the common cold, Holist. Nurs. Pract. 30 (1) (2016) 54–57.
[53] H.A. M, Prevention and treatment of influenza, influenza-like illness, and common cold by herbal, complementary, and natural therapies, J. Evid. Based Compl. Altern. Med. 22 (1) (2017) 166–174.
[54] D. A, H. C, R. L, F.J. S, G. D, Herbal medicine in children with respiratory tract infection: systematic review and meta-analysis, Acad Pediatr. 18 (1) (2018) 8–19.
[55] S. D, R. C, Echinacea for the prevention and treatment of upper respiratory tract infections: a systematic review and meta-analysis, Compl. Ther. Med. 44 (2019) 18–26.
[56] S. W, J. P, T. C, E. M, B. B, C.V. R, et al., A strategy for test article selection and phytochemical characterization of Echinacea purpurea extract for safety testing, Food Chem. Toxicol. 137 (2020) 111125.
[57] M. S, G. M, R. V, M. M-P, Which plant part of purple coneflower (echinacea purpurea (L.) moench) should be used for tea and which for tincture? J. Med. Food 22 (1) (2019) 102–108.
[58] P. C, M. Ś, M. K, S. F, I. P, R. G, Chemical and pharmacological profiles of Echinacea complex, Int. J. Biol. Macromol. 79 (2015) 388–391.
[59] R.M. F, M. C, G. A, L. S, P. P, P. M, Echinacoside and caffeoyl conjugates protect collagen from free radical-induced degradation: a potential use of Echinacea extracts in the prevention of skin photodamage, Planta Med. 61 (6) (1995) 510–514.
[60] J. B, L.A. A, S. G, J.D. P, Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt.,Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties, J. Pharm. Pharmacol. 57 (8) (2005) 929–954.
[61] M. Nyalambisa, I.A. Oyemitan, R. Matewu, O.O. Oyedeji, O.S. Oluwafemi, S.P. Songca, et al., Volatile constituents and biological activities of the leaf and root of Echinacea species from South Africa, Saudi Pharmaceut. J. 25 (3) (2017) 381–386.
[62] F.N. F, G. P, H. L, C.B. L, E.J. K, B.R. C, et al., Echinacea purpurea (L.) Moench modulates human T-cell cytokine response, Int. Immunopharm. 19 (1) (2014) 94–102.
[63] C.A. K, P. W, A.M. V, S. M, Re-opening the stage for Echinacea research - characterization of phylloxanthobilins as a novel anti-oxidative compound class in Echinacea purpurea, Phytomedicine 60 (2019) 152969.
[64] Y.P. J, K. W, Z.J. Z, Y.N. T, D. H, C.Y. H, et al., TLR2/TLR4 activation induces Tregs and suppresses intestinal inflammation caused by Fusobacterium nucleatum in vivo, PloS One 12 (10) (2017), e0186179, 9.
[65] L. Q, Y. C, X. W, R. S, J.M. D, Patterns of variation in alkamides and cichoric acid in roots and aboveground parts of echinacea purpurea (L.) moench, HortScience 40 (5) (2005) 1239–1242.
[66] R. Kabganian, D.J. Carrier, P.A. Rose, S.R. Abrams, S. Sokhansanj, Localization of Alkamides, Echinacoside and Cynarin with Echinacea Angustifolia, 2008, 22 Sep 2008.
[67] C.L. Chen, S.C. Zhang, J.M. Sung, Caffeoyl Phenols and Alkamides of Cultivated Echinacea Purpurea and Echinacea Atrorubens Var. Paradoxa, 2009, 27 Aug 2009.
[68] D.L. S, R.B. W, Effect of drying temperature on alkylamide and cichoric acid concentrations of Echinacea purpurea, J. Agric. Food Chem. 51 (6) (2003) 1608–1610.
[69] D.L. Stuart, R.B.H. Wills, Alkylamide and Cichoric Acid Levels in Echinacea Purpurea Tissues during Plant Growth, 2008, 15 Oct 2008.
[70] K. S, K. I-H, N.B. C, E.W. T, N. S, C.A. W, Role for PPARgamma in IL-2 inhibition in T cells by Echinacea-derived undeca-2E-ene-8,10-diynoic acid isobutylamide, Int. Immunopharm. 9 (11) (2009) 1260–1264.
[71] K. W, R. B, The role of alkamides as an active principle of echinacea, Planta Med. 73 (7) (2007) 615–623.
[72] M.O. T, L.P. C, K. G, Harvest strategies for optimization of the content of bioactive alkamides and caffeic acid derivatives in aerial parts and in roots of echinacea purpurea, J. Agric. Food Chem. 66 (44) (2018) 11630–11639.
[73] K. S, M.H. W, N.B. C, Comparison of alkylamide yield in ethanolic extracts prepared from fresh versus dry Echinacea purpurea utilizing HPLC-ESI-MS, J. Pharmaceut. Biomed. Anal. 49 (5) (2009) 1141–1149.
[74] K. W, W. X, Y. P, A. M, R.P. P, R. B, The endocannabinoid system as a target for alkamides from Echinacea angustifolia roots, Planta Med. 71 (8) (2005) 701–705.
[75] J. G, R. S, U. K, A. S, Echinacea alkylamides modulate TNF-alpha gene expression via cannabinoid receptor CB2 and multiple signal transduction pathways, FEBS Lett. 577 (3) (2004) 563–569.
[76] S. R, A. M, J.Z. C, X.Q. X, J. H, B. F, et al., Alkylamides from Echinacea are a new class of cannabinomimetics. Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects, J. Biol. Chem. 281 (20) (2006) 14192–14206.
[77] A. G, H. S, P. G, E. A, S. S, Z. H, Echinacea purpurea polysaccharide reduces the latency rate in herpes simplex virus type-1 infections, Intervirology 52 (1) (2009) 29–34.
[78] L. Y, L. B, Y. T, J. S, Q. Q, D. S, et al., The immunoregulatory effect of sulfated Echinacea purpurea polysaccharide on chicken bone marrow-derived dendritic cells, Int. J. Biol. Macromol. 139 (2019) 1123–1132.
[79] M. R, A. M, S. L, I. A, A. R, P. A, et al., Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds-practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds, Evid Based Compl. Alternat. Med. 2018 (2018) 5813095.
[80] K. K, S. B, Augmentation of immune response by chicoric acid through the modulation of CD28/CTLA-4 and Th1 pathway in chronically stressed mice, Neuropharmacology 60 (6) (2011) 852–860.
[81] S. P, M.S. L, S. J, S. L, O. K, M.H. K, et al., Echinacea purpurea protects against restraint stress-induced immunosuppression in BALB/c mice, J. Med. Food 21 (3) (2018) 261–268.

[82] D. Y, Y. Y, L. J, Y. T, X. Y, F. H, et al., Anti-inflammatory effects of essential oil in Echinacea purpurea L, Pak. J. Pharm. Sci. 26 (2) (2013) 403–408.

[83] F. C, M. C, B. B, C. A, Effect of Echinacea purpurea (Asteraceae) aqueous extract on antibody response to Bothrops asper venom and immune cell response, Rev. Biol. Trop. 55 (1) (2007) 113–119.

[84] Z. Z, Y. L, L. W, D.S. S, E.S. W, P.A. M, et al., Enhancement of innate and adaptive immune functions by multiple Echinacea species, J. Med. Food 10 (3) (2007) 423–434.

[85] K. Y, P. H, T.K. P, P.J. P, B.O. L, A comparison of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi, J. Ethnopharmacol. 137 (1) (2011) 231–235, 1.

[86] M.R. R, J. G, P. K, R. S, Effects of Echinaforce® treatment on ex vivo-stimulated blood cells, Phytomedicine 18 (10) (2011) 826–831, 15.

[87] S. R, H.N. B, F.M. AB, B.S. A, M.P. W, K.A. S, et al., Effects of chemically characterized fractions from aerial parts of Echinacea purpurea and E. angustifolia on myelopoiesis in rats, Planta Med. 77 (17) (2011) 1883–1889.

[88] S. S-E, H. k-N, N. A, S. G, M. G, D. S, Synergetic effects of oral administration of levamisole and Echinacea purpurea on immune response in Wistar rat, Res. Vet. Sci. 91 (1) (2011) 82–85.

[89] C.Y. W, M.T. C, P.J. Y, W.C. H, C.C. H, S.C. C, et al., Modulatory effects of Echinacea purpurea extracts on human dendritic cells: a cell- and gene-based study, Genomics 88 (6) (2006) 801–808.

[90] D.F. B, M.P. W, C.A. L, L. W, J. B, A.K. S, et al., Echinacea in infection, Am. J. Clin. Nutr. 87 (2) (2008) 488S–492S.

[91] S.A. R, A. C, U. S, M. N, P. N, Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression, Immunobiology 215 (8) (2010) 598–605.

[92] P.W. K, W. C, B.L. K, N.E. K, Δ9-tetrahydrocannabinol suppresses cytotoxic T lymphocyte function independent of CB1 and CB 2, disrupting early activation events, J. Neuroimmune Pharmacol. 7 (4) (2012) 843–855.

[93] A. D, K. M, CB2 Cannabinoid receptors as a therapeutic target-what does the future hold? Mol. Pharmacol. 86 (4) (2014) 430–437.

[94] A. S, K. Z, M. G, T. P, A.J.I. S, A guide to targeting the endocannabinoid system in drug design, Int. J. Mol. Sci. 21 (8) (2020) 2778.

[95] S.Y. C, J.M. S, P.W. H, S.D. L, Antioxidant, antidiabetic, and antihypertensive properties of echinacea purpurea flower extract and caffeic acid derivatives using in vitro models, J. Med. Food 20 (2) (2017) 171–179.

[96] C. B, H. L, R. T, D. O, X. D-L, J. vG, Cannabinoid-induced immunomodulation during viral infections: a focus on mitochondria, Viruses 12 (8) (2020) 875.

[97] T.S. K, L. T, A. F, S. V, M.T. H, G.E. R, et al., Cannabinoid receptor 2 deficiency exacerbates inflammation and neutrophil recruitment, Faseb. J. 33 (5) (2019) 6154–6167.

[98] A. T, Y. S, F.S. N, A.A. R, A. I, A. R-N, et al., Effects of cannabinoid receptor type 2 in respiratory syncytial virus infection in human subjects and mice, Virulence 9 (1) (2018) 217–230.

[99] C.M. C, A. G, A.W. Y, B.M. D, L.A. D, B.K. C, Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells, PloS One 7 (3) (2012), e33961.

[100] S.H. R, N.L. R, S. F, S. R, S.F. M, X. W, et al., Attenuation of HIV-1 replication in macrophages by cannabinoid receptor 2 agonists, J. Leukoc. Biol. 93 (5) (2013) 801–810.

[101] S.E. OS, An update on PPAR activation by cannabinoids, Br. J. Pharmacol. 173 (12) (2016) 1899–1910.

[102] C. C, I. M, S. V, G. P, Pharmacological (or synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease, Molecules 25 (9) (2020) 2076.

[103] P.R. S, M.F. R, J.M. M, A.S. G, Stimulation of peroxisome proliferator-activated receptors alpha and gamma blocks HIV-1 replication and TNFalpha production in acutely infected primary blood cells, chronically infected U1 cells, and alveolar macrophages from HIV-infected subjects, J. Acquir. Immune Defic. Syndr. 31 (1) (2002) 1–10.

[104] L. D, Y. M, M. L, L. Y, H. T, Peroxisome Proliferators Activated Receptor (PPAR) agonists activate hepatitis B virus replication in vivo, Virol. J. 14 (1) (2017) 96.

[105] J. B-R, R. S, P.C. R, R. H, PPAR-gamma activation as an anti-inflammatory therapy for respiratory virus infections, Viral Immunol. 23 (4) (2010) 343–352.

[106] S. H, B. Z, I.S. C, N.P. G, L. J, R. Z, et al., PPAR-γ in macrophages limits pulmonary inflammation and promotes host recovery following respiratory viral infection, J. Virol. 93 (9) (2019) e00030-19.

[107] E. S, S. W, K. K, L.P. C, G. R, S. W, Plant extracts of winter savory, purple coneflower, buckwheat and black elder activate PPAR-γ in COS-1 cells but do not lower blood glucose in Db/db mice in vivo, Plant Foods Hum. Nutr. 67 (4) (2012) 377–383.

[108] D. K, R.B. E-H, K. B, R.K. P, X.C. F, G. W, et al., Isomeric C12-alkamides from the roots of Echinacea purpurea improve basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes, Planta Med. 80 (18) (2014) 1712–1720.

[109] K.B. C, R.K. P, S. P, K. K, L.P. C, Activation of PPARgamma by metabolites from the flowers of purple coneflower (Echinacea purpurea), J. Nat. Prod. 72 (5) (2009) 933–937.

[110] D.-M. Shin, K.-M. Choi, Y.-S. Lee, W. Kim, K.-O. Shin, S. Oh, et al., Echinacea purpurea root extract enhances the adipocyte differentiation of 3T3-L1 cells, Arch Pharm. Res. 37 (6) (2014) 803–812.

[111] L. Peyrin-Biroulet, J. Beisner, G. Wang, S. Nuding, S.T. Oommen, D. Kelly, et al., Peroxisome proliferator-activated receptor gamma activation is required for maintenance of innate antimicrobial immunity in the colon, Proc. Natl. Acad. Sci. U. S. A. 107 (19) (2010) 8772–8777, 11.

[112] B. V, S. O, P.D. B, B. B, V. R, P.D. C, et al., Phytochemical drug candidates for the modulation of peroxisome proliferator-activated receptor γ in inflammatory bowel diseases, Phytother Res. 34 (7) (2020) 1530–1549.

[113] Z. X, L. S, Y. W, J. Z, L. H, C. Z, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir Med. 8 (4) (2020) 420–422.

[114] J. H, D. Q, X.M. T, W. D, X.Y. D, Y. Z, et al., Rosiglitazone promotes ENaC-mediated alveolar fluid clearance in acute lung injury through the PPARγ/SGK1 signaling pathway, Cell. Mol. Biol. Lett. 24 (2019) 35.

[115] T.J. S, V.G. K, R.C. R, Peroxisome proliferator-activated receptor-{gamma} as a regulator of lung inflammation and repair, Proc. Am. Thorac. Soc. 2 (3) (2005) 226–231.

[116] P.J. S, The antifibrogenic potential of PPARgamma ligands in pulmonary fibrosis, J. Invest. Med. 56 (2) (2008) 534–538.

[117] P. A, A.F. A, Is pulmonary vascular disease reversible with PPAR ɣ agonists? Microcirculation 25 (3) (2018), e12444.

[118] K. T, I. Z, K.H. L, R.A. G, S.H. H, H. L, et al., Update of the current knowledge on genetics, evolution, immunopathogenesis, and transmission for coronavirus disease 19 (COVID-19), Int. J. Biol. Sci. 16 (15) (2020) 2906–2923.

[119] L. Y, S. L, J. L, Z. Z, X. W, B. H, et al., COVID-19: immunopathogenesis and Immunotherapeutics, Signal Transduct Target Ther. 5 (1) (2020) 128.

[120] S. K, D. M, S.K. P, R. T, K. D, H. H, Immunopathology and immunotherapeutic strategies in severe acute respiratory syndrome coronavirus 2 infection, Rev. Med. Virol. 30 (5) (2020), e2123.

[121] R.B. T, R. B, K. W, T.C. H, J.D. G, An evaluation of Echinacea angustifolia in experimental rhinovirus infections, N. Engl. J. Med. 353 (4) (2005) 341–348.

[122] S. P, M. S, R. S, J.B. H, Anti-viral properties and mode of action of standardized Echinacea purpurea extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV), Virol. J. 6 (2009) 197.

[123] J.B. H, Applications of the phytomedicine Echinacea purpurea (Purple Coneflower) in infectious diseases, J. Biomed. Biotechnol. 2012 (2012) 769896.

[124] J. L, B. J, C.E. W, G. R, T.M. C, Antiviral activity of metal chelates of caffeic acid and similar compounds towards herpes simplex, VSV-Ebola pseudotyped and vaccinia viruses, Antivir. Res. 160 (2018) 143–150.

[125] S.U. L, C.G. S, C.K. L, Y.S. L, Caffeoylglycolic and caffeoylamino acid derivatives, halfmers of L-chicoric acid, as new HIV-1 integrase inhibitors, Eur. J. Med. Chem. 42 (10) (2007) 1309–1315.

[126] L.Z. S, N.L. C, S.C. M, The American coneflower: a prophylactic role involving nonspecific immunity, J. Alternative Compl. Med. 5 (5) (1999) 437–446.

[127] A. Wacker, W. Hilbig, Virushemmung mit Echinacea purpurea, Planta Med. 33 (1) (1978) 89–102.

[128] S. V, R. S, A. S, J. H, Prevention of influenza virus induced bacterial superinfection by standardized Echinacea purpurea, via regulation of surface receptor expression in human bronchial epithelial cells, Virus Res. 233 (2017) 51–59.

[129] F. E, G.R. K, Effects of non-specific immunostimulants (echinacin, isoprinosine and thymus factors) on the infection and antigen expression in herpesvirus-6 exposed human lymphoid cells, in Vivo 8 (4) (1994) 565–575.

[130] E.J. G-B, M.G. N, N. R, K. A, A. A, N. A, et al., Complex immune dysregulation in COVID-19 patients with severe respiratory failure, Cell Host Microbe 27 (6) (2020) 992–1000, e3.

[131] H. H, Q. M, C. L, R. L, L. Z, W. W, et al., Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors, Emerg. Microb. Infect. 9 (1) (2020) 1123–1130.

[132] J.L. G, S. S, C. K, L. S, E. L, T. W, et al., Pleiotropic effects of interleukin-6 in a "two-hit" murine model of acute respiratory distress syndrome, Pulm. Circ. 4 (2) (2014) 280–288.

[133] C. P, C. T, A. V, G. DS, G. P, Lung under attack by COVID-19-induced cytokine storm: pathogenic mechanisms and therapeutic implications, Ther. Adv. Respir. Dis. 14 (2020), 1753466620933508.

[134] S. Z, L. L, A. S, Y. C, Z. Q, Rational use of tocilizumab in the treatment of novel coronavirus pneumonia, Clin. Drug Invest. 40 (6) (2020) 511–518.

[135] X. D, Y.Y. C, X.X. L, J.J. Z, H. D, Y.Q. Y, et al., Eleven faces of coronavirus disease 2019, Allergy 75 (7) (2020) 1699–1709.

[136] S.M. S, M. A, S.R. S, J.B. H, Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforce): dual actions against respiratory bacteria, Phytomedicine 17 (8-9) (2010) 563–568.

[137] J. B, A.K. S, D. Z, I. S, E. S-R, M. K, Echinacea purpurea stimulates cellular immunity and anti-bacterial defence independently of the strain of mice, Pol. J. Vet. Sci. 6 (3 Suppl) (2003) 3–5.

[138] H. H, M.M. F, H.J. E, Echinacea purpurea and mucosal immunity, Int. J. Sports Med. 28 (9) (2007) 792–797.

[139] C. R, D. B, P. P, P.R.M. R, Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2, Expet Rev. Respir. Med. 14 (9) (2020) 865–868.

[140] J. GH, H.A. N, G. C, M.N. E, D.A. A, N.F. C, et al., SARS, MERS and COVID-19: clinical manifestations and organ-system complications: a mini review, Pathog Dis. 78 (4) (2020) ftaa033.

[141] S. S, Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality, Inflamm. Res. 69 (11) (2020) 1077–1085.

[142] J.C. M, L.F. G, B.J. M, P.A. E, S.C. B, A.M. M, et al., Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome, Crit. Care Med. 45 (2) (2017) 253–262.

[143] J. Tschöp, K.R. Kasten, R. Nogueiras, H.S. Goetzman, C.M. Cave, L.G. England, et al., The cannabinoid receptor 2 is critical for the host response to sepsis, J. Immunol. 183 (1) (2009) 499–505.

[144] Q. H, F. X, Q. Y, J. Z, J. Z, Z. Z, Cannabinoid receptor 2: a potential novel therapeutic target for sepsis? Acta Clin. Belg. 74 (2) (2019) 70–74.
[145] J. S, M.E. K, J. Z, C. L, Experimental cannabinoid 2 receptor-mediated immune modulation in sepsis, Mediat. Inflamm. 2014 (2014) 978678.
[146] J.T. T, R. M, A.M. S, J. Z, M.E. K, C. L, Cannabinoid 2 receptor activation reduces leukocyte adhesion and improves capillary perfusion in the iridial microvasculature during systemic inflammation, Clin. Hemorheol. Microcirc. 61 (2) (2015) 237–249.
[147] M.W. L, M.X. S, Y.H. W, W. W, L.F. Q, X. L, et al., Effect of melilotus extract on lung injury by upregulating the expression of cannabinoid CB2 receptors in septic rats, BMC Compl. Alternative Med. 14 (2014) 94.
[148] A.P. L, Q.H. Y, B. Z, L. Y, Q.W. H, K. C, et al., Cannabinoid receptor 2 activation alleviates septic lung injury by promoting autophagy via inhibition of inflammatory mediator release, Cell. Signal. 69 (2020) 109556.
[149] M. Ç, S. T, A. O, P. Ç, Z. D, The ameliorating effect of cannabinoid type 2 receptor activation on brain, lung, liver and heart damage in cecal ligation and puncture-induced sepsis model in rats, Int. Immunopharm. 78 (2020) 105978.
[150] L.F. B, H.B.M. O, N. dNS, C.L.S. ES, M.N.S. J, E.P. dS, et al., Anti-inflammatory activity of β-caryophyllene combined with docosahexaenoic acid in a model of sepsis induced by Staphylococcus aureus in mice, J. Sci. Food Agric. 99 (13) (2019) 5870–5880.
[151] N.B. C, V. K, J.M. D, A. H, D. E, S.M. L, Echinacea and its alkylamides: effects on the influenza A-induced secretion of cytokines, chemokines, and PGE_2 from RAW 264.7 macrophage-like cells, Int. Immunopharm. 10 (10) (2010) 1268–1278.
[152] C.C. H, C.C. H, L.F. S, Echinacea alkamides prevent lipopolysaccharide/D-galactosamine-induced acute hepatic injury through JNK pathway-mediated HO-1 expression, J. Agric. Food Chem. 59 (22) (2011) 11966–11974.
[153] M. A, S.H. K, H. G, A.A. S, T. A, Avemar and Echinacea extracts enhance mobilization and homing of CD34(+) stem cells in rats with acute myocardial infarction, Stem Cell Res. Ther. 6 (1) (2015) 172.
[154] Z. D, B. E, M. S, L. F, M.A. G, S. H, et al., The antioxidant effect of Echinacea angustifolia and Echinacea purpurea in rat colitis model induced by acetic acid, Bratisl. Lek. Listy 115 (7) (2014) 411–415.
[155] E.H. A, Protective effects of Echinacea on cyproterone acetate induced liver damage in male rats, Pakistan J. Biol. Sci. 11 (21) (2008) 2464–2471.
[156] A.M. A, Y.E. S, S.S. T, A.M. Z, Phytotherapeutic effects of Echinacea purpurea in gamma-irradiated mice, J. Vet. Sci. 8 (4) (2007) 341–351.
[157] R.P. R, COVID-19 and mental health: a review of the existing literature, Asian J. Psychiatr. 52 (2020) 102066.
[158] A. P, R. Z, D.H. B, Influence of psychological stress on upper respiratory infection–a meta-analysis of prospective studies, Psychosom. Med. 72 (8) (2010) 823–832.
[159] N. H, N. H, B. N, O.I. P, G.G. S, R. Z, et al., The effects of an Echinacea preparation on synaptic transmission and the firing properties of CA1 pyramidal cells in the hippocampus, Phytother Res. 26 (3) (2012) 354–362.
[160] Y. I, K. K, G.G. N, R. Y-M, T. P, G. vL, et al., Identification of oxidative stress and toll-like receptor 4 signaling as a key pathway of acute lung injury, Cell 133 (2) (2008) 235–249.
[161] J. S, C. P, K.K. S, M. E, Mitochondria and microbiota dysfunction in COVID-19 pathogenesis, Mitochondrion 54 (2020) 1–7.
[162] I. P, Potential role of endothelial cell surface ectopic redox complexes in COVID-19 disease pathogenesis, Clin. Med. 20 (5) (2020) e146–e147.
[163] J.M. M, B.M. H, A. C-G, K.P. G, B. G, Nrf2 activator PB125 ® as a potential therapeutic agent against COVID-19, Antioxidants 9 (6) (2020) 518.
[164] O.A. K, S.N. K, B. B, A.V. I, Redox biology of respiratory viral infections, Viruses 10 (8) (2018) 392.
[165] A. N, S. M, G. G, G. W, C. M, J. R, et al., Reactive oxygen species as an initiator of toxic innate immune responses in retort to SARS-CoV-2 in an ageing population, consider N-acetylcysteine as early therapeutic intervention, Toxi. Rep. 7 (2020) 768–771.
[166] D. N, P. P, Potential neurological effects of severe COVID-19 infection, Neurosci. Res. 158 (2020) 1–5.
[167] L. T, J. T, A. M, L.H. S, P. M, Antioxidant activity of cichoric acid and alkamides from Echinacea purpurea, alone and in combination, Food Chem. 101 (1) (2020) 74–81.
[168] R. H, T. X, Q. L, F. Y, C. W, T. H, et al., Polysaccharide from Echinacea purpurea reduce the oxidant stress in vitro and in vivo, Int. J. Biol. Macromol. 149 (2020) 41–50.
[169] H. L, D. W, Y. C, M. Y, β-Caryophyllene inhibits high glucose-induced oxidative stress, inflammation and extracellular matrix accumulation in mesangial cells, Int. Immunopharm. 84 (2020) 106556.
[170] P. M, G. P, E. B, M. R, W. C, A. R, SAMITAL®: a new botanical drug for the treatment of mucositis induced by oncological therapies, Future Oncol. 9 (11) (2013) 1717–1725.
[171] A. S, Efficacy and safety of Echinaforce® in respiratory tract infections, Wien Med. Wochenschr. 163 (3-4) (2013) 102–105.
[172] K.D. T, Antiviral activity of Viracea against acyclovir susceptible and acyclovir resistant strains of herpes simplex virus, Antivir. Res. 39 (1) (1998) 55–61.
[173] H. Z, J. B, C.M. I, E. C, W.L. G, A. S, et al., The effect of Echinacea purpurea, Astragalus membranaceus and Glycyrrhiza glabra on CD25 expression in humans: a pilot study, Phytother Res. 21 (11) (2007) 1109–1112.
[174] A.H. E, N. A, R.A. E-S, V.M. F, R.M. S, W.F. A, Comparative immune response and pathogenicity of the H9N2 avian influenza virus after administration of Immulant ®, based on Echinacea and Nigella sativa, in stressed chickens, Comp. Immunol. Microbiol. Infect. Dis. 65 (2019) 165–175.
[175] M. C, E. C, M. R, M. R, C. L, Immunomodulators inspired by nature: a review on curcumin and echinacea, Molecules 23 (11) (2018) 2778.
[176] S.M. A, M.F. M, Echinacea purpurea and Allium sativum as immunostimulants in fish culture using Nile tilapia (Oreochromis niloticus), J. Anim. Physiol. Anim. Nutr. 94 (5) (2010) e31–e39.
[177] D. U, E. K, Effects of ginseng and echinacea on cytokine mRNA expression in rats, Sci. World J. 2012 (2012) 942025.
[178] F. I, W.H. W, F. Y, A. S, U. T, M.A. V, Echinacea purpurea along with zinc, selenium and vitamin C to alleviate exacerbations of chronic obstructive pulmonary disease: results from a randomized controlled trial, J. Clin. Pharm. Therapeut. 36 (5) (2011) 568–576.
[179] B.J. B, I. S, E. S-R, P. S, The modulatory influence of some Echinacea-based remedies on antibody production and cellular immunity in mice, Cent. Eur. J. Immunol. 41 (1) (2016) 12–18.
[180] H. G, M. G, S. B, Potential use of turmeric in COVID-19, Clin. Exp. Dermatol. 45 (7) (2020) 902–903.
[181] H. M, Symptomatic protective action of glycyrrhizin (licorice) in COVID-19 infection? Front. Immunol. 11 (2020) 1239.
[182] M.F. K, R. L, K. M, M. W, K. L, J. L, Potential influence of Nagella sativa (Black cumin) in reinforcing immune system: a hope to decelerate the COVID-19 pandemic, Phytomedicine (2020) 153277.
[183] M. R, S. M, C. S, I. T, G.L. R, Roles of flavonoids against coronavirus infection, Chem. Biol. Interact. 328 (2020) 109211.
[184] M. M, M. Y, A. S, A. K, M. H, Metabolomic profiling of liquid Echinacea medicinal products with in vitro inhibitory effects on cytochrome P450 3A4 (CYP3A4), Planta Med. 76 (4) (2010) 378–385.
[185] S.R. P, S.M. R, J.D. H, C. C, C.Y. M, R.M. A, et al., Echinacea purpurea significantly induces cytochrome P450 3A activity but does not alter lopinavir-ritonavir exposure in healthy subjects, Pharmacotherapy 30 (8) (2010) 797–805.
[186] J. M, M. V, C. M, S. C, E. N, B. C, Herb-drug interaction between Echinacea purpurea and etravirine in HIV-infected patients, Antimicrob. Agents Chemother. 56 (10) (2012) 5328–5331.
[187] M. C, M.A.R. DG, G.N. R, SARS-CoV-2: recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus, Curr. Med. Chem. 27 (27) (2020) 4536–4541.
[188] K.Y. L, J.W. R, J.H. K, Immunopathogenesis of COVID-19 and early immunomodulators, Pediatr. Allergy Immunol. 31 (Suppl 26) (2020) 75–78.
[189] H. J, L. M, B. D, C. L, R. B, H.P. M, et al., Transport of alkamides from Echinacea species through Caco-2 monolayers, Planta Med. 68 (5) (2002) 469–471.
[190] K. W, R.F. F, H. D, R. B, V. B, Pharmacokinetics and tissue distribution of dodeca-2E,4E,8E,10E/Z-tetraenoic acid isobutylamides after oral administration in rats, Planta Med. 75 (12) (2009) 1306–1313.
[191] A.L. H, J. TC, E. E, The safety of herbal medicinal products derived from Echinacea species: a systematic review, Drug Saf. 28 (5) (2005) 387–400.
[192] C. F, K. S, A critical evaluation of drug interactions with Echinacea spp, Mol. Nutr. Food Res. 52 (7) (2008) 789–798.
[193] G. C, T. J, S.C. M, Dietary Echinacea purpurea during murine pregnancy: effect on maternal hemopoiesis and fetal growth, Biol. Neonate 89 (2) (2006) 133–138.
[194] D. P, J.J. D, E. M, G. K, Safety and efficacy of echinacea (Echinacea angustafolia, e. purpurea and e. pallida) during pregnancy and lactation, Can. J. Clin. Pharmacol. 13 (3) (2006) e262–e267.
[195] E. B, E. S, J. N, B. B, J. C-W, E. S-R, Influence of Echinacea purpurea intake during pregnancy on fetal growth and tissue angiogenic activity, Folia Histochem. Cytobiol. 45 (Suppl 1) (2007) S35–S39.
[196] P.G. N, E. S, M. F, G. C, A. G, G.M. L, et al., Oral Echinacea purpurea extract in low-grade, steroid-dependent, autoimmune idiopathic uveitis: a pilot study, J. Ocul. Pharmacol. Therapeut. 22 (6) (2006) 431–436.
[197] R.K. R, K. G, K. S, E. B, Y. Q, D. B-D, et al., Regulation of human immune gene expression as influenced by a commercial blended Echinacea product: preliminary studies, Exp. Biol. Med. 228 (9) (2003) 1051–1056.
[198] P. G, K. W, I. G, D. V, B. P, S. I, et al., Pharmacokinetics and immunomodulatory effects of phytotherapeutic lozenges (bonbons) with Echinacea purpurea extract, Phytomedicine 15 (8) (2008) 547–554.
[199] S. Dall'Acqua, G. Miolo, G. Innocenti, S. Caffieri, The photodegradation of quercetin: relation to oxidation, Molecules 17 (8) (2012) 8898–8907.
[200] B. D, S. DA, R. B, C. A, B. P, S. I, et al., Immunomodulation mediated by a herbal syrup containing a standardized Echinacea root extract: a pilot study in healthy human subjects on cytokine gene expression, Phytomedicine 21 (11) (2014) 1406–1410.
[201] J.R. T, M.J. K, C.P. S, J. F, T.R. M, M.G. K, Into the eye of the cytokine storm, Microbiol. Mol. Biol. Rev. 76 (1) (2012) 16–32.
[202] F. C, L. C, L. C, F. M, M. R, The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system, Cytokine Growth Factor Rev. 53 (2020) 25–32.
[203] J.C. G, S.M. H, A. P, M.A. H, J.K. H, N.A. Z, et al., The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo, Clin. Pharmacol. Ther. 75 (1) (2004) 89–100.
[204] D.W. K, K.H. S, M.J. C-L, K.Y. O, J.W. O, J.K. C, et al., Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia, J. Enzym. Inhib. Med. Chem. 29 (1) (2014) 59–63.
[205] S. S, D. S, K. W, R. Z, B. S, A. K, et al., Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus, Planta Med. 80 (2-3) (2014) 177–182.
[206] J.Y. P, H.J. Y, H.W. R, S.H. L, K.S. K, K.H. P, et al., Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors, J. Enzym. Inhib. Med. Chem. 32 (1) (2017) 504–515.

[207] A. P, M.K. K, M. H, S. G, Natural plant products: a less focused aspect for the COVID-19 viral outbreak, Front. Plant Sci. 11 (2020) 568890.
[208] K. U, E. F, V. P, T. V, Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2, Biomed. Pharmacother. 131 (2020) 110668.
[209] S.C.J. J, R. K, L.D. D, Remdesivir: review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19, Pharmacotherapy 40 (7) (2020) 659–671.
[210] Y.X. D, X.P. C, Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection, Clin. Pharmacol. Ther. 108 (2) (2020) 242–247.
[211] S. Y, P. S, T. B, M. C, A. J, Y. L, et al., Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment, Clin. Immunol. 218 (2020) 108517.
[212] J. L, J.J. M, M. S, A. R, J. H, E.J. S, et al., Anti-complement C5 therapy with eculizumab in three cases of critical COVID-19, Clin. Immunol. 219 (2020) 108555.
[213] K. W, W. C, Z. Z, Y. D, J.Q. L, P. D, et al., CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells, Signal Transduct Target Ther. 5 (1) (2020) 283.
[214] A. C, M. I, M. G, V. G, A. P, C. G, et al., Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review, Pulmonology 27 (1) (2021) 52–66.
[215] V. M, R. P, C. I, A. B, E. M, F. F, et al., Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy, J. Immunother. Canc. 8 (2) (2020), e001089.
[216] J.G. R, K. K-Z, M.R. M, C.J. L, Y. R, D.N. F, Pharmaco-immunomodulatory therapy in COVID-19, Drugs 80 (13) (2020) 1267–1292.
[217] E. M, Covid-19: anti-TNF drug adalimumab to be trialled for patients in the community, BMJ 371 (2020) m3847.
[218] L. C, J.D. D, M.G. C, D.A. J, K.M. W, The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antivir. Res. 178 (2020) 104787.
[219] J. S, P.M. C, S. C, G. P, G. C, G. T, Azithromycin in COVID-19 patients: pharmacological mechanism, clinical evidence and prescribing guidelines, Drug Saf. 43 (8) (2020) 691–698.
[220] J. A, G.B. dO, B.D. S, G.H. T, Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes, Diabetol. Metab. Syndrome 12 (2020) 80.
[221] H. G-K, F. J, Anti-inflammatory properties of drugs used to control COVID-19 and their effects on the renin-angiotensin system and angiotensin-converting enzyme-2, J. Pharm. Pharmaceut. Sci. 23 (2020) 259–277.
[222] B.L. B, J. M, Treatment for emerging viruses: convalescent plasma and COVID-19, Transfus. Apher. Sci. 59 (3) (2020) 102790.
[223] H. S, C. Z, P. H, S. H, Y. D, X. W, et al., Successful treatment with plasma exchange followed by intravenous immunoglobulin in a critically ill patient with COVID-19, Int. J. Antimicrob. Agents 56 (2) (2020) 105974.
[224] K.C.H. L, D.W. S, G.C. P, Potential role of statins in COVID-19, Int. J. Infect. Dis. 96 (2020) 615–617.