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
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]. Auto-phagy [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]. A 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-II 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 viral 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 hyper-inflammatory 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 hyper-inflammatory 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 caffeic acid, chlorogenic acid, cichoric acid, echinacoside and alkalamide, 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,
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<br>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-CS mononclonal antibody | [212] |
| Meplalamab              | 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<br>interferes with glycosylation of ACE2 and interaction of spike protein | [208] |
| Ivermectin              | inhibits importin α/β, which mediates nuclear transport of viruses<br>blocks the nuclear trafficking of RNA viral proteins | [218] |
| Azithromycin            | antiviral, anti-inflammatory and immunomodulatory<br>limits viral entry and replication<br>decreases mucus production and recovers the lung infections<br>inhibits interaction of ACE2 with SARS-CoV-2 spike protein | [219] |
| Dexamethasone           | reduces cytokine responses and exerts anti-inflammatory effects<br>exerts anti-fibrotic effects | [220] |
| Type I, III interferon, interferon β-1a and interferon α-2b | exerts antiviral effects by inhibiting viral replication<br>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<br>augments ACE2 expression<br>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. simulata, and E. tennesseensis. Among them, after E. angustifolia (black sapon) 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 meta-analyses 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, choric acid, and chlorogenic acid as the major phenolic compounds; polysaccharides; and glycoproteins [56]. Caftaric acid is highly abundant in aqueous extracts of flowers, and choric acid is highly present in ethanolic extracts of flowers and roots [57]. The roots contain pyrroliizidine alkaloids, namely, tussilagine, isotussilagine, and essential oils [58]. The flowers and roots of E. purpurea additionally contain cyanarin 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 sesquiterpenes and monoterpenes 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, cedrel 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, choric 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]. Phylloanthohbilins present in the leaf extracts of *E. purpurea* have exhibited free-radical scavenging activity and have restored glutathione levels to counter oxidative stress [63]. Fractans 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 (cafeic acid derivatives, chlorogenic acid, and choric 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 choric 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 alkylamides in the petals, disc, flowers, and seeds (mainly in the outer surface), and a moderate amount of alkylamides in the flower head receptacles [72]. Alkamides (undeca-2E,4E-diene-8,10-diynoic acid isobutylamides and dodeca-2E,4E,8Z,10E-tetraenoic acid isobutylamides, undeca-2E,4E,8Z,10E,12Z-pentatetraenoic acid isobutylamides, and α- and β-ent-alkamides) 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 lipooxygenases, 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 immunomodulatory 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-kB, 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 PPARY [94, 96].

Mice deficient in CB2R showed increased susceptibility and vulnerability to ability in 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 cross-talk interaction between CB2R [99] and PPARY family and inhibit replication of the virus in monocytes and macrophages [100]. Furthermore, ligands activating CB receptors interact or exhibit crosstalk with the PPARY family, which consists of three subtypes, PPARY, PPARβ/δ, and PPARγ; these receptors are encoded by distinct genes and regulated by steroids and lipid metabolites [101]. The PPARY 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, PPARYγ, which is mainly expressed in adipocytes and macrophages upon upregulation, exerts anti-inflammatory responses; this effect has renewed the interest in using PPARYγ 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 PPARYγ activation in macrophages [102]. Additionally, PPARYγ agonists have been shown to inhibit the replication of numerous viruses including HIV, RSV, hepatitis B, and hepatitis C [103, 104]. Furthermore, PPARYγ agonists have been shown to reduce morbidity and mortality in infections with influenza A virus [105]. PPARYγ 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 influenza virus A and RSV [106]. The extract of *E. purpurea* has been shown to stimulate PPARYγ 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/2E-tetraenoic acid 2-methylbutylamides, C12-alkamides, which act on 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]. PPARYγ 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, PPARYγ 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 PPARYγ 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]. PPARYγ agonism by *Echinacea* may represent a promising therapeutic approach. On the basis of available studies demonstrating the affinity of *Echinacea* to CB2R and PPARYγ, 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 (IFNa/β) and type II interferon (IFNγ), 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* has been shown to be effective against rhinoviruses [121], influenza virus [122], RSV [44], herpes virus [44], adenoviruses [44], and coronaviruses [43, 123]. Another compound, choric 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, choric 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 immune 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 isoprinosterone 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 a 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]. Tocillizumab 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 Streplococcus 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 patients [136]. The antibacterial effects of Echinacea, such as isoprinosterone, have exhibited immunostimulatant properties through enhancing the reactivity of the human defense system against lymphotropic human herpesvirus-6 latent infection in lymphoid cells [129].

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 bacteriaemia [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, bacteriaemia, 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-CoV2 receptor α-2B2V-2.

E. purpurea and the alkaloid docedes-2E,4E,8Z,10Z(E)-tetraenoic acid isobutyramide, 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 anti-oxidant 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 organprotective effect of E. purpurea might aid in reducing complications and multiorgan failure in COVID-19.

7. Antioxidant activity of Echinacea

In addition to immuno-inflammatory changes, macrophages and neutrophils can produce numerous ROS including hydrogen peroxide (H2O2), superoxide (O2•−) and hydroxyl (OH•) 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 choric 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 choric acid by providing better surface access by preventing lipid oxidation in the lipophilic component of the emulsion and facilitating the revival of choric acid by providing alyclic hydrogen to the one-electron oxidized choric acid [167]. *E. purpurea* has been shown to augment endogenous antioxidants, exert ferric reducing properties, Fe²⁺ 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/Keap1/ARE 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 phytopharmaceutical formulations, including SAMITAL® (IndenaSpA, Milan, Italy), which contains *E. angustifolia* [170], Echinforce® (Bioforce, Switzerland), which contains *E. purpurea* [171], and Viracea®, a topical formulation from Destiny BioMedX 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, immunomodulator, 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/CDP at 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 choric 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...
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 contrast to dysregulated immune-inflammatory homeostasis. Provided the organprotective 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 adjunct in COVID-19. *Echinacea* preparations comprise a unique blend of numerous phytochemicals, including phenolics, alkaloids, alkalamides, 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 adjunct in COVID-19 and as an immune-boosting agent in people at risk or with comorbidities.

Declarations

Author contribution statement

M.F. Nagoor Meenan; 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; Contributed reagents, materials, analysis tools or 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.

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