Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Could natural products modulate early inflammatory responses, preventing acute respiratory distress syndrome in COVID-19-confirmed patients?

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ABSTRACT

Background: The ARDS (Acute Respiratory Distress Syndrome) is a severe respiratory syndrome that was recently associated as the main death cause in the COVID-19 pandemic outbreak. Hence, in order to prevent ARDS, the pulmonary function maintenance has been the target of several pharmacological approaches. However, there is a lack of reports regarding the use of effective pharmaceutical active natural products (PANPs) for early treatment and prevention of COVID-19-related ARDS. Therefore, the aim of this work was to conduct a systematic review regarding the PANPs that could be further studied as alternatives to prevent ARDS. Consequently, this work can pave the way to spread the use of PANPs on the prevention of ARDS in COVID-19-confirmed or -suspected patients.

Methods: The search strategy included scientific studies published in English from 2015 to 2020 that promoted the elucidation of anti-inflammatory pathways targeting ARDS by *in vitro* and/or *in vivo* experiments using PANPs. Then, 74 studies regarding PANPs, able to maintain or improve the pulmonary function, were reported.

Conclusions: The PANPs may present different pulmonary anti-inflammatory pathways, wherein (i) reduction/attenuation of pro-inflammatory cytokines, (ii) increase of the anti-inflammatory mediators' levels, (iii) pulmonary edema inhibition and (iv) attenuation of lung injury were the most observed biological effects of such products in *in vitro experiments* or in clinical studies. Finally, this work highlighted the PANPs with promising potential to be used on respiratory syndromes, allowing their possible use as alternative treatment at the prevention of ARDS in COVID-19-infected or -suspected patients.

1. Introduction

COVID-19 is an infectious disease caused by the type-2 coronavirus, SARS-CoV-2, which is responsible for promoting respiratory disorders. Its first case was reported in December 2019 in Wuhan (Hubei – China), a city that plays an important role on the Chinese culture dissemination by the market of natural products, such as plants and exotic meats including live animals, which are widely used on local food production [1].

Concerning the beginning of COVID-19, reports describe that more than 700 people were considered suspect COVID-19 cases, including those who had contact with the market, their families and health professionals that performed the first health care of these patients. Subsequently, after the PCR tests development, more than 40 cases were attested and, in January 9th 2020, the first death was confirmed. A few days later, in January 20th, the Chinese National Health Commission assumed the SARS-CoV-2 human-human transmission at the same time that more 140 new cases were identified [2].

Then, in light of the human-human transmission, the COVID-19 quickly spread worldwide and became present in several countries as France, Germany, United States of America, United Kingdom, Italy, Spain, Mexico, Brazil and others. Accordingly, the World Health Organization (WHO) decreed COVID-19 as a pandemic outbreak in March 11th [2]. In June 1st 2020, 6 million COVID-19 cases had been reported worldwide, among which 374,927 deaths occurred [3].

Regarding COVID-19 pathophysiology, after SARS-CoV-2 infection, most of the patients remain asymptomatic or show mild symptoms as fever, dry cough, dyspnea, shortness of breath and bilateral lung

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infiltrates [1]. In addition, up to 20 % of the diagnosed patients tend to progress to acute respiratory distress syndrome (ARDS), which facilitates the pneumonia occurrence, leading to septic shock and death [4]. Although the immune response mechanism to SARS-CoV-2 infection has not yet been fully elucidated, it is believed, based on the ARDS and the virus-induced pneumonia characteristics, that the immune cells hyperactivation by the SARS-CoV-2 results in an excessive inflammatory cytokine production (cytokine storm). This phenomenon causes a remarkable inflammatory reaction in the lung tissue, leading to the COVID-19-confirmed patients' hospitalization and need for intensive care [4]. Herein, it is important to note that the correlation of COVID-19 infected patients' progression to the ARDS has been widely studied and the current available data is based on clinical, epidemiological and experimental observations.

Additionally, clinical features have been fundamental to guide the COVID-19 patient's management. In fact, according to the clinical symptoms and signs of the patients, it is possible to define the more suitable management approach. Therefore, it is possible to classify the COVID-19 patients in three different stages, wherein the Stage I is related to patients with non-severe clinical features, whereas the Stage III involves COVID-19 infected patients able to develop ARDS (Table 1) [5].

Then, according to each stage, distinct treatment approaches are needed to (i) treat the symptoms, (ii) prevent the COVID-19 clinical evolution and (iii) avoid ARDS development.

The use of pharmaceutical active natural products (PANPs) stands out as a promising strategy to prevent the COVID-19 evolution, mainly in Stage II patients. Indeed, some of these products are able to reduce the edema formation, the immune cell degranulation or even suppress the airway inflammation/hyperresponsiveness. In addition, the preventive treatment, also called early treatment, can be a reliable approach as important as the ARDS treatment [6]. Therefore, the aim of this work was to provide a systematic review concerning PANPs used by the folk medicine that may help to prevent the ARDS evolution in COVID-19-diagnosed patients.

2. SARS-CoV-2 infection and pathogenesis of COVID-19

The SARS-CoV-2 is a human coronavirus responsible for the COVID-19, a potentially fatal disease responsible for the pandemic outbreak in 2020. In this scenario, the coronavidae family is characterized by enveloped viruses with a positive sense single-stranded RNA genome [7]. This virus family can be classified in four genera (α, β, γ and δ), among which the SARS-CoV-2 is included in the β genus [7]. In addition, their genome is able to encode four main proteins that present a key role in the pathogenesis and virus infection ability: spike (S), nucleocapsid (N), membrane (M) and envelope (E) proteins [8].

In general, a viral infection initiates by the binding of viral protein to cellular host membrane-receptors, allowing the virus attachment into host cells. Simultaneously, according to the virus biochemical features (genome, proteins and pathogenicity degree), an innate immune response is triggered to prevent the virus replication/infection dissemination and also to prevent the damage of host cells and tissues [9].

Regarding the SARS-CoV-2 infection, it is shown that the virus is transmitted by respiratory fluid droplets/aerosols and infects, mainly, the lower respiratory tract cells. Indeed, the viral S protein, responsible for interacting with the angiotensin-converting enzyme 2 (ACE2) receptors in the host cells, promotes the virus attachment, leading to a conformational change in the S protein and triggering endosome formation, which enables the virus entry in host cells [10].

Subsequently, the viral genome reaches the cytoplasm and the uncoated viral RNA translates the pp1a and pp1b proteins, responsible for encoding the non-structural proteins and, also, for the replication-transcription complex (RTC). This complex contributes to the production and replication of sub genomic RNA, which encodes the accessory and structural SARS-CoV-2 proteins. Then, the M, S and E viral proteins are inserted on the endoplasmic reticulum and, moreover, carried to the endoplasmic reticulum-Golgi intermediate compartment, wherein the viral nucleocapsid is formed. Finally, the vesicles containing the formed virus is transported to the host cells membrane, allowing its release, dissemination and the infection [10].

Herein, it is important to note that the viral cycle replication induces an innate immune response in order to prevent the virus replication and its dissemination. In light of this, during the virus incubation time, the infected cells release substances that can promote injury to lung and other organs cells [6]. In order to control the injury, neutrophiles, macrophages, natural killer cells (NKS) and also the immune proteins act as the first line defense [6,11]. These cells, in addition to the dendritic cells (DCs) and epithelial lung cells, promote a coordinated immune response, characterized by a low production of antiviral interferon factors (IFNs) and a high level of proinflammatory cytokines (IL-1β, IL-6, TNF) and chemokines (CCL-2, CCL-3 and CCL-5) [11]. In this early stage of infection, symptoms as fever, myalgia and dry cough can be observed [6].

In this scenario, the suitable production of IFNs molecules is the key role to control the viral replication and decrease the inflammatory reaction on the pulmonary tissue. However, due to the unsolved immunological issues, a delay of the IFNs release in SARS-CoV-2 early stages infection has been observed, which compromises the antiviral response [11]. Therefore, the excessive increase in the cytokines and chemokines attract many inflammatory cells (neutrophiles and monocytes), resulting in a remarkable infiltration of these cells on the lung tissue, leading to a huge lung injury and disease progression [6,11].

In this scenario, a rapid viral replication and a remarkable inflammatory reaction on pulmonary tissue may be observed, which contribute to (i) the fibrin leakage to pulmonary space, (ii) the thromboembolic insults and (iii) the apoptosis of lung epithelial and endothelial cells. The latter causes damage in the microvascular and alveolar pulmonary environments, resulting on edema formation and hypoxia [6,11].

Herein, it is important to highlight that, in light of the immune response and the inflammatory reaction promoted by the SARS-CoV-2 infection, anti-inflammatory drugs should be able to control the disease progression. However, the current immunological concepts have some limitations to fully explain and elucidate the real pathologic pathway induced by the SARS-CoV-2, which results in aberrant immunological inflammatory reactions.

Moreover, Lee and Colleagues (2020) [6] presented the Protein-Homeostasis-System (PHS) hypothesis. According to these

Table 1
COVID-19 infected patients' clinical classification. Adapted from Siddiqi and Mehra (2020) [5].

COVID-19	Stage I (early inflammation)	Stage II (moderate inflammation)	Stage III (severe inflammation)
Clinical symptoms	Malaise, fever and dry cough	Cough, fever and hypoxia ($PaO2/FiO_2$ < 300 mm Hg)	ARDS, shock and cardiac failure
Clinical signs	Lymphopenia	Abnormal chest imaging, low-normal procalcitonin and transaminitis	Increase on inflammatory markers (CRP, LDH, IL-6 and troponin)

ARDS (Acute Respiratory Distress Syndrome); CRP (C-reative protein); FiO2: fractional inspired oxygen; IL-6 (Interleukin type 6); LDH (Lactate dehydrogenase); mm Hg: millimeters of mercury; PaO_2: arterial oxygen partial pressure.

authors, in addition to the identified immunological pathways, (i) the infected host cells, (ii) the damaged cells by the inflammatory reaction and (iii) the lung tissue injury may contribute to the release of proteins, fragments or by-products that can induce immune reactions able to intensify the inflammatory response [6]. These reactions may be associated to the disease development and progression due to the long-term nonspecific hyperreactions promoted by these proteins. This hypothesis presents itself as a new immunological concept with remarkable importance to the complete elucidation of the SARS-CoV-2 pathogenesis and infection progression.

In light of these unsolved immunological issues, failing to treat the COVID-19 disease in its early stages, may lead to (i) intense inflammatory reactions, (ii) excessive levels of pro-inflammatory cytokines ("cytokine storm") and, also, (iii) lungs immunopathological changes; which can further progress to ARDS, leading to the COVID-19 infected patients' death.

3. Acute respiratory distress syndrome (ARDS)

ARDS was first described in 1967 by Ashbaugh et al. as an acute inflammatory lung injury associated to dyspnea, tachypnoea, loss of lung-compliance and bilateral alveolar infiltration, which may lead to pulmonary hypoxia and fibrosis [12]. Currently, ARDS diagnosis is defined according to the 4 criteria proposed by the Berlin definition, which includes (i) respiratory symptoms developed at least one week from the clinical evaluation or the appearance/evolution of new symptoms during the past week; (ii) bilateral opacities related to pulmonary edema, which are identified by chest radiograph or computed tomographic scan; (iii) respiratory dysfunction not correlated to cardiac failure or fluid overload; and (iv) moderate to severe impairment of oxygenation, evaluated by the PaO_2/FiO_2 ratio [13,14]. According to this parameter, ARDS can be classified as mild (PaO_2/FiO_2 201−300 mmHg), moderate (PaO_2/FiO_2 101−200 mmHg) or severe ($PaO_2/FiO_2 \leq 100$ mmHg) [15].

In this context, the inflammatory response and symptoms observed on ARDS patients can be triggered by a wide variety of factors and etiological agents, as non-infectious (aspiration gastric content, pulmonary contusion, inhalation burns and near drowning) and infectious agents (bacterial, viral, parasitic and fungal agents), among which the MERS-CoV and SARS-CoV viruses can be highlighted [15–17]. Furthermore, specific pathologic findings from ARDS patients can be identified according to the etiologic agent. Among those, diffuse alveolar damage, hypoxia, remarkable immune cells infiltration and hyaline membrane formation in alveolar region are the most common [15]. In addition, it is important to note that ARDS may present distinct characteristics according its etiology. Although it may display similar immunopathogenesis, its severity is directly related to the levels/amounts of released substances according to the etiological cause.

Recently, the SARS-CoV-2 infection has been listed as an important agent on ARDS clinical development due to the COVID-19 pandemic outbreak, since up to 20 % of the COVID-19-confirmed patients tend to develop ARDS, which facilitates the pneumonia occurrence, leading to septic shock and death [4]. Indeed, the ARDS triggered by viral infections may be more aggressive to pulmonary tissue since the intense viral replication and the immune response to control this issue can facilitate bacterial opportunist infection and pneumonia appearance. Then, in addition to the viral infection and the inflammatory damage, opportunistic bacterial infections contribute to a remarkable pulmonary injury, which may lead to the ARDS progression, resulting in patient death [15].

Additionally, endothelial cells were recently correlated with ARDS derived from SARS-CoV-2 infection, since these cells are able to express leukocyte adhesion molecules and, then, facilitate the accumulation and extravasation of leukocytes and neutrophils to inflammatory site, contributing to an increase in the inflammatory lung response [18]. In addition to the aforementioned factors related to the ARDS development from COVID-19, it is important to note that the PHS hypothesis can also be related to the ARDS pathogenesis. In such case, proteins derived from host-infected cells or damaged cells can contribute to increase the immune inflammatory response [6,15].

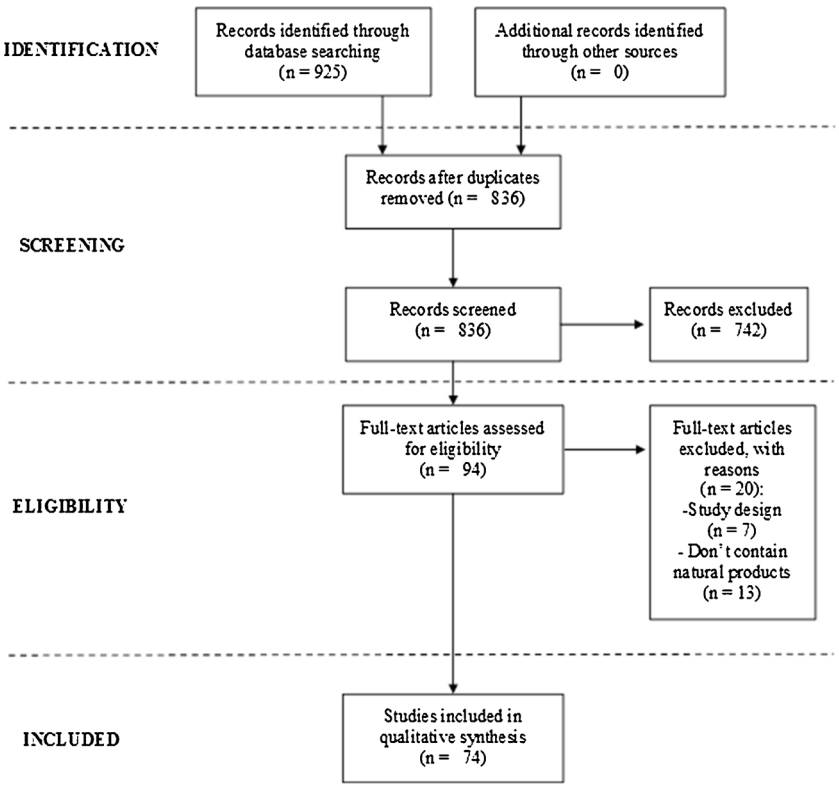
This feature, in addition to the cytokine storm also related to the COVID-19-confirmed patients, leads to the ARDS symptoms development and requires the patient hospitalization and intensive care to its management, which involves mechanical ventilation and use of antibiotic drugs, when the pneumonia is diagnosed. Based on this, the current treatment of COVID-19-related ARDS mainly focus on supportive therapies to reduce damages promoted by lung inflammation, fibrosis and mechanical ventilation itself, since there is no specific antiviral drug to successfully treat the SARS-CoV-2 [4]. Additionally, other factor that difficult the specific pharmacological treatment is the phenotypic variety of this syndrome, since recent research have identified different phenotypes of COVID-19-related ARDS by heterogeneous clinical, radiologic, pathologic and biological features [19].

In fact, Robba *et. al.* (2020) proposed that different phenotypes of COVID-19 related ARDS may require different treatment approaches. Their findings showed, based on chest computed tomography (CT), that clinical presentation of ARDS on COVID-19-confirmed patients present specific features and may be divided into 3 main phenotypes: (i) a group that present multiple, focal and possibly over perfused ground-glass opacities, which is characterized by good compliance and severe hypoxemia, requiring treatment by anti-inflammatory drugs and inhaled NO; (ii) patients with inhomogeneously distributed atelectasis and peribronchial opacities, which includes patients that require high positive end-expiratory pressure; and (iii) a group with a patchy ARDS-like pattern, mainly characterized by alveolar edema, which involve patients that need steroids and extracorporeal membrane oxygenation [20].

Therefore, the investigation of different pharmacological approaches in the treatment of ARDS related to SARS-CoV-2 infection is still necessary, considering not only the syndrome complexity, but also that each different clinical feature requires distinct management strategies. Hence, some authors have already suggested that the early treatment of ARDS can be a promising approach to the patients' effective treatment [17,18]. Then, it is important to investigate the therapeutic strategies for the prevention of ARDS in COVID-19 patients, among which the use of pharmaceutical active natural products (PANPs) stands out as a suitable strategy that could be further investigated as an alternative on the treatment. This rationale is supported by the PANPs ability to promote anti-inflammatory activities both *in vivo* and *in vitro*, which could potentially prevent the ARDS evolution.

4. Methodology

The PRISMA checklist/recommendation was used to conduct the literature search [21]. The literature search was performed in the Web of Science, PubMed and Scopus data base, using the keywords registered in Medical Subjects Headings (MeSH): "Natural products" AND "Acute Respiratory Distress Syndrome" OR "ARDS" OR "ARDS, Human" OR "ARDSs, Human" OR "Human ARDS". A total of 925 articles (Web of Science – 696, Scopus – 139, PubMed – 90) were obtained. The inclusion criteria's (papers published in English from 2015 to 2020) and the exclusion criteria's (articles that did not perform *in vitro* or *in vivo* (human or animal) experiments and articles that did not present a detailed methodology) were used to filter the found manuscripts. Finally, 74 studies regarding the use of PANPs with potential ability to prevent the ARDS progression on COVID-19 confirmed patients were selected. Supplementary bibliography was used to discuss and contextualize the manuscript sections. Scheme 1 illustrates the used search strategy.



Scheme 1. Flowchart of the manuscripts' evaluation after the performed search strategy.

5. Biological activities of pharmaceutical active natural products (PANPs)

Historically, PANPs, wherein plants, animals and microorganisms represent the main sources, have been widely used by different folk cultures to treat different biological disorders, acting, notably, as antimicrobial, anti-viral and anti-inflammatory agents [22]. In this regard, the literature reports show the anti-viral activity against both RNA and DNA viruses, such as type 1 and type 2 *herpes simplex virus* (HSV-1 and HSV-2*), dengue virus* type 2, *influenza virus and Junin virus* [23].

In addition, a recent published review showed the applicability of different traditional Chinese herbal medicines in the treatment of COVID-19-related ARDS. These medicines are obtained from different herbal compounds that show anti-human coronavirus (anti−HCoV) activity and were used during the previous coronavirus outbreak in China. Although their clinical use is still not fully evidenced, *in vitro* and *in silico* studies are being performed and promising results have been observed [24].

On the other hand, another important treatment option that may be used on COVID-19-related ARDS treatment is the anti-inflammatory approach, in which many PANPs can be used, mainly for the prevention of symptoms. In this context, pathogens-associated inflammation, including ARDS, involves a complex biological response usually triggered by (i) stimuli related to infections and tissue damage, which presents clinical signs such as heat, pain, redness and edema, and (ii) activation of pathogen recognition receptors, such as toll-like receptors (TLR) found on the surface of the immunity cell membranes, in which the expression of multiple pro-inflammatory cytokines and chemokines, such as TNF-α, IL-1, IFN-γ and IL-6, is observed [25].

The inflammation pathway is also strongly related to the arachidonic acid (AA) metabolism, a component of the cell membrane lipids, which generates different bioactive pro-inflammatory mediators through three metabolic pathways. The cycle-oxygenase pathway is responsible to produce vasodilator prostaglandins, such as prostaglandin E2 (PGE2) and prostacyclin I2 (PGI2), and also a platelet aggregating agent called thromboxane A4. AA may also be converted into leukotrienes and lipoxins through lipoxygenase pathway [26].

Therefore, traditional treatment that targets these inflammatory pathways to overcome the cellular damage and promote tissue repair has been explored [22]. Moreover, PANPs have also been known to inhibit inflammation through different immunomodulatory mechanisms, such as inhibition of AA and histamine pathways [27]. In addition, PANPs may act through pulmonary anti-inflammatory pathways, such as the upregulation of IL-10 production and decrease of oxidative stress [22,27]. These properties can be found in many different sources of PANPs [22].

Regarding the pulmonary inflammation in SARS-CoV-2-infected patients, different PANPs can be described as probable treatment, since ARDS has a similar pathway to other chronic pulmonary inflammatory diseases, wherein the lower airways are affected, leading to the release of pro-inflammatory cytokines and interleukins [27]. In this context, several literature reports described PANPs that present mechanism of action against ARDS physiopathologic/biochemical conditions, not only by the increase of anti-inflammatory cytokines (IL-4, IL-10) and IFN-γ levels, but also by the attenuation of the airway hyperresponsiveness and inhibition of mast cells degranulation, decreasing the inflammatory pathways caused by the histamine [22].

Therefore, based on these evidences, PANPs may be useful on the early treatment of COVID-19-confirmed patients, since many compounds promote suitable biological activities, preventing the disease evolution and the beginning of ARDS symptoms. The use of PANPs would (i) reduce the use of conventional medicines for COVID-19 related ARDS, increasing their market availability for patients who have advanced symptoms; (ii) treat mild respiratory symptoms; and (iii) prevent ARDS in COVID-19-confirmed or –suspected asymptomatic patients or those who have no exacerbated symptoms. Indeed, PANPs with scientific evidence to be promising alternatives to COVID-19-related ARDS treatment will be discussed in the following section. To achieve this goal, a search strategy was performed to include scientific studies published in English over the last five years regarding the elucidation of

anti-inflammatory pathways targeting pulmonary disorders by *in vitro* and/or *in vivo* experiments using PANPs.

6. Pharmaceutical active natural products with potential to treat ARDS symptoms

The use of PANPs for the treatment of inflammatory disorders has been reported since ancient times [22]. Notwithstanding their broad use, there is a lack of scientific evidence regarding their efficacy against the ARDS caused by the SARS-CoV-2 virus. However, as previously mentioned, the current treatment for COVID-19-related ARDS also consists in managing symptoms, especially respiratory disorders caused by the inflammation mediators. Hence, several herbal preparations, isolated classes of natural compounds and their derivatives have been reported to directly modulate the expression of different inflammation mediators [22], as presented in the Table 2.

6.1. Herbal preparations, extracts and plant blends

Plant and animal extracts, blends and phytotherapic preparations have been widely used due to their potential to treat and prevent ARDS symptoms. Similarly, popular Chinese herbal medicines have been overviewed due to their potential in the treatment of ARDS related to COVID-19, not only *via* anti-inflammatory pathways, but also in a broader range of pharmacological activities, such as antiviral [24].

Fusu, a plant blend made of *Aconitum carmichaelii Debx, Carapax Testudinis, Fructus Amomi, Rhizome Zingiberis, Radix Glycyrrhizae Preparata* and *Herba Ephedrae* has been widely used in China to treat Acute Lung Injury (ALI) due to its ability to inhibit inflammatory factors and attenuate lung capillary leaks [38]. As displayed in Table 2, the *in vivo* results from Gao et al. (2018) [38] are promising for early ARDS treatment based on its results in LPS-induced lung injury. Similar, *in vivo* investigations regarding LPS-induced lung injury have been performed for *Physalis alkekengi* L. var. franchetii [68], *Portulaca oleracea* hydroethanolic extract [69], Lianqinjiedu decoction [70], *Aster tataricus* extract [71], *Cordyceps sinensis* extract [72] and *Ulmus davidiana* extract [74]. Such studies were performed to investigate the effect of these complexes (with not reported active ingredients by these authors). Differently, a Sini decoction was tested against a mice model in which ARDS was induced by *Escherichia coli.* Notwithstanding its different induction method, the study followed similar investigations as the previously mentioned PANPs. After a twice a day oral administration of 5 g/kg, the Sini decoction was able to reduce the inflammatory factors in lung tissue, angiotensin II and angiotensin II type 1 receptor expression and MPO activity. Hence, the lung injury displayed an improvement.

Overall, although no specific active compound was reported, the studies demonstrated that several types of administration and dosage regimens resulted in inhibition of inflammatory cytokines release, such as IL-β, IL-6, TNF-α, PGE2, and TGF-β, increase of white blood cells counts and improvement in histological examinations [68–72,74]. These *in vivo* results in animals are promising, considering the potential of these compounds to be further studied for the early treatment of stage 1 and stage 2 COVID-19 patients.

Further studies have been performed using Xuanbai Chengqi decoction [67] and Rhubarb [66], which were submitted to clinical trials. Xuanbai Chengqi has been traditionally used since the late 1700s in China [67]. A decoction of this natural product was tested as treatment for ARDS. The clinical study determined that the lung compliance, either static or dynamic, were significantly higher in patients treated with the decoction rather than the control group. In addition, fatality rate was lower in treated patients. Similarly, Rhubarb, a plant commonly used as a cooking ingredient, was investigated regarding its ability to impact on extravascular lung water in ARDS patients. Overall, this PANP not only increased the oxygenation index after 5 days of treatment, but also reduced the extravascular lung water index in the same time when compared to the control group. Therefore, these Chinese natural products could be effectively useful in early treatment of ARDS patients.

6.2. Alkaloids

Alkaloids are secondary metabolites from plants that were initially defined as a nitrogen-based heterocyclic compound. Nowadays, alkaloids are heterocyclic nitrogenous compounds that may present different atoms, as -Br, -I, -Cl and -S. Although produced by a wide variety of organisms, plant derived alkaloids are worth highlighting [101]. They show several pharmacological activities *in vivo*. Among them, preventive ARDS effect could be achieved by inhibiting pharmacologic mediators of ALI.

Berberine is a major active compound from the rhizome of Coptis chinensis (*Rantus chinensis*, Ranunculaceae) [31]. This alkaloid had its effect investigated on the endothelial glycocalix integrity, since this structure is known to be destroyed in conditions such as ARDS. Berberine was able to reduce damage and to improve glycocalyx conditions by the inhibition of factors as reactive oxygen species. Yu et al. (2016) investigated the potential of Tetrahydroberberrubine, a berberine derivative, against LPS-induced lung injury in mice [35]. The study revealed that after a single oral dose of this alkaloid the lung wet-to-dry ratio decreased. In addition, the pulmonary edema, infiltration of inflammatory cells and coagulation were downmodulated by this alkaloid [35].

On the other hand, other alkaloids isolated from *Dendrobium crepidatum* [32] were able to improve lung activity *in vivo* by the inhibition of nitric oxide production and by the downregulation of tool-like receptor (TRL)4-mediated myeloid differentiation factor 88/mitogen-activated protein kinase signaling pathway. Protostemonine, an alkaloid isolated from *Stemona sessifolia,* also known as “Baibu” in traditional Chinese medicine, belongs to a group of alkaloids known to display beneficial respiratory properties [33,34]. This isolated molecule was able to attenuate the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and to reduce the iNOS expression. Furthermore, this molecule reduced lung edema in mice model and suppressed of p38 MAPK [33,34].

Tabersonine, an alkaloid obtained from *Catharanthus roseus,* was reported to suppress the k63-liked polyubiquitination of TRAF6, which suppressed NF-κB and p38 MAPK/MK2 signaling cascades. By consequence, the pro-inflammatory mediators production was inhibited even in the presence of LPS and the anti-inflammatory cytokines increased [36]. Notwithstanding the specific pathways, all the displayed alkaloids act by inhibiting pro-inflammatory mediators and increasing anti-inflammatory mediators in the presence of LPS as an inductor of ALI. Therefore, since ALI is a known precursor of ARDS, it could be inferred that these molecules are promising for early treatment of this syndrome at the initial stages of COVID-19.

6.3. Flavonoids

Flavonoids are a wide class of molecules with anti-inflammatory activity. These secondary metabolites are chemically composed by 15 carbons with two aromatic rings connected by a three-carbon link. These compounds are known to improve health and delay the onset of several diseases [101]. In fact, regarding their anti-inflammatory activity, computational studies have demonstrated that phospholipase A2 can be inhibited by several flavonoids [102], such as quercetin, kaempferol and galangin. In addition, flavonoids may prevent immunoglobulin E (IgE) synthesis and mast cell degranulation [103]. Based on their wide application to respiratory disorders, diets rich in flavonoids may show beneficial results in patients with ARDS, which could be further explored in order to prevent COVID-19 patients to develop such syndrome.

Acacetin is a flavone naturally found in several plants [45,48]. This O-methylated compound has been investigated as potential candidate to treat ARDS. Sun et al. (2018) and Wu et al. (2018) investigated this compound’s potential *via* two distinct mechanisms [45,48]. Sun et al.

Table 2
Pharmaceutical Active Natural Products (PANPs) with potential activity to prevent ARDS.

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
Adenosine derivate	Cordycepin	LPS-induced rat lung injury	*In vivo*	Wistar rats had the acute lung injury intravenously induced by LPS (30 mg/kg body weight) and treated, intravenously, with 1, 10 or 30 mg/kg body weight of cordycepin.	Heme oxygenase-1 expression and enzymatic activity enhancing. Nuclear factor erythroid 2-related factor 2 activation. Regulation of cytokine secretion.	[28]
Adipocytokine	Omentin	LPS-induced acute respiratory distress syndrome in mice and pulmonary endothelial cells	*In vivo* and *in vitro*	Omentin levels were previously monitored in human individuals with ARDS to ensure the omentin clinical significance in ARDS. ARDS was stimulated in mice with LPS (5 mg/kg) and treated with omentin injection (3×10^7 PFU). In addition, pulmonary endothelial cells were isolated, cultured and treated with 300 ng/mL of omentin (adenoviral vector expressing omentin (ad-omentin) and one-shot of recombinant human omentin (rh-omentin)). The evaluation of omentin permeation, the angiogenic potential and cytotoxicity were conducted.	Akt/ eNOS pathway activation and alleviation of pulmonary inflammatory response and endothelial barrier injury by omentin.	[29]
	Vaspin	LPS-induced acute respiratory distress syndrome in mice and LPS-induced inflammation in human pulmonary microvascular endothelial cells	*In vivo* and *in vitro*	Mice had ARDS stimulated by LPS. Adenoviral vector expressing vaspin (ad-vaspin) at 3×10^7 PFU was injected as treatment. Human pulmonary microvascular endothelial cells were isolated, cultured and treated with vaspin at 10 ng/mL following LPS (100 ng/mL during 2 h) exposition.	Alleviation of pulmonary inflammatory response and pulmonary endothelial cells barrier dysfunction. Akt/GSK-3β pathway activation. Inflammation and reactive oxygen species attenuation.	[30]
Alkaloid	Berberine	LPS-induced mice lung injury and LPS-induced inflammation in endothelial cells	*In vivo* and *in vitro*	Mice were pretreated with berberine (50, 100 and 200 mg/kg) following ARDS induced by intraperitoneal injection of LPS (20 mg/kg). After LPS exposition, mice were also treated orally with berberine at the same aforementioned concentrations for three days. *In vitro* evaluation was performed using human vein endothelial cells, LPS-induced inflammation and berberine pretreatment at 1.25, 2.5 and 5 mM.	Inhibition of the syndecan-1 shedding and heparan sulfate. Decrease of pro-inflammatory cytokines production (TNF-α, IL-1β, IL-6), and inhibition of NF-κB signaling pathway activation.	[31]
	Total alkaloids from *Dendrobium crepidatum*	LPS-induced lung injury in mice	*In vivo*	Alkaloids (100 and 200 mg/kg) were administered by gavage in mice as pretreatment. LPS at 5 mg/kg was used to induce lung injury in mice 1 h after the pre-treatment.	The alkaloids inhibited the nitric oxide production and promoted downregulation of tool-like receptor (TRL)4-mediated myeloid differentiation factor 88/ mitogen-activated protein kinase signaling pathway.	[32]
	Protostemonine	*Staphylococcus aureus*-induced lung injury in mice	*In vivo*	Mice had lung injury induced by intratracheal administration of heat-killed methicillin-resistant *Staphylococcus aureus* at 2×10^8 CFU/mouse saline solution (50 μL). Protostemonine at 20 mg/kg injected intraperitoneally as treatment after 0.5 h of lung injury induction.	Attenuation of heat-killed methicillin-resistant *Staphylococcus aureus*-induced pathological injury, pulmonary neutrophil infiltration, tissue permeability and the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6). Decreases the iNOS expression.	[33]
	Protostemonine	LPS-induced lung injury in mice	*In vivo*	Mice had lung injury induced by intratracheal injection of LPS (5 mg/kg) and immediately treated with protostemonine (10 mg/kg). One group was monitored for 4 h and another one for 24 h. The latter received a second administration dose after 12 h of lung injury induction.	Inflammatory cell infiltration attenuation. Pro-inflammatory cytokine (TNF-α, IL-1β and IL-6) reduction. Lung edema elimination. Myeloperoxidase activity inhibition. Suppression of p38 MAPK, iNOS expression and NO production.	[34]
	Tetrahydroberberrubine					[35]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
		LPS-induced mice lung injury and LPS-induced inflammation in HTP-1 cells	*In vivo* and *in vitro*	Mice had lung injury induced intravenously using LPS (30 mg/kg) after 1 h of pretreatment with tetrahydroberberrubine at 2, 10 and 50 mg/kg. The human monoblastic leukemia cells were cultured and treated with tetrahydroberberrubine at 1, 5 and 10 mM for 1 h previous to inflammation induction using LPS (500 ng/mL).	Edema, coagulation and inflammatory cells infiltration reduction. Decrease in total cells count, total protein and nitrate/nitrite content in BALF. Significant decrease in TNF-α and nitrate/nitrite in plasma and myeloperoxidase activity reduction. Decrease and/or suppression of inflammatory markers such as TNF-a, NO, MAPKs JNK and p38, Akt, and NF-kB subunit p65 in cells.	
	Tabersonine	LPS-induced mice lung injury. LPS-induced lung injury in mouse bone marrow derived macrophages and LPS-induced inflammation in HEK 293 T, RAW 264.7 cells.	*In vivo* and *in vitro*	Mice had lung injury induced by LPS at 5 mg/kg and were subsequently treated with tabersonine at 20 and 40 mg/kg. Cells were isolated, cultured, stimulated using LPS (concentration not reported) and treated with tabersonine.	Attenuation of pathological lung injury. Inhibition of neutrophil infiltration, MPO activity and TNF-α, IL-1β and IL-6 expression. Suppression of NF-κB and p38 MAPK/MK2 signaling cascades and K63-linked polyubiquitination of TRAF6 reduction.	[36]
Alkene	Trans-anethole from *Foeniculum vulgare Mill*	LPS-induced mice lung injury	*In vivo*	Mice had lung injury induced using LPS saline solution (24 mg/kg) for three days following treatment with trans-anethole at 36.4, 72.8 and 145.6 mg/kg once a day for seven days.	Elimination of lung histopathological changes, decrease in inflammatory cells count, noteworthy IL-7 mRNA expression. Increase in IL-10 mRNA expression and Treg cells. Reduction in Th7 cells in spleen tissues.	[37]
Blend of plants	Fusu	LPS-induced lung injury in mice and LPS-induced inflammation in human umbilical vein endothelial cells (HUVEC)	*In vivo* and *in vitro*	Acute lung injury was induced by intravenous LPS administration (3 mg/kg). Two hours after, fusu at 2, 4 and 6 g/kg was used as treatment. HUVEC were sensitized with LPS and treated.	Lung injury improvement, recovery of the vascular endothelium loss and injury. Decrease in CD31 signal, heparanase1 expression and inflammatory responses. *In vitro* decrease in cells death and injury. Mitochondrial transmembrane potential stabilization and decrease of lactate dehydrogenase leakage.	[38]
Carotenoid	Crocin	LPS-induced acute respiratory distress syndrome in mice and LPS-induced inflammation in HUVEC	*In vivo* and *vitro*	Mice were pretreated with crocin at 15, 30 and 60 mg/kg. After 7 h, ARDS was induced in mice using intravenous LPS (20 mg/kg) administration for 6 h. HUVEC were pretreated with crocin at 20 μM for 1 h following inflammation with LPS at 1 μg/mL during 6 h.	Improvement of pulmonary vascular permeability. Inhibition of inflammatory signaling pathways, nuclear factor κB, mitogen-activated protein kinase, heparinase, and MMP-9 and cathepsin L expression. Protection of endothelial glycocalyx heparan sulfate degradation.	[39]
Coumarin	Isofraxidin	LPS-induced lung injury in mice	*In vivo*	Lung injury was induced using LPS (5 mg/kg) in mice 1 h after the pretreatment (intraperitoneal injection) with isofraxidin (5, 10 and 15 mg/kg). Lung injury severity was evaluated after 6 h of LPS induction.	Mortality reduction and decrease in lung wet-to-dry weight. TNF-α, IL-6 and PGE2 plasma and BALF levels decrease. Reduction in neutrophils and macrophages count in BALF and in MPO activity. Inhibition in lung histopathological changes and COX-2 expression.	[40]
	Umbelliferone	LPS-induced lung injury in mice	*In vivo*	Acute lung injury was induced by intranasal administration of LPS saline solution (50 μL) at 3.2 mg/mL 1 h after the pretreatment with umbelliferone (10, 20 and 40 mg/kg). Umbelliferone was administered by gavage and lung injury severity was evaluated 12 h after LPS induction.	Decrease on the wet-to-dry lung weight ratio. Attenuation of inflammatory cell infiltration in lung tissue. Reduction of the monocyte MCP-1, IL-6, TNF-α and IL-1β in BALF. MPO and MDA activity reduction and increase in the SOD activity.	[41]
	Imperatorin	MH-S alveolar macrophages and zymosan-induced mice lung injury	*In vivo*	Imperatorin at 4 mg/kg, intraperitoneally injected was used as pretreatment of mice for three consecutive days. Subsequently, zymosan (4 mg/kg) was	Reduction in iNOS and COX-2 expression. Decrease in IL-6 and TNF-α production. Signaling pathways of JAK/STAT and NF-κB inhibition. Reduction of	[42]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
				administered by instillation to induce lung injury. The imperatorin protective effect was observed after 24 h of the lung injury induction.	immune cell infiltration, pulmonary fibrosis and edema.	
DNA blend compounds	Polydeoxyribonucleotide and Pirfenidone	LPS and TGF-β-induced ARDS in human lung epithelial cell (A549)	*In vitro*	LPS and TGF-β at 1 μg/ml and 5 μg/mL, respectively, were used to induce ARDS in A549 cells. Polydeoxyribonucleotide at 2, 4, 8 and 16 μg/ml and pirfenidone at 100, 200, 500 and 1000 μg/ml were used as treatment.	Suppression of connective tissue growth factor, hydroxyproline, TNF-α and IL-1β expressions by both the polydeoxyribonucleotide and pirfenidone combined therapy and the pirfenidone monotherapy. Inhibition of collagen type I and fibroblast growth factor expressions.	[43]
Docosahexaenoic acids derived	Resolvin D1	Mechanical stretch and acid-induced pulmonary fibrosis in mice and human lung epithelial (BEAS-2B) cells	*In vivo* and *in vitro*	Mice had the pulmonary fibrosis induced by intratracheal acid aspiration following mechanical ventilation for 24 h. Subsequently, mice were treated with resolvin D1 at 0.01, 0.1 and 1 μg for five consecutive days. Resolvin D1 at 0.01 nM/μL was used as pretreatment in BEAS-2B cells, which were exposed to acid for 10 min before being subjected to 48 h of mechanical stretch.	Inhibition of mechanical stretch-induced mesenchymal markers (vimentin and α-smooth muscle actin). Stimulation of epithelial markers. Antifibrotic effect.	[44]
Flavonoid	Acacetin	LPS-induced mice lung injury	*In vivo*	Lung injury was induced by intratracheal instillation of LPS at 10 mg/mL. After 2 h, acacetin at 50 mg/kg was diluted in 5 % DMSO solution and intraperitoneally injected.	Attenuation of inflammatory histopathological alterations and edema. Reduction in TNF-α and IL-1β levels in lung tissues. Suppression of NO production. HO-1 levels elevation. Nrf-2 activity increase.	[45]
	Puerarin	Human lung fibroblasts cell line (HLF1) and Pulmonary injury induced by ischemia-reperfusion in rabbits	*In vitro* and *in vivo*	HLF1 cells were cultured and treated with puerarin at 200, 400 and 600 μg/mL. Pulmonary injury was induced in rabbits by ischemia-reperfusion and treated by auricular puncture of puerarin at 30 mg/kg.	Stimulation of HLF1 cell to apoptosis and cell growth inhibition. Upregulation of caspase 3. Downregulation of Bcl-2, TGF-β1, and Smad3. Reduction in IL-1, IL-2 and IL-4 production. Increase in IL-10 levels. Slight expression of Fas/FasL mRNAs in intima and extima of small pulmonary artery, alveoli, and bronchiole epithelia. Reduction in levels of apoptotic index, wet-to-dry ratio of lung tissue weight and index of quantitative assessment of histologic lung injury. Amelioration of abnormal changes in lung tissue morphology.	[46,47]
	Acacetin	Sepsis-induced acute lung injury in mice	*In vivo*	Mice were pretreated with acacetin at 20, 40 and 80 mg/kg. Two hours after, sepsis-induced acute lung injury was performed by cecal ligation and puncture.	Attenuation of lung injury and edema. Reduction of protein and inflammatory cytokine concentration. Decrease of infiltrated inflammatory cell number in BALF. Reduction in MPO activity. Regulation of iNOS, COX-2, SODs and HO-1.	[48]
	Astilbin	LPS-induced mice lung injury and LPS-induced inflammation in human umbilical vein endothelial cells (HUVEC)	*In vivo* and *in vitro*	Endothelial cells and mice were pretreated with astilbin at 12.5, 25 and 50 μg/ml or mg/kg, respectively. 24 h after, lung injury was induced using LPS at 1 μg/mL (*in vitro* study) and at 50 mg/kg (*in vivo* study).	Attenuation of pulmonary histopathological changes and neutrophil infiltration. Suppression of MPO and MDA activities. Decrease of the IL-6 and TNF-α expression. Decrease in indexes of pulmonary edema, lung wet-to-dry weight ratios. Inhibition of MAPK pathways and heparanase. Reduction of heparan sulfate production.	[49]
	Gnaphalium affine methanolic extract	LPS-induced inflammation in RAW 264.7 macrophages	*In vitro*	RAW 264.7 macrophages had the inflammation induced by LPS at 500 ng/ml after 1 h of treatment	Inhibition of NO, iNOS and IL-6 and TNF-α production. Modest	[50]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
				with *Gnaphalium affine* methanolic extract following inflammatory markers expression quantification.	inhibition on human neutrophil elastase (HNE).	
	Hydroxysafflor yellow A from *Carthamus tinctorius* L	LPS-induced acute respiratory distress syndrome in mice	*In vivo*	LPS at 15 mg/kg were intraperitoneally injected to induce ARDS in mice in the first and third days. After, hydroxysafflor yellow A (14, 28, 56 mg/kg) was intraperitoneally injected to mice once daily from day 1–10.	Attenuation of body weight loss and pathologic changes in pulmonary inflammation. Expression reduction of TNF-α, IL-1β, IL-6, TGF-β1, Col I, Col III, α-SMA, MD-2, TLR4 and CD14 at the mRNA (RT-PCR). Reduction of protein levels. Inhibition of nuclear factor NF-κB and α-SMA. Alleviation of slight collagen deposition.	[51]
	Hesperetin	LPS-induced lung injury in mice and LPS-induced inflammation in RAW264.7 and BEAS-2B cells	*In vivo* and *in vitro*	Mice were pretreated with hesperetin at 25 and 50 mg/kg, for seven consecutive days by gavage. After the pretreatment, mice had lung injury induced, orally, with LPS at 5 mg/kg. RAW264.7 and BEAS-2B cells had the inflammation induced using LPS (5 μg/mL) for 2 h following the treatment with hesperetin at 10 and 40 μM.	Reduction of MPO activity. Inhibition of MAPK activation. Regulation of IκB degradation. Blocking the interaction between MD-2 and its coreceptor TLR4. Lung protective effect.	[52]
	Silymarin	LPS-induced rats acute respiratory distress syndrome	*In vivo*	LPS was instilled to induce ARDS in rats after the pretreatment with silymarin at 50, 100 and 200 mg/kg. Silymarin was intraperitoneally administered for five consecutive days.	Mitigation of lung wet-to-dry ratio and protein level in BALF. Amelioration of the pulmonary function and lung histological changes. Reduction on lymphocytes, macrophages and neutrophils infiltration. Inactivation of multiple mitogen-activated protein kinase signaling pathways. Downregulation of the inflammation.	[53]
	Silibinin	LPS-induced lung injury in mice	*In vivo*	Intratracheal instillation was performed to induce lung injury in mice with LPS (10 μl dissolved into 50 μl of PBS). After lung injury induction, mice were treated with silibinin at 10, 20 and 40 μg/kg, intraperitoneally administered.	Inhibition of inflammatory cytokines production in BALF. Suppression of NF-κB activation and NLRP3 inflammasome expression.	[54]
	Ginsenoside Rb1	*Staphylococcus aureus*-induced mice acute lung injury	*In vivo*	*S. aureus* at 1×10^7 CFU/10 μL was intranasally administered (80 μL) to induce lung injury in mice. 24 h after, mice were treated intraperitoneally with Rb1 at 10 and 20 mg/kg thrice in intervals of 8 h.	Attenuation of physical morphology, histopathological variation, wet-to-dry weight ratio of lungs and the phosphorylation of p65, ERK and JNK. Inhibition of the IL-1β, IL-6, TNF-α production and the activation of TLR2.	[55]
Ginsenoside	Total ginsenosides and ulinastatin	Septic acute lung injury and acute respiratory distress syndrome	Clinical study	Patients with acute lung injury and ARDS (n = 80) were divided in two groups (UTI group and ulinastatin + ginsenosides synergize group). Ginsenosides synergize treatment was performed by injection (100,000 units dissolved in 500 ml of 5 % glucose, 3 times daily, and 100 ml of ginsenosides dissolved in 5 % glucose 2 times daily).	Significant decrease in acute lung injury scores. Improvement of pulmonary vascular permeability index, extravascular lung water index, oxygenation index, cardiac index, intrathoracic blood volume index and central venous pressure. Decrease in APACHE II scores.	[56]
Glucoside	Fraxin from Cortex Fraxin	LPS-induced mice acute distress syndrome	*In vivo*	LPS at 20 mg/kg was intraperitoneally administered in mice to induce ARDS following the treatment with fraxin at 10, 20 and 40 mg/kg, intragastrical administered, for 7 days, once a day.	Alleviation of pathological changes in the lung tissues. Inhibition of IL-6, TNF-α, and IL-1β. Activation of NF-κB and MAPK signaling pathways. Lung inflammatory responses were reduced. Inhibition of ROS and MDA expression. Increase of the SOD activity. Increase in pulmonary vascular permeability and reduction of lung edema.	[57]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
	Polydatin	LPS-induced mice acute respiratory distress syndrome and LPS-induced inflammation in BEAS-2B cells	*In vivo* and *in vitro*	Mice were intratracheally injected with LPS (5 mg/kg) to induce ARDS following treatment with polydatin at 45 mg/kg. Beas-2B cells were exposed to LPS at 0.5 mM and treated with polydatin at 50 μM.	Inhibition of matrix metalloproteinase-9 expression. Facilitation of Parkin translocation to mitochondria. Activation of Parkin-dependent mitophagy. Protection against mitochondria-dependent apoptosis in ARDS.	[58]
	Forsythoside B	LPS-induced mice lung injury and LPS-induced inflammation in RAW 264.7 macrophages	*In vivo* and *in vitro*	Mice were intraperitoneally pretreated with forsythoside B at 50 and 100 mg/kg. Two hours after, LPS (concentration not reported) was instilled to induce lung injury. Cells had inflammation induced by LPS at 1 μg/ml before the treatment with forsythoside B at 40, 80 and 160 μg/mL.	Suppression of the edema exudation and lung pathological changes. Attenuation of lung inflammation. Decrease in inflammatory cell infiltration and downregulated expression of cytokines, chemokines, and inducible enzymes. Inhibition of the activation of TLR4/NF-κB signaling pathway.	[59]
	Salidroside	LPS-induced mice lung injury	*In vivo*	Mice were intraperitoneally pretreated with salidroside at 10, 20 and 40 mg/kg following the induction of lung injury by instillation of LPS at 0.5 mg/kg.	Reduction of inflammatory cells in BALF. Decrease of the wet-to-dry ratio of lungs. Attenuation of histological lung changes. Inhibition of TNF-α, IL-1β, and IL-6 production. Inhibition of phosphorylation of IkB-α, p65 NF-kB, and the expression of TLR4.	[60]
Glycoprotein	Ulinastatin	LPS-induced acute respiratory distress syndrome in mice and human umbilical vein endothelial cells (HUVEC)	*In vivo* and *in vitro*	Mice were intraperitoneally pretreated with ulinastatin at 100,000 U/kg and LPS at 20 mg/kg 1 h before the ARDS induction with LPS at 20 mg/kg. HUVEC cells were LPS-stimulated and treated with ulinastatin at 1000 U/mL.	Attenuation of pulmonary pathological changes, pulmonary edema, and vascular permeability. Inhibition of endothelial glycocalyx destruction. Decrease of heparin sulfate production. Reduction of the active form of heparanase (50 kDa) expression and heparanase activity.	[61]
	Histidine-rich Glycoprotein	Cecal ligation puncture model in mice	*In vivo*	Sepsis was induced in mice by cecal ligation puncture. The cecum was punctured once (mild sepsis) or twice (severe sepsis) following the return to the peritoneal cavity. Subsequently, the animals were treated with histidine-rich glycoprotein at 4 or 20 mg/kg immediately or 6, 24 and 48 h after sepsis induction.	Improvement of mice survival. Inhibition of tight attachment of neutrophils to pulmonary vasculatures, subsequent immunethrombosis, DIC state, lung inflammation, hypercytokinemia, and activation of VECs. Neutrophils permeation was preserved. Inhibition of ROS production.	[62]
	Oleic acid	LPS-induced mice acute respiratory distress syndrome	*In vivo*	Mice were pretreated with oleic acid at 3 and 10 mg/kg. 30 min after, LPS at 8 mg/kg was administered to induce ARDS in the animals.	Suppression of the superoxide anion and elastase. Mitigation of MPO activity and TNF-α, and IL-6 expression. Decrease of pulmonary neutrophil recruitment and lung damage.	[63]
Lipid	*Acrocomia crispa* fruits lipid extract	LPS-induced mice lung injury	*In vivo*	Mice were pretreated with emulsified lipid extract of *Acrocomia crispa* fruits at 25, 50, 100 and 200 mg/kg by gavage administration. Posteriorly (1 h after the pretreatment), LPS at 20 mg/kg was intraperitoneally administered to induce lung injury in mice.	Reduction of lung edema, lung weight/body weight ratio. Reduction of histological score.	[64]
Lipoxygenase-derived eicosanoid	Lipoxin A4	LPS-induced mice lung injury and in alveolar epithelial type II cells	*In vivo* and *in vitro*	LPS at 10 mg/kg was intratracheally administered to induce lung injury in mice following treatment with lipoxin A4 (10 μg/mouse). Cells were isolated from lungs of grossly normal appearance.	Induction of alveolar AT II cells proliferation. Inhibition of AT II cells apoptosis. Reduction of cleaved caspase-3 expression and epithelial–mesenchymal transition. Attenuation of lung injury. Downregulation of p-Akt and p-Smad expression.	[65]
Not reported	Rhubarb	Extravascular lung water (EVLW) in patients with acute	Clinical study	Patients with ARDS were treated with rhubarb at 30 g/day and	Increase of oxygenation index. Decrease of extravascular lung	[66]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
		respiratory distress syndrome		compared to conventional therapy during seven days.	water and pulmonary vascular permeability index levels.	
	Xuanbai Chengqi decoction	Patients with exogenous pulmonary acute respiratory distress syndrome	Clinical study	Prevention of infection, organ function support, shock resuscitation treatment, correction on the disturbance of water and electrolyte balance, and maintenance of acid– base balance and lung-protective ventilation strategy were conducted for patients in both the control and the treatment groups. In addition, Xuanbai Chengqi decoction (400 mL) was administered by rectal *via* twice a day for 3−5 days.	Increase of static lung compliance and dynamic lung compliance. Reduction of plateau pressure, peak airway pressure and positive end-expiratory pressure. Decrease in both the incidence rate and the fatality rate of complications (abdominal distension and ventilator-associated pneumonia).	[67]
	Physalis alkekengi L. var. franchetii	LPS-induced mice lung injury	*In vivo*	Mice were pretreated with *Physalis alkekengi L.* at 500 mg/kg by gavage for seven days. After the last treatment dose administration, LPS at 5 mg/kg was intraperitoneally administered to induce lung injury in mice. Six hours after, blood samples were collected and the experiments were assessed.	Reduction on TNF-α expression and oxidation products accumulation. Decrease of NF-κB, p-p38, ERK, JNK, p53, caspase-3 and COX-2 levels. Enhance the translocation of Nrf2 from the cytoplasm to the nucleus. Reduction of oxidative stress injury and inflammation. Reduction of cells apoptosis.	[68]
	Portulaca oleracea hydroethanolic extract	LPS-induced rat lung injury	*In vivo*	*Portulaca oleracea* hydroethanolic extract was used in the pretreatment of rats at 100 and 200 mg/kg. 1 h after, LPS at 50 mg/kg was intraperitoneally administered to induce lung injury.	Reduction of IL-β, IL-6, TNF-α, PGE2, and TGF-β levels. Increase of IL-10 level. Improvement of white blood cells level, MPO, MDA, SOD and CAT activities. Decrease the lung wet-to-dry ratio and interstitial edema index.	[69]
	Lianqinjiedu decoction	LPS-induced inflammation and acute lung injury in rats	*In vivo*	Lianqinjiedu decoction at 0.61 mg/kg was orally administered to treat lung injury induced by LPS, intraperitoneally administered, at 0.005 mg/kg in rats.	Reduction of body temperature, IL-6, TNF-α levels and lung injuries. Block of TLR4/NF-κB p65 signaling activation in lung tissue.	[70]
	Aster tataricus extract	LPS-induced mice lung injury	*In vivo*	Lung injury was previously induced in mice by intranasal administration of LPS at 2 mg/kg once a day for three days. Posteriorly, mice were orally treated with *Aster tataricus* extract (3.5 g/kg) once a day for five days.	Inhibition of inflammatory cytokines release. Repair of vascular endothelial.	[71]
	Cordyceps sinensis extract	LPS-induced mice lung injury	*In vivo*	Lung injury was induced in mice by LPS (2.4 mg/kg) intratracheal instillation. After 4 and 8 h from lung injury induction, mice were treated with *Cordyceps sinensis* extract at 10, 30 and 60 mg/kg.	Reduction of histopathological injury degree, wet-to-dry weight ratio and MPO activity. Inhibition of neutrophils and macrophages count in BALF. Reduction of TNF-α, IL-1β, IL-6 and NO levels. Reduction of protein and mRNA levels of iNOS, COX-2 and NF-κB p65 DNA binding ability.	[72]
	Sini decoction	*E. coli*-induced mice acute lung injury	*In vivo*	Mice lung injury was induced by *E. coli* intratracheal injection at 5×10^8 CFU/40 μL PBS for four hours. Subsequently, mice were treated with sini decoction at 5 g/kg twice a day by oral administration, for seven days.	Amelioration of lung injury by reduction of inflammatory factors in lung tissue and MPO activity. Decrease of ACE, angiotensin II and angiotensin II type 1 receptor expression. Activation of ACE 2-Angiotensin-(1−7)-Mas pathway.	[73]
	Ulmus davidiana extract	LPS-induced lung injury in rats and RAW 264.7	*In vivo* and *in vitro*	*Ulmus davidiana* extract at 200 mg/kg was administered by gavage for three days as pretreatment agent. Subsequently, LPS at 7 mg/kg was intratracheally infused in rats for 1−2 minutes to induce lung injury and observed for seven days. RAW 264.7 cells were cultured and exposed to *Ulmus davidiana* extract at 1.25, 2.5, 5, 10, 20, 40 and 80 μg/mL.	Amelioration of IL-1β mRNA expression, nitrite levels and TNF-α expression. Reduction of nitrite/nitrate, total protein, LDH and TNF-α levels in BALF. Reduction of alanine aminotransferase and aspartate transaminase activities.	[74]
Phospholipid	Surfactants-derived phospholipids	Porcine neonatal triple-hit acute	*In vivo*	Pigs with 2.5 kg were intubated and mechanically ventilated for	Improvement of the oxygenation index, the ventilation efficiency	[75]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
		respiratory distress syndrome		approximately 76 h. ARDS was induced by: repeated broncho-alveolar lavage (approximately 16 lavages were need every 5 min); injurious ventilation (overventilation by doubling the mechanical ventilation to 15 mL/kg for two hours); and endotracheal LPS instillation (2.5 mg/pig).	index, the compliance and the resistance of the respiratory system, and the extra-vascular lung water index. Suppression of the acid sphingomyelinase activity and dependent ceramide production, linked with the suppression of the inflammasome. NLRP3/ASC/caspase-1 complex, and the pro-fibrotic response represented by the cytokines TGF-β1 and IFN-γ, MMP-1/8, and elastin. Reduction of IκB-kinase activity. Inhibition of polymorpho-nuclear leukocyte activity (MMP-8, myeloperoxidase). The alveolar-capillary barrier functions were maintained. Reduction of the alveolar epithelial cell apoptosis and, consequently, the pulmonary edema was reduced.	
Phytotherapy agent	YiQiFuMai	Particulate matter-induced mice acute lung injury	*In vivo*	Mice had lung injury induced by intratracheal instillation of particulate matter (40 μL) at 50 mg/kg. 30 min after, mice were treated with YiQiFuMai at 0.33, 0.67, 1.34 g/kg by intravenous administration and monitored for 24 h.	Reduction of lung pathological injury and the lung wet-to-dry weight ratios. Inhibition of MPO activity. Decrease of IL-1β and TNF-α. Reduction in NO levels and total proteins in BALF. Increase of mammalian target of rapamycin (mTOR) phosphorylation. Suppression of TLR4, MyD88, autophagy-related protein LC3 II and Beclin 1 expression.	[76]
Plant extract and polyphenol	*Ilex kaushue* aqueous extract and 3,5-dicaffeoylquinic acid	LPS-induced mice lung injury	*In vivo*	Mice were pretreated intraperitoneally with *Ilex kaushue* aqueous extract at 250 and 500 mg/kg and 3,5-dicaffeoyl-quinic acid at 25 and 50 mg/kg. 1 h after, LPS at 5 mg/kg was administered by intratracheal injection and monitored during 6 h.	Inhibition of human neutrophil elastase activity. Reduction of superoxide generation. Attenuation of the Src family kinase (SRKs)/ Vav signaling pathway. Pulmonary protection.	[77]
Polyethylene alkynes	Atractylodin	LPS-induced mice lung injury	*In vivo*	Mice were pretreated with atractylodin at 40 and 80 mg/kg by intraperitoneal infection. 1 h after, LPS at 0.5 mg/kg was intranasally infused and monitored during 12 h.	Attenuation of pulmonary histopathological changes. Reduction of the MPO activity, the wet-to-dry weight ratio of the lungs, protein leakage and infiltration of inflammatory cells. Inhibition of TNF-α, IL-6, IL-1β and MCP-1 secretion in BALF. Inhibition of NLRP3 inflammasome and TLR4 activation.	[76]
Polyphenol	*Rosmarinus officinalis* methanolic extract and rosmarinic acid	Rat models of systemic inflammation (lung, liver, kidney)	*In vivo*	Paw edema was induced by sub-plantar injection (0.1 mL) of λ-carrageenan 1 % after 30 min of pretreatment with *Rosmarinus officinalis* at 10, 25 and 50 mg/kg. Hepatic ischemia reperfusion by surgical procedure after 30 min of pretreatment with *Rosmarinus officinalis* at 10, 25 and 50 mg/kg. Thermal injury was performed by dorsal rat immersion into water at 99 °C for 10 min after 5 min of pretreatment with *Rosmarinus officinalis* at 10, 25 and 50 mg/kg.	Paw edema reduction. Reduction of the serum concentration of AST and ALT and LDH. Reduction of multiorgan dysfunction markers (liver, kidney, lung) by modulating NF-κB and mettaloproteinase-9.	[78]
	Curcumin	Sepsis-induced acute lung injury	*In vivo*	30 μl of a lethal dose of *Klebsiella pneumoniae* (500 CFU) was administered into the mice by hypopharyngeal injection after 2 h of the administration of curcumin (1 μg/μL). Subsequently, the same	Decrease of *Klebsiella* hemolysin gene; TNF-α; IFN-β; nucleotide-binding domain, leucine-rich–containing family, pyrin domain– containing-3; hypoxia-inducible factor 1/2α and NF-kB.	[79]

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Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
				dose of curcumin was also administered after 2, 6 and 24 h of the sepsis induction.	Improvement of cell survival. Reduction of injury, inflammation and mortality.	
	Caffeic acid phenethyl ester (CAPE) from propolis	Mouse primary peritoneal macrophages (MPMs) activated by LPS	*In vivo* and *in vitro*	Mice had lung injury induced by LPS at 5 mg/kg by intratracheal injection. 30 min after, they were treated with CAPE at 15 mg/kg. Mouse primary peritoneal macrophages cells had inflammation induced by LPS (0.5 μg/mL) for 24 h after 30 min of pretreatment with CAPE.	Prevention of LPS/MD-2/TLR4 complex formation. Acute lung injury protective effects by reduction of TNF-α, IL-6 levels and MPO activity.	[80]
	Bergenin	LPS-induced mice lung injury	*In vivo*	Mice had lung injury induced by intranasal administration of LPS at 20 mg/kg. 30 min and 12 h after, they were treated with bergenin at 50, 100 and 200 mg/kg.	Decrease of pulmonary edema. Improvement of histological changes. Reduction in MPO activity. Decrease of IL-1β and IL-6 production in BALF and IL-1β, TNF-α and IL-6 production in serum. Inhibition of NF-κB p65 phosphorylation and the expression of MyD88.	[81]
	Lycium barbarum polysaccharide	LPS-induced mice ARDS and LPS-induced inflammation in HPMECs	*In vivo* and *in vitro*	*Lycium barbarum* polysaccharide at 200 mg/kg was administered by gavage. 2 h after, LPS 5 mg/kg was intratracheally instilled in mice to induce ARDS. HPMECs were exposed to LPS at 200 μg/mL for 2 h and, then, treated with *Lycium barbarum* polysaccharide at 100 ng/mL.	Attenuation of lung inflammation and pulmonary edema. Increase in cell viability and decrease of apoptosis and oxidative stress. Inhibition of caspase-3 activation and ROS production. Reversion of dysfunction of endothelial cells migration. Suppression of NF-κB activation.	[82]
Polysaccharide	*Oudemansiella radicata* polysaccharides	LPS-induced mice lung injury	*In vivo*	LPS at 5 mg/kg was intraperitoneally injected for three successive days in mice. Subsequently, the treatment with *Oudemansiella radicata* polysaccharides at 200 and 400 mg/kg/day was performed for 3 days.	Alleviation of lung injury. Prevention of lung oxidative stress by reduction of serum levels of C3, CRP and GGT and increase of pulmonary activities of SOD, GSH-Px, CAT and T-AOC. Downregulation of MDA and LPO contents. Reduction of TNF-α, IL-1β, and IL-6 levels in BALF.	[83]
	Oudemansiella radicata enzymatic- and acid-hydrolyzed mycelia polysaccharides	LPS-induced mice lung injury	*In vivo*	LPS at 5 mh/kg/day was intraperitoneally injected for three successive days. Subsequently, *Oudemansiella radicata* enzymatic- and acid- hydrolyzed mycelia polysaccharides at 600, 900 and 1200 mg/kg/day was administered by gavage for 30 days.	Decrease of hs-CRP and C3 levels in serum. Increase of SOD, GSH-Px, CAT values and the level of T-AOC. Reduction of MPO activity. Downregulation of MDA and LPO contend. Reduction of TNF-α, IL-1β, and IL-6 levels.	[84]
	Kochia scoparia fruits polysaccharides	LPS-induced mice lung injury	*In vivo*	Mice were pretreated with *Kochia scoparia* fruits polysaccharides at 125 and 250 mg/kg by gavage. After 30 min, LPS at 5 mg/kg was intratracheally instilled to induce lung injury and monitored for 6 h.	Selective inhibition on human neutrophil elastase. Reduction of elastase activity, neutrophil infiltration, TNF-α and IL-6 levels, and neutrophil NET formation.	[85]
Quinone	2-Hydroxymethyl anthraquinone from *Hedyotis diffusa* Willd	LPS-induced mice lung injury and LPS-induced inflammation in RAW 264.7 cells.	*In vivo* and *in vitro*	Mice were pretreated with 2-Hydroxymethyl anthraquinone from *Hedyotis diffusa* Willd at 10 and 40 mg/kg by intraperitoneal injection. 1 h after, LPS at 5 mg/kg was intratracheally administered to induce lung injury. The animals were monitored for 7 h. Different concentrations of 2-Hydroxy-methyl anthraquinone from *Hedyotis diffusa* Willd and LPS at 1 μg/mL were incubated with RAW 264.7 cells for 24 h.	Attenuation of pulmonary edema, myeloperoxidase activity, and TGF-β1 and IL-6 levels. Increase of SOD and GSH levels and decrease of MDA level in serum. Suppression of NO, TGF-β1, TNF-α, IL-6, and IL-1β expression. Antagonization of TLR4 expression and the activation of NF-κB.	[86]
	Shikonin	LPS-induced mice lung injury, mouse primary peritoneal macrophages (MPMs) and human THP-1 monocytes	*In vivo* and *in vitro*	Mice were pretreated with shikonin at 12.5 and 25 mg/kg by gavage for seven consecutive days. Subsequently, LPS at 5 mg/kg was intratracheally instilled. Cells were incubated with shikonin at 0.4, 1, or 2.5 μM for 30 min and, then,	Promotion of interferences in the TLR4 activation. Inhibition of TNF-α and IL-6, IL-1β, COX2, ICAM1 and VCAM1 expressions. Inhibition of MAPK and NF-κB activation. Prevention of lung	[87]

(*continued on next page*)

Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
				exposed to LPS at 0.5 μg/mL for 24 h.	injury. Reduction of inflammatory cell infiltration.	
Saponin	Glycyrrhizic Acid	Sepsis-induced acute lung injury in rats	*In vivo*	Sepsis was induced in rats by cecal ligation and puncture. Subsequently, mice were treated with glycyrrhizic acid at 25 and 50 mg/kg by intraperitoneal injection and monitored for 24 h.	Alleviation of lung injury. Decrease of lung wet-to-dry weight ratio and total protein content in BALF. Increase of survival rate. Reduction of TNF-α, IL-1β and IL-6 levels and MPO activity. Inhibition of NO production and iNOS expression. Attenuation of MDA production. SOD activity was preserved. Mitigation of expression level of p-IκB-α.	[88]
Steroid	Ruscogenin	LPS-induced lung injury in mice and murine lung vascular endothelial cells (MLECs)	*In vivo* and *in vitro*	LPS at 5 mg/kg was used to induce lung injury in mice by intratracheal instillation for 24 h. 1 h after, ruscogenin at 0.1, 0.3, and 1 mg/kg was orally administered. Lung cells were isolated and cultured for posterior evaluation of inflammation signals.	Attenuation of lung injury and pulmonary endothelial apoptosis. Inhibition of activation of TLR4/MYD88/NF-κB pathway in pulmonary endothelium. Amelioration of apoptosis by suppressing TLR4 signaling.	[89]
	Senegenin	Sepsis-induced acute lung injury in rats	*In vivo*	Sepsis was induced in mice by cecal ligation and puncture. Subsequently, mice were treated with senegenin at 15, 30 and 60 mg/kg by gavage for 5 consecutive days.	Attenuation of lung injury. Reduction of lung wet-to-dry weight ratio, protein leak, leukocytes infiltration and MPO activity. Decrease in MDA contends. Increase of SOD activity and GSH level. Decrease of TNF-α and IL-1β levels. Inhibition of NF-κB translocation.	[90]
	Bardoxolone	LPS-induced mice lung injury	*In vivo*	Mice were pretreated with bardoxolone at 10 and 20 mg/ml by intraperitoneal injection. 1 h after, mice received LPS at 0.5 mg/kg by intranasal instillation and monitored for 24 h.	Reduction of lung wet-to-dry weight ratio and protein concentration, neutrophil infiltration, MDA and MPO levels. Improvement of SOD and GSH activities. Amelioration of histopathological changes. Improvement of ROS production, TNF-α, IL-6 and IL-1β release, and the expression of inducible iNOS, COX2 and HMGB1. Suppression of NF-kB signaling. Amelioration of p38, extracellular signal-regulated kinase 1/2 (ERK1/2) and JNK activation. Induction of Nrf2 signaling.	[91]
Terpene	Bigelovii A	LPS-induced mice lung injury and MH-S alveolar macrophages	*In vivo* and *in vitro*	Mice were pretreated with bigelovii A at 10 mg/kg by intraperitoneal instillation. Subsequently, mice lung injury was induced by LPS intranasal instillation and monitored for 18 and 60 h. Cells were cultured and treated with bigelovii A at 0.1, 1, 10 and 50 μM. Subsequently, cells were exposed to LPS at 100 ng/mL for 4 h.	Alleviation of lung injury. Reduction of f IL-6, MCP-1, MIP-1α, and MIP-2 levels, neutrophil infiltration, and lung permeability. Downregulation of inflammatory mediators. Attenuation of NF-κ B and CCAAT/ C/EBPδ activation. Inhibition of p38 MAPK and ERK1/2 phosphorylation.	[92]
	Bisabolol	Sepsis-induced mice acute lung injury	*In vivo*	Sepsis was induced in mice by cecal ligation and puncture. Bisabolol at 30 mg/kg was orally administered 2 days before the sepsis induction.	Decrease of histological changes. Suppression of TNF-α, IL-6, IL-1β and MIP-2 levels in BALF. Reduction of lung wet-to-dry ratio, MPO activity, total inflammatory cells, and NO production in lung tissue. Inhibition of IκB-α degradation. NF-κB pathway activation blocking.	[93]
	Dehydrocostus Lactone	LPS-induced mice lung injury, RAW 264.7 and primary lung macrophages	*In vivo* and *in vitro*	Mice had lung injury induced by LPS at 5 mg/kg by intratracheal injection. Subsequently, dehydrocostus lactone at 5 and 20 mg/kg was intraperitoneally	Inhibition of iNOS, NO, TNF-α, IL-6, IL-1β, and IL-12 p35 expression. Suppression of NF-κB activity *via* p38 MAPK/MK2 and	[94]

(*continued on next page*)

Table 2 (*continued*)

PANPs class	PANPs	Experimental		Experimental conditions	Biological response	Reference
		Design	Model			
				administered. Cells were incubated with dehydrocostus lactone at 0, 3, 5, 10 and 30 μmol/L for 30 min. Subsequently, cells were exposed to LPS at 100 ng/mL for 8 h.	Akt signaling. Attenuation of pathological injury.	
	Euphorbia factor L2	LPS-induced mice lung injury and LPS-induced inflammation in RAW 264.7 cells.	*In vivo* and *in vitro*	Mice were pretreated (2 h before lung injury induction) and/or treated (2 h after lung injury induction) with euphorbia factor L2 at 10, 20 and 40 mg/kg. Lung injury was induced by LPS at 1 mg/mL by intratracheal instillation. Mice were monitored for 24 h. Cells were treated with euphorbia factor L2 at 1, 5, 10 and 25 μM for 2 h and, then, exposed to LPS at 1 μg/mL for 24 h.	Attenuation of pathological changes. Improvement of survival. Suppression of neutrophil recruitment and transmigration. Decrease of IL-1β, IL-6, TNF-α, IL-8 levels and MPO activity in BALF. Inhibition of NF-κB signaling activation. Downregulation of IKKα/β and IκB-α. Suppression of p65 translocation and DNA-binding activity.	[95]
	Isoalantolactone	LPS-induced acute lung injury and bone marrow cells from mice and HEK293 cells	*In vivo* and *in vitro*	Mice were pretreated with isoalantolactone at 20 mg/kg by intraperitoneal administration 1 or 13 h before lung injury induction. Lung injury was induced by intratracheal injection of LPS at 5 mg/kg and monitored for 6 or 24 h. Cells were isolated from mice and cultured for subsequent investigation. HEK293 cells were cultured and pretreated with isoalantolactone at 2.5, 5, 10, 20 μM.	Suppression of NO, TNF-α, IL-1β, and IL-6 expression and NF-κB, ERK, and Akt activation. Downregulation of non-degradable K63-linked polyubiquitination of TRAF6. Suppression of lung pathological changes, neutrophil infiltration, pulmonary permeability.	[96]
	α-bisabolol nanocapsules	LPS-induced mice acute lung injury	*In vivo*	α-bisabolol nanocapsules at 30, 50 and 100 mg/kg were administered by gavage 4 h before lung injure induction. LPS at 1 μg/μL was intranasally instilled. In addition, airway activity was assessed by mechanical ventilation in tracheostomized mice by mechanical ventilation at tidal volume =0.25 mL, positive end-expiratory pressure =0.160 cm H_2O, and respiratory frequency = 100 breaths/min for30 minutes.	Reduction of airway hyperreactivity (AHR), neutrophil infiltration, MPO activity, chemokine levels (KC and MIP-2) and tissue lung injury. Reduction in phosphorylation levels of ERK1/2, JNK, and p38 proteins.	[97]
	Picfeltarraenin IA	LPS-induced human pulmonary endothelial (A549) and THP-1 cells inflammation	*In vitro*	Cells were cultured and exposed to LPS at 1, 10 and 100 μg/ml for 6, 12 and 24 h. Subsequently, cells were treated with picfeltarraenin IA at 0.1, 1, 10 and 100 μmol/L for 24 h.	Inhibition/suppression of PGE2 production, and IL-8 and COX2 expressions.	[98]
	HJB-1-Derivative of 17-Hydroxy-Jolkinolide B	LPS-induced mice acute respiratory distress syndrome	*In vivo*	Mice were pretreated with HJB-1-Derivative of 17-Hydroxy-Jolkinolide B at 2 and 10 mg/kg by intraperitoneal administration. 1 h after, LPS at 0.2 μg/μL was intranasally instilled and animals were monitored for 24 h.	Alleviation of pulmonary histological changes, inflammatory cells infiltration and lung edema. Reduction of TNF-α, IL-1β and IL-6 expression in BALF. Suppression of IκB-α degradation, NF-κB p65 subunit nuclear accumulation and MAPK phosphorylation.	[99]
Vitamin	Vitamin D	LPS-induced mice lung injury and primary type II alveolar epithelial cell	*In vivo* and *in vitro*	Mice were pretreated with supplementation of 0.1, 1.5, 10 mg/kg $125(OH)_2$ -vitamin D_3 or 25(OH)-vitamin D_3 by intragastric injection for 14 days. Subsequently, lung injury was induced by LPS (0.24 mg) for 24 h. AT II cells were isolated from patients, cultured and, then, examined.	Stimulation of epithelial type II and AT II cells proliferation. Inhibition of AT II cells apoptosis and epithelial mesenchymal transition. Attenuation of lung injury.	[100]

ACE: angiotensin converting enzyme; Akt: Protein kinase B; ALT: alanine aminotransferase; APACHE II: Acute Physiology and Chronic Health Evaluation II; AST: aspartate aminotransferase; AT II cells: epithelial type II cells; BALF: broncho alveolar lavage fluid; Bcl-2: B-cell lymphoma 2; BEAS-2B cells: human non-tumorigenic lung epithelial cell line; C/EBPδ: enhancer-binding protein δ; C3: complement component 3; CAT: nucleoside sequence (cytosine-alanine-thymine); CCAAT: nucleoside sequence (cytosine-cytosine-alanine-alanine-thymine); CD 14: cluster differentiation 14; CD31: cluster of differentiation 31; CFU: colony-forming unit; Col: collagen; COX-2: cyclooxigenase-2; CRP: c-reactive protein; DIC state: Disseminated intravascular coagulation; DMSO: Dimethyl sulfoxide; DNA: Deoxyribonucleic acid; eNOS:

Endothelial nitric oxide synthase; ERK: Extracellular signal-regulated protein kinase; GGT: gamma-glutamyl transferase; GSH-Px: Glutathione peroxidase; GSK: glycogen synthase kinase; HEK293 cells: Human embryonic kidney 293 cells; HMGB1: high mobility group box 1; HO-1: Heme oxygenase-1; hs-CRP: high-sensitivity C-reactive protein; HPMECs: human pulmonary microvascular endothelial cells; ICAM1: intercellular Adhesion Molecule 1; IFN-γ: interferon-gamma; IkB-α: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IKKα/β: inhibitor of nuclear factor kappa-B kinase subunit alpha/beta; IL-1: interleukin-1; IL-10: interleukin-10; IL-12 p35: p35 subunit of interleukin-12; IL-1β: interleukin-1 beta; IL-2: interleukin-2; IL-6: interleukin-6; IL-7: interleukin-7; IL-8: interleukin-8; iNOS: inducible nitric oxide synthase; IκB: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; JAK/STAT: janus kinase/signal transducer and activator of transcription; JNK: c-Jun N-terminal kinase; K63: lysine-63; KC: kerotinocyte chemoattractant; LDH: lactate dehydrogenase; LPS: Lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: chemotactic protein-1; MD-2: myeloid differentiation-2; MDA: malondialdehyde; MH—S alveolar macrophages: murine alveolar macrophages cells; MIP-1α: macrophage inflammatory protein alpha; MIP-2: macrophage inflammatory protein-2; MK2: MAPK-activated protein kinase 2; MMP: matrix metalloproteinase; MPO: myeloperoxidase; mRNA: messenger ribonucleic acid; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa light chain enhancer of activated B cells; NLRP3: NLR family pyrin domain containing 3; ASC: apoptosis-associated speck-like protein; NO: nitric oxide; Nrf2: nuclear factor erythroid-related factor 2; PFU: plaque forming units; PGE2: prostaglandin E2; p-p38: phosphorylated-p38 mitogen-activated protein kinases; RAW 264.7: macrophage-like, Abelson leukemia virus transformed cell line derived from BALB/c mice; RNA: ribonucleic acid; ROS: reactive oxygen species; RT-PCR: reverse transcription polymerase chain reaction; Smad3: a protein in a pathway that helps prevent tumors; SOD: superoxide dismutase; SRKs: Src family kinase; Vav: family of proteins involved in cell signaling; T-AOC: total antioxidant capacity; TGF-β1: transforming growth factor beta 1; Th7 cells: T helper 17 cells; THP-1 cells: human monocytic cell line derived from an acute monocytic leukemia patient; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor alpha; TRAF6: tumor necrosis factor receptor associated factor 6; Treg cells: regulatory T cells; VCAM1: vascular cell adhesion protein 1; VECs: vascular endothelial cells; α-SMA: α-smooth muscle actin.

(2018) determined that this compound could reduce lung injury and edema by decreasing inflammatory cells and MPO activity [48]. In addition, this molecule was able to regulate iNOS, COX-2, superoxide dismutase and Heme oxygenase-1. Wu et al. (2018), on the other hand, further investigated such mechanisms and concluded that this compound was able to elevate HO-1 levels and Nrf-2 activity, whereas decreasing TNF-α and IL-1β levels [45].

Astilbin, also known as isoastilbin, is a flavonol compound that has been submitted to *in vitro* and *in vivo* studies regarding its anti-ARDS potential [49]. This molecule was used as treatment to LPS-induced mice lung injury and LPS-induced inflammation in human umbilical vein endothelial cells. Indeed, astilbin was able to suppress MPO and MDA activities and decrease IL-6 and TNF-α expression. Overall, this molecule attenuated pulmonary histopathological changes and neutrophil infiltration. Similar outcome was observed in an *in vitro* study with *Gnaphalium affine* [50]. This plant species grows extensively in Asia and is rich in flavonoids. An *in vitro* investigation of its anti-ARDS potential was conducted by Ryu et al. (2016), who produced a methanolic extract of this PANP that was able to inhibit NO production, iNOS expression and IL-6 and TNF-α levels in LPS-induced inflammation model in RAW 264.7 macrophages. Such result provides a hopeful perspective to *in vivo* studies regarding this promising PANP [50].

Other flavonoid molecules have been tested against different models and in different administration regimens, displaying similar outcomes. Hydroxysafflor yellow A, from *Carthamus tinctorius* L [51], Hesperetin [52] and Silibinin [54] were able to reduce LPS-induced ARDS in mice, whereas Silymarin reduced ARDS in rats [53] and Puerarin was able to improve the pulmonary changes provoked in rabbits [46,47]. Overall, it can be inferred that the flavonoid compounds found in the literature with possible application against ARDS act in the reduction of inflammatory mediators involved with the increase in ARDS symptoms. The animals treated with such compounds displayed not only changes in such mediators, but also reduced pathologic changes in pulmonary inflammation and amelioration of abnormal lung tissue morphology. From such *in vivo* studies it could be suggested that proper phytotherapy dosage forms based on these compounds are promising candidates to clinical studies of early ARDS treatment in stage 1 and stage 2 COVID-19 patients.

6.4. Polyphenols and coumarins

Among several other existing classes of natural compounds, the polyphenols represent a large number of currently used molecules. These are derived either from the phenylpropanoid pathway or the polyketide acetate/malonate pathway in plant biochemistry. Several classes of specific phenolic compounds are known, such as coumarins, xanthones, flavonoids, lignans and others [101]. Bergenin, curcumin and caffeic acid phenethyl ester, examples of polyphenols, are obtained from different plant sources. These polyphenols are responsible for the anti-inflammatory effects on the airways [79–81]. In fact, curcumin is the main curcuminoid from *Curcuma longa* L. in regard to pharmacological effects [79]. A sepsis-induced ALI model in mice was used to investigate this molecule's effect in the inflammatory pathways. Zhang et al. (2019) observed that this compound was able to reduce lung injury, inflammation, and mortality, by decreasing of TNF-α, IFN-β, NF-kB and other inflammation-related factors [79]. Similarly, bergenin and caffeic acid phenethyl ester decreased edema and ALI by the reduction of TNF-α, IL-6 levels, MPO activity and further inflammatory factors.

In addition, several literature reports also showed that plant-based extracts rich in polyphenols were tested for its therapeutic application in preventing ARDS by ALI reduction. *Rosmarinus officinalis* methanolic extract and rosmarinic acid [78] were investigated for different inflammation models in rats. The results indicated that the extract containing this polyphenol decreased dysfunction markers in liver, kidney, and lung by the modulation of NF-κB and mettaloproteinase-9. Similarly, *Ilex kaushue* aqueous extract and 3,5-dicaffeoylquinic acid reduced mice lung injury. Chen et al. (2016) demonstrated that this extract inhibited neutrophil elastase activity and superoxide generation. Furthermore, this extract promoted pulmonary protection [77].

Coumarins are phenolic compounds made of benzene and α-pyrone rings. Isofraxidin, a coumarin isolated from *Sarcandra glabra* and *Acanthopanax senticosus*, has been reported to display anti-inflammatory activity [40]. Niu et al. (2015) showed that this molecule decreased the mortality in mice by lung injury after intraperitoneal injections up to 15 mg/kg [40]. The authors observed an inhibitory effect in lung histopathological changes and COX-2 expression. Furthermore, inflammatory cytokine levels were also decreased. Similar anti-inflammatory and promising *in vivo* results from lung injury mice models were obtained from the studies of Wang et al. (2019) with umbelliferone [41] and Li et al. (2019) with imperatorin [42].

6.5. Glucosides

Glucoside is a broad classification attributed to molecules bound to glucose. These compounds can be identified according to the glucoside linkage between the molecules [101]. Fraxin, a major component extracted from the Chinese herb *Cortex Fraxini*, is a glucoside molecule with several pharmacological and biological activities [57]. This compound has also been investigated by the well-established LPS-induced mice ALI model. It was able to reduce pathological changes in the lung tissue of the studied animals. Additionally, lung inflammatory responses were reduced, as IL-6, TNF-α, and IL-1β productions were inhibited. On the other hand, polydatin, a molecule that can be extracted from the *Polygonum cuspidatum*, has proven to be useful in LPS-induced ARDS by inhibiting apoptosis in rats [58]. Li et al. (2019) showed that

mitochondria-dependent apoptosis and, by consequence, prevents lung injury in ARDS, which encourages further studies on ARDS therapy [58].

Liu et al. (2019) conducted similar studies regarding Forsythoside B and its effect on LPS-induced mice lung injury and inflammation in RAW 264.7 macrophages [59]. This molecule is a phenylethanoside presented in several plants and displays known neuroprotective, antibacterial and antioxidant properties. The authors investigated this compound's anti-inflammatory properties and observed that the pretreatment with this molecule may reduce lung histopathological changes and edema, decrease inflammatory cell infiltration in the lung and inhibit inflammatory cytokines. Similar results were found for salidroside by Lu et al. (2016), who demonstrated that this glucoside is also able to reduce histological lung changes and inhibit inflammatory cytokines [60].

6.6. Terpenes and carotenoids

Terpene is a broad nomenclature that includes different subclassifications, such as terpenoids, and represents the most numerous and chemically diverse secondary metabolites among the plants [101]. Bisabolol [93] and bisabolol nanoparticles [97] were reported to reduce airway hyperreactivity and lung tissue injury by suppressing inflammatory mediators in mice acute lung injury models. Regardless of their chemical structure differences, similar findings are applied to other terpenes, such as bardoxolone [91], bigelovii A [92], dehydrocostus lactone [94], euphorbia factor L2 [95], isoalantolactone [96] and HJB-1-derivative of 17-Hydroxy-Jolkinolide B [99]. Picfeltarraenin IA, on the other hand, has been responsible for downregulating PGE2 production, IL-8 and COX2 expressions, but no overall responsiveness was assessed in the animals [98]. Details regarding the individual terpene studies are provided in Table 2.

Furthermore, carotenoids are types of tetraterpenoids. They derive from two diterpenes and result in molecules that usually display conjugated polyene chromophores. Therefore, they are usually known as pigments. These molecules are usually found in chloroplasts and chromoplasts of plants [101]. Zhang et al. (2020) reported that crocin was able to improve pulmonary vascular permeability in mice *via* inhibition of inflammatory signaling pathways and inflammation-related protein expression regulation [39]. Overall, the studies regarding the use of terpenes in animal models of lung injury showed promising results, which suggested their further investigation in clinical studies.

6.7. Saponins and ginsenosides

Saponins are molecules that display surfactant activity due to their amphiphilic properties caused by the presence of terpene and sugar groups. These molecules are largely presented in various plant species and are also triterpenoid glucoside molecules [101]. Among this group, research has been conducted regarding the effect of glycyrrhizic acid on lung injury [88]. A sepsis-induced mice model was used by Zhao et al. (2016), who determined that this saponin reduced lung injury and decreased lung wet-to-dry ratio. Furthermore, this molecule was able to increase survival rates in mice by reducing several inflammatory mediators [88].

Moreover, ginseng triterpene saponins are also known as ginsenosides. This class of compounds accounts for most of the ginseng's biological activities [101]. Ginsenoside Rb1, one of the major compounds from ginseng, attenuated histopathological variations in lung injury in mice. Similar to the previously mentioned saponin, this compound was also able to reduce the expression of inflammatory mediators [55]. Another study conducted to investigate the effect of total ginsenoside in association with a trypsin inhibitor (ulinastatin) was conducted in humans. This study revealed that the ginsenosides enhanced the effect of ulinastatin in improving oxygenation index, pulmonary permeability index and further scores related to lung injury progression [56].

6.8. Quinones, Glycoproteins and polysaccharides

Quinones are derived from aromatic compounds that underwent oxidation. 2-hydroxymethyl anthraquinone, a quinone extracted from *Hedyotis diffusa* Willd, reduced pulmonary edema in mice after LPS-induced lung injury [86]. This compound was also able to promote the suppression of several inflammatory mediators, as NO, TGF-β1, TNF-α, IL-6, and IL-1β. In addition, NF-κB was activated and the TLR4 expression was downregulated. Further promising results from quinones can also be found for Shikonin, a compound that also interferes on TLR4 activation and modulates several inflammatory mediators. Additionally, Zhang et al. (2018) also observed that this quinone caused a reduction of inflammatory cell infiltration [87].

Glycoproteins are compounds who display proteins covalently bound to the oligosaccharide chains in their amino acid side chains. Concerning these compounds, two manuscripts accounted for the study of isolated glycoproteins against lung injury. Ulinastatin, as previously mentioned in association to ginsenosides, was also studied separately by Wang et al. (2016) in mice, who reinforced the possible application of this molecule due to its ability to reduce pulmonary pathological changes and edema in LPS-induced ARDS mice model [61]. Differently, histidine-rich glycoprotein was able to improve mice survival, inhibition of ROS production and further phenomena in a sepsis induced model [62]. These results highlight the remarkable potential of glycoproteins in improving lung function, even after sepsis.

Another class of compounds that has been studied due to their potential in preventing and treating ARDS are the polysaccharides. Our search strategy was able to include 4 research papers about such compounds. Overall, the studies used LPS-induced mice lung injury models to determine whether the proposed treatments could improve the animals' health conditions. *Lycium barbarum* polysaccharide [82], *Oudemansiella radicata* polysaccharides [83], *Oudemansiella radicata* enzymatic- and acid- hydrolysed mycelia polysaccharides [84] and Kochia scoparia fruits polysaccharides [85] showed positive results regarding the improvement of mice lung injuries. Among the most expressive findings, the polysaccharides appear to reduce lung injury by decreasing neutrophil's infiltration, reducing oxidative stress and downregulating inflammatory pathways.

6.9. Lipids, steroids and other compounds

Lipids and lipid-derived molecules have been extensively studied regarding their inflammatory pathways' modulation [26]. Oleic acid, a fatty acid that occurs naturally in animals and plants, and usually administered as a food supplement, showed promising effect against ARDS in mice. This molecule decreased pulmonary damage and neutrophil recruitment. Furthermore, this molecule also regulated inflammatory cytokines [63]. Similar results were found by Mena et al. (2019) for a lipid extract of *Acrocomia crispa* fruits, which reduced mice lung edema and histological scores after LPS-induced mice lung injury [64]. Spengler et al. (2017), on the other hand, conducted an *in vivo* study in a porcine ARDS model to investigate the anti-inflammatory effects of surfactant-derived phospholipids [75]. The study revealed that these compounds greatly improved overall lung conditions. Among their findings, it is possible to highlight the improvement of oxygenation, ventilation efficiency and compliance. In addition, biochemical investigations revealed the suppression of inflammasomes, reduction of cell apoptosis and inhibition of polymorphonuclear leukocyte activity.

Additionally, steroids are terpenoid lipids with four primary rings that are differentiated by changing the number of carbon atoms, types of functional groups and side chains. The studies conducted by Wu et al., (2020) and Liu et al. (2016) for Ruscogenin [89] and Senegenin [90], respectively, corroborate the findings previously mentioned for other lipids. Although steroids have their specific class based on their chemical specificities and endocrine functions, their anti-inflammatory effect on lung injury were also related to the inhibition of inflammatory

mediators, the reduction of cell apoptosis and the leukocyte activity modulation.

Other hydrocarbon-based molecules identified in the studies from our literature search did not show any unconclusive or contradictory results concerning their effect in improving lung function in the studied models. Overall, their activities corroborate the pathways described for all lipids mentioned in this section. Among those, the search identified studies concerning cordycepin [28], trans-anethole from Foeniculum vulgare Mill [37], resolvin D1 [44], lipoxin A4 [65] and atractylodin [76].

6.10. Animal-derived compounds

Although less usual, the use of animal-derived PANPs could also be an interesting approach for the treatment of mild respiratory and asthma-like symptoms in unhospitalized COVID-19 patients. A noteworthy example is the use of nucleotides from DNA blends [43]. Polydeoxyribonucleotide and pirfedidone were assessed against LPS and TGF-β-induced ARDS in human lung epithelial cells (A549). Hwang et al. (2020) showed that the genetic material, individually or combined, were able to suppress TNF-α and IL-1β along with tissue growth factor [43].

Adypocytokines, on the other hand, are molecules naturally produced by adipose cells that act as cytokine mediators. These molecules can also be of synthetic origin, as many experiments have generated analogs and derivates [29,30]. Omentin and Vaspin are molecules of interest among this class due to their vast application to several endocrine modulation [29,30]. Omentin, initially discovered in Paneth cells, is mainly secreted from the visceral fat. After administration in LPS-stimulated mice, omentin was able to increase activation of protein kinase B and eNOS pathways and to reduce inflammatory pulmonary response to LPS stimuli [29]. Similarly, vaspin (visceral adipose tissue-derived serine protease inhibitor; also known as Serpin A12) was administered in mice and caused an improvement in pulmonary response, with the attenuation of inflammation and reactive oxygen species [30].

6.11. Vitamins

Although not having a fully elucidated role on the potential prevention of COVID-19-related ARDS, vitamins are a group of substances causally related to immunocompetence. Besides their activities related to the stimulation of defensins, some vitamins can directly act in the inflammatory responses [22]. Vitamin D has been studied concerning the treatment of lung injury [100]. Zheng et al. (2020) showed that 125 $(OH)_2$-vitamin D_3 or 25(OH)-vitamin D3 could attenuate lung injury *via* inducing alveolar type II cells proliferation and migration, inhibiting TGF-β induced Epithelial-Mesenchymal Transition and reducing epithelial cell apoptosis [100]. These *in vivo* animal results are promising for propelling clinical studies regarding lung injury, since vitamin D is already marketable as an easy-access dietary supplement that could be a suitable alternative as an early-treatment and preventive treatment for COVID-19 stage 1 and stage 2 patients.

7. Conclusion and limitations

Facing the severity of COVID-19-related ARDS, it is imperative that public health departments standardize and publicize treatments accessible to the population who are not in need to be hospitalized. This part of the infected population faces an unprecedented situation in which they are not aided by health professionals and there is no effective medicine to be used in order to prevent the appearance or aggravation of respiratory symptoms. Hence, the use of natural products could be an eligible alternative, especially for the population who are in the least developed countries in which the financial aspects of the pandemic impairs the use of expensive drugs for “at home” treatments. This manuscript presented the current aspects of research using PANPs for the prevention of ARDS in COVID-19-confirmed patients. From this point of view, a series of PANPs were presented in order to provide a new insight to the medical community regarding the possibilities for respiratory symptoms prevention by using plant extracts, isolated natural compounds, animal-derived products and others in stage 1 and stage 2 COVID-19-confirmed or -suspected patients. The provided information is based on current research for the prevention, decrease and elimination of lung injury, the mechanisms of action of the presented natural compounds and their direct correlation to the physiopathology of ARDS. Therefore, this review showed that plant extracts, decoctions and other mixtures containing vitamin D, polyphenols, flavonoids, alkaloids, glycosides and other molecules are promising candidates to be further studied regarding their effectiveness and safety for the prevention of ARDS symptoms in COVID-19 stage 1 and stage 2 patients.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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