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*Review Article*

# *Ulquts Al Hindi (Sasereus sp)* has Candidate Covid-19 drug Through Regulation of Cytokines Produced by the Innate Immune System

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## Abstract

SARS-COV-2 virus is a new coronavirus variant that causes the severe acute respiratory syndrome. COVID-19 can cause abnormalities in various organs. It is due to increased levels of cytokines causing a cytokine storm. Cytokine storms occur due to an increase in the innate immune system to eliminate infectious agents. Activation of the production of inflammatory mediators causes pulmonary fibrosis, interstitial fluid infiltration, and impermeability in blood vessels. Qutshul al Hindi, or in Latin called Sausurea sp contains anti-inflammatory activity. However, the study about the definite benefit of bioactive in this plant against COVID-19 and their mechanism, especially to the immune system, needs more explanation. Therefore, this review discusses their mechanism against COVID-19 by activating immune cells. In the literature research, we approach the studies that examine the secondary metabolite of Qutshul al Hindi that is effective in activating and enhancing the immune response against covid 19. Our literature review shows that qutshul al Hindi (Sausurea sp) has anti-inflammatory activity by inhibiting expression and activity of cytokine proinflammation induced by the innate immune system. So that this plant is a promising herb as a therapeutic candidate for covid-19 by regulating the immune system to produce and activate cytokine pro-inflammatory.

**Keywords** : COVID-19, Innate Immune, SARS-CoV-2, Ulquts Al Hindi, inflammatory

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## 1 Introduction

At the end of 2019, Wuhan, China, reported that respiratory tract infections were caused by a new variant of the coronavirus that causes severe acute respiratory syndrome. The virus is the SARS-CoV-2 virus, also known as covid-19[1]. The COVID-19 virus is a beta-coronavirus similar to the virus found in bats. This virus is a new type of virus. Based on WHO data (2022), there were 572,239,451 confirmed cases, with 6,390,401 people dying. There were 6,207,098 positive cases in Indonesia, with 156,993 people dying from covid-19[2]. COVID-19 effect to the respiratory system and causes several symptoms, including fever, loss of taste or smell and respiratory disorder. There are several other symptoms, such as diarrhea, and sore throat, to severe symptoms, such as shortness of breath[3].

Severe cases of covid-19 could result in death. This condition is suspected to be due to increased cytokine protein levels (cytokine storm) [4]. Cytokine storm is a condition where cytokine protein increases due to the increased expression of proinflammatory genes. [5]. Cytokine storms produce acute inflammation of various organs, causing organ damage. [6]. Cytokine storms occur due to an increase in the innate immune system, which aims to eliminate infectious agents[7]. The innate immune system is the first of body defence, consisting of physical protection such as skin, phagocytic cells such as monocyte, neutrophils, macrophages cell, and inflammatory mediators protein. [8]. Research conducted by Wan et al (2020) and Huang et al (2020) showed an increase in IL-6, IL-10, IL-2, IL-7, TNFα, MIP1A, and MCP1, which are inflammatory mediators, in ICU patients or with severe symptoms. [9], [10]. Patients who had severe clinical symptoms had a high ratio of lymphocyte neutrophils (NLR) values[11]. This increase in inflammatory mediators is due to the upregulation of the signaling pathway of the NFκB protein. The increase in protein will increase the migration of neutrophils and macrophages into the lungs, further increasing the number of proinflammatory chemokines at the cellular and circulation level[12]. Neutrophils, components of the innate immune system, are closely related to the condition of fibrosis in the respiratory system that causes acute respiratory syndrome. In addition, the accumulation of neutrophils and leukocytes in the spacing and urinary tracts will trigger blood clots in the lungs and kidneys, thereby increasing the toxicity of SARS CoV-2 diseas [13]. NSAID and glucocorticoid efectively attenuate the organ damage by cytokine storm but the treatment by NSAID and Glucocorticoid have side effect for in gastrointestinal and urinary system [14].

The hadith of Rasulullah SAW reads, "Has told us Sadaqah bin Al-Fadl has informed us Ibn 'Uyainah he said: I heard Az Zuhri from 'Ubaidullah from Umm Qais bint Mihshan said, "I heard the Prophet say, "Use Indian wooden branch because in it there are seven kinds of healers and it can eliminate diseases (poisons) among them is inflammation of the lungs." Ibn Sam'an, in his hadith, "Because there is a cure for seven types of diseases, including inflammation of the lung (chest)." Then I went to the Prophet while carrying my baby who had not eaten food; then my baby urinated on him, so he asked for water and sprinkled it." (Narrated by Al Bukhari). Based on this hadith, it is known that there is potential in this plant for healing respiratory system diseases. The plant is Qutshul al Hindi as *Sausurea lappa or Saussurea costus* in Latin. Qutshul al Hindi is known to have the activity to treat problems including stomach acid, liver disorders, inflammation, cancer, skin and respiratory tract disorders. Some studies showed the activity of the plant in the respiratory tract. Ethanolic extract of *Saussurea lappa,* that kind containing cynaropicrin, can inhibit immunomodulators (Table 1)[15]. The terpenoid content in *Saussurea lappa,* such as costunolide, dehydrocostuslactonre can prevent the signalling of NF-κB and levels of IL-13 and TNF-α and inhibit neutrophils from producing proinflammatory cytokines. [16], [17]. In this study, we explain the benefits and potential of chemical compounds found in the Saussurea plant as an alternative treatment for respiratory infections, specifically SARS-CoV-2.

## 2 Method

This review was developed by article written in the English Language. The author used several databases such as Google Scholar, PubMed, and Science Direct from 1998-2022. The keywords are

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Ulquts al Hindi, Sausareus, inflammatory, and innate immunity on title or abstract of the article. Inclusion criteria are Research Article, systematic reviews, and meta-analyses. Exclusion criteria are no full access, irrelevant botanical species. This review focused on phytochemicals tested in preclinical studies.

## 3 Result and Discussion

### 3.1 Taxonomy

*Saussurea costus* is a plant of the class Magnoliopsida belonging to the family Asteraceae[18]. S. costus can only be found in the subalpine part of the Indian Himalayas, particularly in the areas of Jammu, Kashmir, Himachal Pradesh and Uttaranchal as well as the northern himalayan part of Pakistan and China at altitude of 3200–5000 meter [19].

*Saussurea costus* is also known as Saussurea lappa, Aucklandia costus, and Aucklandia lappa [20]. This plant, for centuries believed to have medicinal properties and is documented in the book of Ayurweda under the name kushta, quts al hindi in the hadith of Thibun Nabawi, and in materia medika of the Tang Dynasty. Traditionally, people in India, China and Arabia have used S. costus as a remedy for a wide variety of diseases such as asthma, gastritis, salesma, pharyngitis, inflammation, diarrhea and hepatoprotectors, tuberculosis, rheumatism and leprosy [21], [22].

The high economic and pharmaceutical value of the S. costus caused this plant to be overexploited for medicinal and research purposes, which ultimately led it to be recorded in Appendix I of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) as a plant that is in the brink of extinction[21].

### 3.2 Compound content

The root *of Saussurea costus* s reported to contain phytochemical compounds such as flavonoids, steroids, lignans, alkaloids, glycosides, antaquinones, monoterpenes, sesquiterpenoids, and triterpenes. Essential oil from *S. costus* root has higher levels of sesquiterpenoids with the main compounds are dehydrocostus lacton, and Costunolid[23], [24], [25]. The sesquiterpenes and flavonoids of the *S. costus* roots are known as the main active compounds responsible for it's various pharmacological activities[21], [26], [27].

The groups of sesquiterpenes commonly contained in *S. costus,* based on its carbocyclic skeleton, were Guaiane, Eudesmane, and Germacrane[23], [28]. The sesquiterpenes sourced from *S. Costus* are Dehydrocostus lactone, α-Cyclocostunolide, β-Cyclocostunolide, Alantolactone, Isoalantolactone, β Costic acid; 11β, 13- Dihydro-3-epizaluzanin C, 11, 13-Epoxy-3-ketodehyrocostus lactone[28]; Isozaluzanin, Zaluzanin, Mokko lactone, 11,13 Dihydroglucoaluzanin C, Isodehydrocostus lactone[29]; Cynaropicrin[30]; Lappalone, 1β, 6α- Dihydroxycostic acid ethyl ester[31]; Saussureamine A, B, C, D[32]; 12- Methoxy-dihydrodehyrocostus lactone[33]; 11,13-Epoxydehydrocostus lactone, 11,13-Epoxyisozaluzanin C[34]; Saussurealdehyde, Isodehydrocostuslactone-15-aldehyde[35]; Saussureal, 13-Sulfodihydrosantamarine, 13- Sulfodihydroreyosin[36]; 11β, 13- Dihydroreyosin, Reynosin, Magnolialide, 4βHydroxyendesin- 11(13)-en-12-al, 4α--4βMethyldihydrocostol, α-Costol, Isocostic acid, Santamarine[37]; Arbusculin A, colaritin[38]; and Dihydrocostunolide, Costunolide[39].

Some flavonoids that were successfully isolated from the roots of S. lappa include Luteolin-7-O-D-glucoside, Apigenin-7-O-β-D-glucoside and Rutin[40]; Kaempferol 3-Oβ-Dglucopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 6)-β-Dgalactopyranoside 7-O-(6'''-O-acetyl-β-Dgluco-pyranosyl-(1 → 3)-[α-Lrhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside, 3′[(3R)-3-Acetoxy-5,5-dimethylcyclopent-1-en-1-yl]-4′-Omethylscutellarein 7-O-(β-O-6'''O-acetylglucopyranosyl-(1 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-Dglucopyranoside and Kaempferol 3-O-β-D-glucopyranosyl-(1 → 2)-β-D-(6 α′-O-caffeoyl) galactopyranoside 7-O-(β-D-6'''-O-acetyl-β-D glucopyranosyl-(1 → 3)-[β-L-rhamnopyranosyl-(1 →

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2)]-β-D glucopyranoside, and Kaempferol 3-O-α-L-(2α′, 3α'-(E)-di-p-coumaroyl) rhamnoside 7-O-(6'''-O-acetyl-β-D glucopyranosyl-(1 → 3)-[α-Lrhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside[41].

### 3.3 Pathophysiology of COVID-19

#### 3.3.1 Characteristics and Transmission of SARS CoV-2

COVID-19 is a disease that affects the respiratory and is caused by the SARS-CoV-2 virus. Animals are suspected of being the main hosts of this virus. It has similarities with the SARS-CoV and MERS-CoV viruses and is the latest type of betacoronavirus[42]. It is an RNA virus consisting of about 30 kb of nucleic acid[43]. Six functional proteins play a role in the transmission and replication of the virus. These proteins are replicas (ORF1a/ORF1b), envelope (E), Nucleocapsid (N), and spike (S)[44].

COVID-19 spread through direct as well as indirect transmission. Direct transmission occurs when an infected person emits droplets, by sneezing, to a person who has not been directly infected, while indirect transmission occurs through the air containing the automated virus released by the infected person through sneezing or coughing or when droplets hit the surface of a solid object that is used together and then someone touches the mucous layer of the body [45], [46]. Therefore, masks have been shown to reduce the risk of SARS-CoV-2 infection[47].

#### 3.3.2 Innate immunity and SARS CoV-2

Viruses in the respiratory tract enter epithelial cells through the ACE-2 protein. The virus internalises into the cell through the spike proteins S1 and S2. The spike proteins S1 and S2 will be active after undergoing two stages of protease processing. Viruses that have entered the cell will then replicate and propagate along the cells in the all part of respiratory tract and activate the immune system[3].

The immune system plays a vital role in the body's defences against dangerous agents, including COVID-19 infection. The immune system is the first line of defence, known as the innate immune system[48]. It will minimise viral infections through the work of innate immune system cells, such as macrophages, monocytes, dendritic cells, and NK cells. In addition to cells, there is INF as a mediator of resistance to viruses. Proinflammatory cytokines such as IL-12, TNF-alpha, IL-6, and IL-18 are also involved in viral resistance. The production of cytokines is due to introducing infection sensors, in this case, TLR or cytosolic receptors, by infectious agents[8], [49]. In COVID-19 infection, the activation of the innate immune system prevents cell propagation by producing cytokines that will stimulate the death of infected cells[50]. In the condition of a person who has COVID-19 with severe illnesses, there is an activation of the innate immune system, as evidenced by an increase in neutrophil levels, followed by an increase in inflammatory mediators [9], [11], [51].

Virus components that are pathogen-associated molecular patterns (PAMPs) will be recognised by Pattern Recognition Receptors (PRR) such as Toll-Like Receptors (TLR), C-Type Lectine receptors (CLRs), or RIG-1 Receptors (RLRs). The introduction of PAMPs in PRR will trigger the activation of the innate immune system to produce interferons, cytokines, and chemokines[43]. The SARS-CoV-2 virus will stimulate increased Interferon expression and induce proinflammatory cytokines such as IL-6, TNF-α, and IL-1 through the introduction to MDA-5 and RIG-1 as PRR[52].

Proinflammatory cytokines cause changes in the alveolus to form pulmonary oedema [53]. Pulmonary oedema is an imbalance between the formation and discharge of fluid in the lung tissue that causes a buildup of fluid in the pulmonary interstitium. Pulmonary oedema is due to the decreased expression of the Na-K-ATPase protein, aquaporin-5, due to an increase in TNFα levels. This condition causes an increase in fluid in the pulmonary tissue, thus increasing pulmonary fibrosis. In addition, in covid-19 infection, there is an increase in bradykinin levels, which is responsible for the leakage of blood vessels and causes the formation of edema in the pulmonary. The decrease in peptidoglycan levels is due to an increase in metalloproteinase levels, leading to a decrease in the permeability of blood vessels. As a

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result, this condition causes the formation of thickening of the interstitium, as well as the impermeability of blood vessels and leakage in blood vessels which causes angioedema [53], [54].

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Covid-19 spread through direct as well as indirect transmission. Direct transmission occurs when an infected person emits droplets, by sneezing, to a person who has not been directly infected, while indirect transmission through the air containing the automated virus released by the infected person through sneezing or coughing or droplets hitting the surface of a solid object that is used together and then someone touches the mucous layer of the body [45], [46]. Therefore, masks have been shown to reduce the risk of SARS-CoV-2 infection[47].

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The immune system plays a vital role in the body's defenses against dangerous agents, including covid-19 infection. The immune system is the first line of defense worked by non spesific imunity known as the innate immune system[48]. It will minimize viral infections through the work of innate immune system cells, such as macrophages, monocytes, dendritic cells, and NK cells. In addition to cells, there is INF as a mediator of resistance to viruses. Proinflammatory cytokines such as IL-12, TNF alpha, IL-6, and IL-18 are also involved in viral resistance. The production of cytokines is due to introducing infection sensors, in this case, TLR or cytosolic receptors by infectious agents[8], [49]. In covid-19 infection, the activation of the innate immune system prevents cell propagation by producing cytokines that will stimulate the death of infected cells[50]. In the condition of a person who has covid-19 with severe illnesses, there is an activation of the innate immune system as evidenced by an increase in neutrophil levels followed by an increase in inflammatory mediators[9], [11], [51].

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### 3.5 Possible Mechanism *of Saussurea costus* in the Treatment of COVID-19

Trinh et al. l (2020) investigated the immunomodulatory activity of herbal formulation KM1608, which is composed of *Saussurea lappa*, *Terminalia chebula*, and *Zingiber officinale*. *The herbal formulation* KM1608 *has been reported* to contain 0.94-1.5% dehydrocostus lactone. It had the potential as an immunostimulant by stimulating the expression of immune cytokines (interferon (IFN)-α, -β, IL-1β, -6, IL-10, inducible nitric oxide synthase (iNOS)), and cyclooxygenase-2 (COX-2) in RAW 264.7 murine macrophages at a concentration 25–100 μg /mL [55].

Prawiro et al. (2021) researched the effect of formulation honey, Saussurea lappa, and Nigella sativa on mice's cellular and humoral immune responses. They reported that mice given this formula had increased Th2, Th17A, and sIgA levels. Meanwhile, in mice immunised orally with a regimen of Sars-cov-2 epitope (administrated protein epitope, envelope protein epitope B, and membrane protein epitope C), honey, Saussurea lappa, and Nigella sativa showed increased β-defensins in the intestinal mucosa.[56] Saussurea lappa ethanol extract, prepared according to homoeopathic principles based on Homoeopathic Arzneibuch's instructions at a dose of 10 μl, was effective in increasing leukocyte phagocytic activity in goat blood in vitro. S. lappa ethanol extract is also able to inhibit the proliferation of lymphocytes and TNF-α, which might contribute to suppressing the formation of excessive inflammatory responses in the body[57]

Alantolactone is one of the sesquiterpene constituents in the Saussurea lappa root. This constituent had evaluated its ability on the phagocytosis and cytokine release by THP1-derived macrophages. Alantolactone can enhance phagocytosis by increasing the uptake of Staphylococcus aureus, acidifying phagosomes, and stimulating phagosome-lysosome fusion. This compound can also reduce the production of ROS and superoxide. Alantolactone inhibits the production of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8, decreases the concentration of p65, the subunit responsible for activating NF-κB and cytokine production, and simultaneously stimulates the release of anti-inflammatory mediators such as IL-10 and TGF-β[58]

Dichloromethane fraction of *S. costus* in vitro assay exhibited 78% inhibitions of *Cytokine-induced neutrophil chemoattractant* (CINC) IL8 in rat macrophages, and compared with dexamethasone showed 51% inhibition on the CINC induction. It can conclude that S. costus had better activity than dexamethasone[59].

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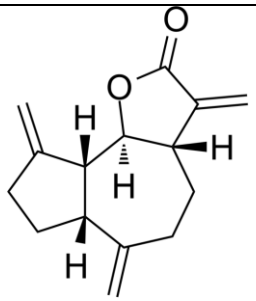
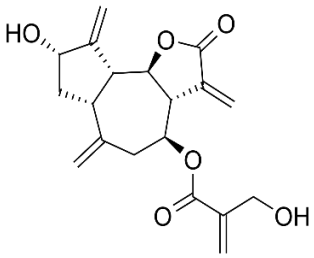
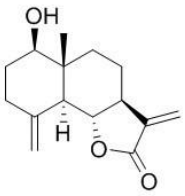
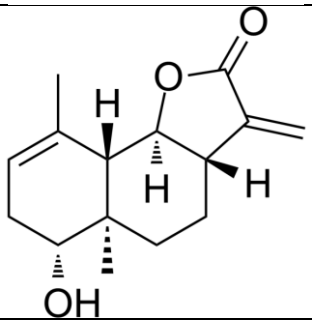
Table 1 The reported chemical constituents of Saussurea sp. with anti-inflammatory activity

| Compound Group | Compounds | Chemical Structure | Mechanism of Action | Ref |
|---|---|---|---|---|
| Sesquiterpene lactone | Dehydrocostus lactone |  | • Inhibited the NO production by suppressing iNOS gene expression<br>• Inhibited the NF-kB activation | [21],[60], [61] |
| | Cynaropicrin |  | • Inhibited the TNFα production and release<br>• Attenuated the accumulation of NO and interferon-γ release<br>• Inhibited the pro-inflammatory mediator production<br>• Inhibited the lymphocyte production | [21], [62], [63] |
| | Reynosin |  | Inhibited the TNFα production | |
| | Santamarine |  | | |

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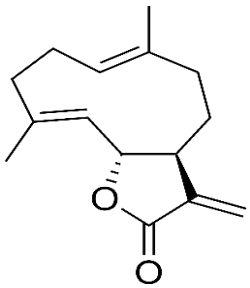
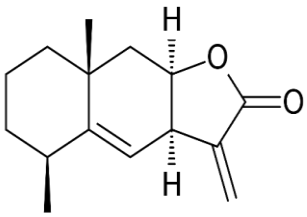
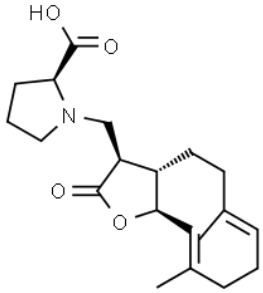
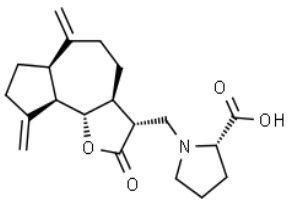
| | | | | |
|---|---|---|---|---|
| | Costunolide |  | • Inhibited the mRNA and protein expression of IL-1ß<br>• Inactivated of AP-1 transcription factor<br>• Inhibited the MAPK phosphorylation , SAPK/JNK and p38 MAP kinase | [21], [64], [65] |
| | Alantolactone |  | • Attenuated NF-kB pathway activation<br>• Suppressed the p-P65 protein expression<br>• Increased mRNA and protein expression of Nrf2-regulated genes | [66] |
| | Saussureamine A |  | Inhibited the induction of iNOS and activation of NF-kB | [21], [64] |
| | Saussureamine B |  | | |

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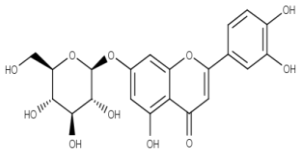
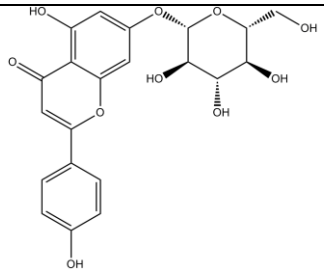
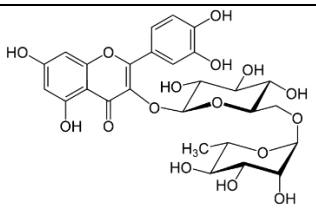
| | | | | |
|---|---|---|---|---|
| Flavonoids | Luteolin-7-O -D-glucoside |  | • Inhibited the IL-6 and TNFα secretion<br>• Inhibited the STAT3 activity<br>• Inhibited the metalloproteinase (MMP2, MMP7, MMP9 and EMT) expression<br>• Regulated the MAPK signaling pathway through the blockage of the activation of JNK, p38, AP-1, and NF-kB | [27], [67], [68], [69], [70], [71] |
| | Apigenin-7-O-β-D-glucoside |  | • Inhibited the NO production and secretion<br>• Inhibited the increase of IL-6 and TNFα<br>• Inhibited the phosphorylation of NF-kB/NLRP3 signaling pathway<br>• Inhibited the COX2 expression | [72], [73], [74], [75], [76], [77] |
| | Routine |  | • Inhibited the HMGB1<br>• Inhibited the HMGB1 receptor, TLR4 and RAGE | [78] Yoo et al., 2014 |

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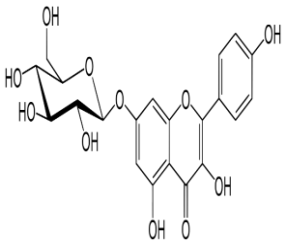
| | | | | |
|---|---|---|---|---|
| | Kaempferol glucoside |  | • Inhibited the NF-kB binding activity with DNA and myeloid differentiation factor 88<br>• Suppressed the IL-6, IL-1ß, IL-18 and TNFα release<br>• Increased mRNA and protein expression of Nrf2-regulated genes<br>• Inhibited the TLR4 | [79], [80], [81], [82], [83] |

## 4 Conclusion

Ulquts Al Hindi (Sasereus sp) is known to have many chemical constituents, including compounds from the Sesquiterpene lactone and flavonoid groups. Based on the results of literature studies, it is known that the chemical compounds present in these plants can inhibit the production or activity of inflammatory mediators produced by the innate immune system. This inhibition causes a decrease in the risk of organ damage due to activation of the cytokine storm by activation of the innate immune system. Therefore this plant is a promising herb as a therapeutic candidate for covid-19 by regulating the immune system to produce and activate pro-inflammatory cytokines. The mechanism is the inhibition of inflammatory cytokines discharge and inhibition of the recognition of COVID-19 to the immune system so that the immune system is not activated. The data shown is still based on preclinical evaluation, and to confirm it requires further clinical study. In addition, it is necessary to ascertain further the pharmacokinetic and pharmacodynamic aspects to ensure the efficacy of these compounds.

## 5 Declarations

### 5.1 Acknowledgements

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### 5.2 Author contributions

The names of the authors listed in this journal contributed to this researc. Data collection were performed by Helmi and hajrah, The first draft of the manuscript was written by Noviyanty Indjar Gama. All authors read and approved the final manuscript."

### 5.3 Ethics

This research does not require a code of ethics so it does not have a code of ethics.

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### 5.4 Conflict of Interest

This research was conducted independently of any financial or personal biases. The authors maintain that no specific affiliations or private relationships have exerted influence over the results or the editorial process of the manuscript.

### 5.5 Funding Statement

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