IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

INFLAMMASOMES: PROMISING TARGETS IN THERAPEUTIC STRATEGIES FOR COVID 19

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ABSTRACT : Clinical symptoms caused by SARS-CoV-2, the virus that was responsible for the spread of COVID-19, vary from no symptoms to severe pneumonia and death. Several studies point to the critical role of inflammatory cytokines in initiating and exacerbating the immune response, leading to the overproduction of cytokines as well as chemokines and ultimately resulting in a cytokine storm. A significant contributing factor to the uncontrolled pro-inflammatory response to the viral infection is the activation of the NLRP3 inflammasome, a part of the innate immune system. For the creation of therapeutic approaches to treat COVID-19, this inflammasome can be employed as a target. The NLRP3 inflammasome's structure is described in this review, along with the many methods that have been used to target it.

Keywords: ***NLRP3 inflammasomes, Anakinra, Lipoxin, Cytokines, Ginseng.***

I. INTRODUCTION:

SARS-CoV-2 is a coronavirus that causes respiratory disease and the reason behind this is covid-19, which is extremely infectious. This virus had been reported in December 2019 and Wuhan, China, is where it first appeared. Since then, millions of cases have been reported throughout the world, with symptoms ranging from minor flu-like symptoms to serious respiratory diseases[1,2,3,4,5]. With an incubation period of two to fourteen days, this illness is contagious through inhalation or contact with contaminated droplets[6]. The Betacoronavirus family, which also includes lethal members like MERS-CoV and SARS-CoV, includes SARS-CoV-2. This virus has single-stranded RNA (+ssRNA)[7]. The HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 viruses are responsible for moderate respiratory symptoms[8,9]. Real-time reverse transcription polymerase chain reaction (RT-PCR) and next-generation sequencing were used to research and characterize this virus[10]. Covid 19 first appeared in China, where it spread quickly over the nation and thereafter to neighboring nations. Due to the seriousness of the outbreak and its potential for worldwide spread, the WHO first declared it a global health emergency in March 2020. This outbreak resulted in hundreds of deaths with an 11 % mortality rate[11]. When the outbreak happened in 2020, there were no approved vaccines or antiviral medications for treating covid infection[12]. But currently, there are multiple approaches and drug delivery systems that have shown a reasonable degree of success[13,14,15].

It has been scientifically proven that those who are covid positive and have co-morbid conditions are more likely to experience severe symptoms and even die[16,17,18,19,20]. A "cytokine storm" or an excess of pro-inflammatory cytokines seems to be the cause of severe SARS-COV-2 infections. Local and systemic inflammation are both caused by the protein complexes produced by the innate immune system defined as inflammasomes.

The induction of inflammatory cell death, or pyroptosis, via gastrin D, a member of a family of pore-forming proteins involved in the anti-inflammatory response, and the activation of caspase, which regulates the release of the crucial pro-inflammatory cytokines IL-1 and IL-28, are two main effects of inflammasome activation[21]. In response to inflammasomes, the body's immune system produces an excessive amount of cytokines and chemokines. This response which is also known as ‘cytokine storm’ results in the secretion of cytokines IFN-γ, TNF-α, IL-6, IL-1, IL-18, CXCL8, and CXCL10. However, this exaggerated response can have harmful effects on the body[22]. Other viral illnesses like influenza, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS) are also linked to excessive cytokine production[23]. Effective cytokine storm management involves providing supportive care to ensure that vital organs function correctly, identifying and removing the factors that are causing the immune system to overreact, and using non-specific immunosuppressive medications to minimize the damage caused by an activated immune system[24].

In addition, drugs such as dexamethasone and tocilizumab may be prescribed for the treatment and management of cytokine storms[25]. In a different study, the authors noted the positive benefits of corticosteroid therapy on the clinical outcomes of patients with severe Covid-19-associated pneumonia who additionally showed signs of immunological hyperactivity[26]. There has been extensive discussion of the effect of dexamethasone medication on patients with Covid-19[27,28]. For the treatment of seriously ill Covid-positive patients, data on the administration of intravenous immunoglobulin therapy (IVIG) have been published in several journals[29.30.31.32.33].

With a specific focus on NLRP3 inflammasomes, this review highlights the role of inflammasomes in increasing Covid-19 symptoms and therapeutic approaches to reduce the dangers involved.

II. INFLAMMASOMES:

Multiprotein complexes called inflammasomes are formed by the host in response to pathogen infections and tissue damage. Amongst the various inflammasomes, the NLRP3 or nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 has been widely characterized and consists of three parts – the NLRP protein, the adapter-apoptosis associated protein subunit containing a caspase recruitment domain (ASC) and the inactive enzyme procaspase-1.

The NLRP3 protein contains the leucine-rich repeat (LRR) domain, the NACHT (central nucleotide-binding) domain, and the pyrin domain (PYD) (Figure 1). Further, the protein ASC is made up of the PYD and the caspase recruitment domain (CARD).

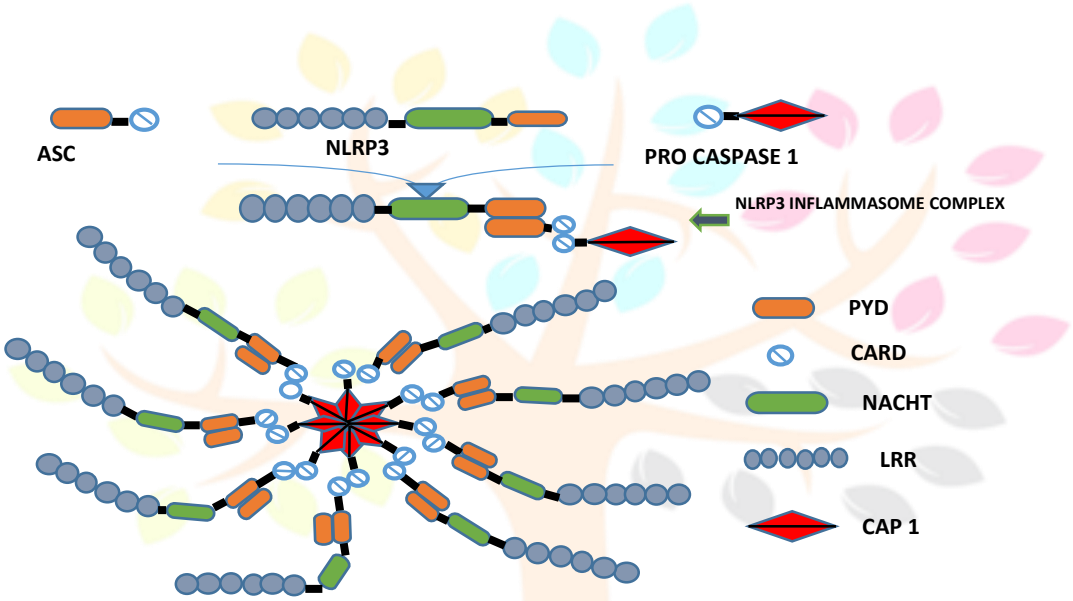

Figure 2.1: Diagrammatic representation of NLRP3 Inflammasome Structure

The two stages of NLRP3 inflammasome activation are priming and activation. The inflammasome components NLRP3, procaspase-1, and pro-IL-1 are upregulated during the priming process. Toll-like receptors (TLRs) and the protein NOD2 (which contains a nucleotide-binding oligomerization domain) promote this transcriptional upregulation at infection sites[34].

Priming may also be induced by inflammatory cytokines including tumor necrosis factor (TNF) and IL-1, which promote NF-kB and gene transcription[35]. Primed NLRP3 responds to stimuli, thereby initiating the activation and development of the inflammasome complex.

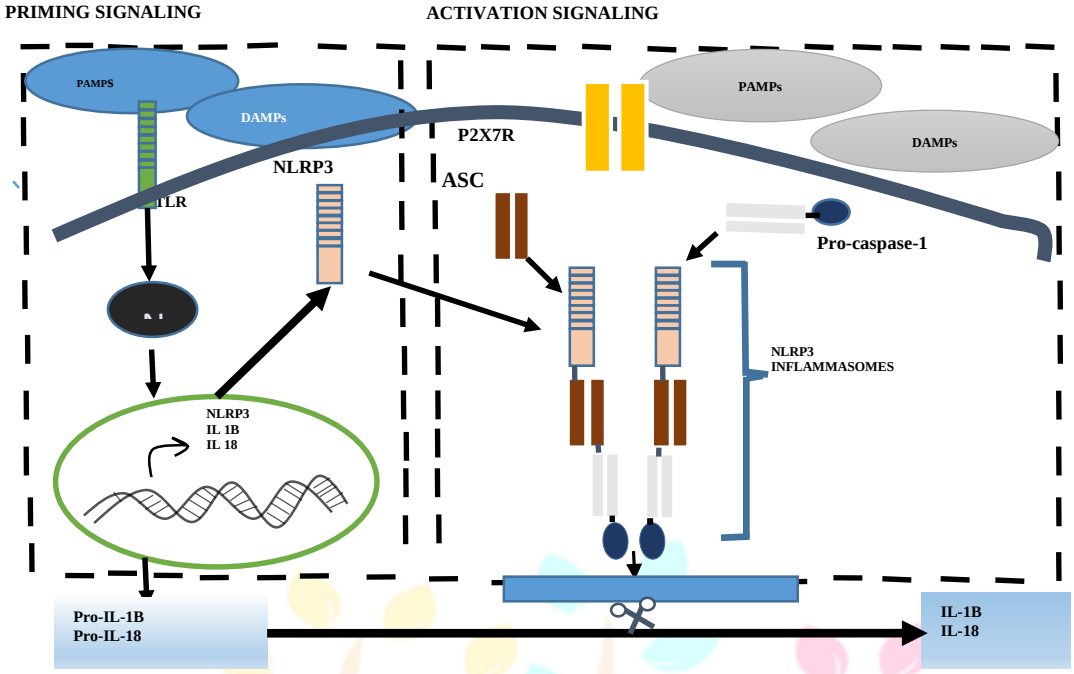

Figure 2.2: Diagrammatic representation of the mechanism of NLRP3 inflammasome pathway

Activation of NLRP3 inflammasomes is also brought about by Pathogen Associated Molecular Patterns (PAMPs), Damage Associated Molecular Patterns (DAMPs), pore-forming channels or toxins, ATP, viral RNA, and activated crystal particles. These stimuli promote the rearrangement of NLRP3, ASC, and caspase 1 into a multiprotein complex. The interactions between PYD and NLRP3 lead to the binding of NLRP3 to ASC. Next, ASC enlists pro caspase 1 via CARD (Figure 2).

This NLRP3 activation triggers the release of cytokines IL-1 and IL-18. These responses highlight the importance of NLRP3 inflammasome in protecting the host against infections. However, prolonged overstimulation of NLRP3 inflammasome increases the chances of acute respiratory distress syndrome (ARDS), mortality, and cytokine storm[36]. In a study conducted by Rodrigues et al., inflammasomes were implicated in the pathogenesis of covid 19, thus signifying the possibility that these inflammasomes contribute to the severity of symptoms and therefore are likely targets for the treatment of covid 19[37,38].

III. THERAPEUTIC STRATEGIES FOR COMBATING COVID 19 THROUGH TARGETING OF NLRP3 INFLAMMASOMES

Targeting IL-1 and IL-18 is a viable strategy to prevent the excessive inflammatory response because NLRP3 inflammasome stimulation is mediated by the production of these cytokines. Numerous chronic inflammatory disorders have been found to have activated inflammasomes and excessive IL-1 activity, which are successfully controlled by medications. Many of these medications have been switched over to treating covid-19. The clinical symptoms of COVID-19 have been observed to be less severe when IL-1 receptor antagonists such as anakinra and canakinumab are used[39,40,41,42]. Additionally investigated as potential therapeutic approaches are the anti-IL-6 receptor monoclonal antibodies sarilumab and tocilizumab[43,44,45,46].

In the therapeutic setting, Anakinra, a modified form of human IL-1RA, was studied, although the outcomes were conflicting[47,48,49]. Other investigations have shown that NLRP3 suppression is a preferable method for controlling the hyperimmune response. IL-6 release by SARS-CoV-2-infected human monocytes was reduced by the NLRP3 inhibitor glyburide[50]. A considerable drop in the rate of hospitalization or mortality has been noted due to indirect NLRP3 inhibition by colchicine[51,52]. Recent research on SARS-CoV-2-infected rats shows that NLRP3 activation and pulmonary inflammation are inhibited[53]. A cytokine release, neutrophil and macrophage activation, and B cell antibody formation are all inhibited by the autocoid anti-inflammatory drug lipoxin, which decreases inflammation[54]. Also, by preventing viral entry, preventing viral replication, downregulating the production of ACE2, and suppressing pro-inflammatory cytokines, lipoxins further control SARS Cov infection[55]. Furthermore, it has been reported that lipoxin inhibits the inflammatory changes brought on by the activation of the NLRP3 inflammasome, mTOR, and MAPK[56]. The influence of lipoxin on inflammasomes was studied by Zhou et al[57].

The study concluded that conclusion that lipoxin prevented the activation and arrangement of the NLRP3 inflammasome. Lipoxin also reduced oxidative stress and the precursors to the activation of the NLRP3 inflammasome, as well as total reactive oxygen species (ROS). Furthermore, lipoxins aided in the overactivation of NADPH oxidase and the reduction of mitochondrial malfunction, which decreased the hyperimmune response.To effectively treat COVID-19, lipoxin, lipoxin analogs, and lipoxin receptor agonists may therefore play a significant role. Through modification of the mitogen-activated protein kinase (MAPK) signaling pathway, one such agonist, BML-111, triggered autophagy in lung alveolar macrophages and protected the host from

acute lung injury (ALI). Furthermore, BML-111 induced autophagy, prevented these cells from dying from apoptosis, stifled inflammation, and accelerated the recovery of damaged lungs[58]. Preclinical research must be supported by clinical data, although. Included in the list of ginseng's bioactive substances are phytosterols, ginsenosides, polysaccharides, essential oils, glycosides, and saponins[59,60,61]. Ginsenosides and saponins are two of the more than 150 natural phytochemicals that have been investigated and found to offer health benefits in the treatment of cardiovascular, metabolic, inflammatory, autoimmune, and cancerous conditions. Ginseng's phytoconstituents, such as ginsenosides and saponins, have been categorized as nutraceuticals with the potential to reduce the triggering and priming stages of inflammatory responses. As a result, ginseng use may lower the risk of COVID-19[62].

IV. CONCLUSION

In patients with severe COVID, there is a risk of uncontrolled cytokine release, pneumonia, and acute lung injury. These conditions can lead to acute respiratory distress syndrome, disseminated intravascular coagulation, multisystem failure, and eventually death. Amongst the several approaches studied for minimizing these risks, targeting inflammatory cytokines as well as NLRP3 inflammasome holds great promise. The inflammasome is a complex multiprotein moiety that activates caspase-1 leading to the activation of IL-1 and IL-18 in infections such as CoV infection. Inflammasome, however, is a double-edged sword; inflammasome activation is necessary for fighting infection, yet prolonged over-activation of the inflammasomes can lead to hyper-activated inflammatory response leading to sepsis, intravascular coagulation, acute kidney injury, and ultimately death. The mechanisms underlying the adverse events associated with unregulated inflammasome activity are elevated levels of the inflammatory cytokines IL-1β, IL-6, and IL-18. Several strategies have been reported for targeting cytokines and inflammasomes. These have been discussed in detail in this review and hold promise to cure the symptoms associated with severe covid 19 infections. As more and more data about the efficacy of the drugs targeting the cytokines and inflammasomes emerge, effective treatment regimens for Covid 19 can be developed.

V. ACKNOWLEDGEMENTS

The authors thank the Management of Gahlot Institute of Pharmacy, Koparkhairane, India for providing the facilities necessary for compiling the review.

REFERENCES

[1] Freeman, T.L. and Swartz, T.H. (2020) 'Targeting the NLRP3 inflammasome in severe COVID-19', Frontiers in Immunology, 11. doi:10.3389/fimmu.2020.01518.

[2] Huang, Q. et al. (2020) 'Targeting inflammation and cytokine storm in COVID-19', Pharmacological Research, 159, p. 105051. doi:10.1016/j.phrs.2020.105051.

[3] Kasti, A.N. et al. (2021) 'Probiotics regulating inflammation via NLRP3 inflammasome modulation: A potential therapeutic approach for covid-19', Microorganisms, 9(11), p. 2376. doi:10.3390/microorganisms9112376.

[4] Paniri, A. and Akhavan-Niaki, H. (2020) 'Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in Cytokine storm modulation', Life Sciences, 257, p. 118114. doi:10.1016/j.lfs.2020.118114.

[5] Bauernfeind, F.G. et al. (2009) 'Cutting edge: NF-KB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression', The Journal of Immunology, 183(2), pp. 787–791. doi:10.4049/jimmunol.0901363.

[6] Singhal, T. (2020). A review of coronavirus disease-2019 (COVID-19). The indian journal of pediatrics, 87(4), 281-286.

[7] Kramer, A., Schwebke, I. and Kampf, G. (2006) 'How long do nosocomial pathogens persist on inanimate surfaces? A systematic review', BMC Infectious Diseases, 6(1). doi:10.1186/1471-2334-6-130.

[8] Zumla, A. et al. (2016) 'Coronaviruses — drug discovery and therapeutic options', Nature Reviews Drug Discovery, 15(5), pp. 327–347. doi:10.1038/nrd.2015.37.

[9] Channappanavar, R., Zhao, J. and Perlman, S. (2014) 'T cell-mediated immune response to respiratory coronaviruses', Immunologic Research, 59(1–3), pp. 118–128. doi:10.1007/s12026-014-8534-z.

[10] Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., ... & Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine, 382(8), 727-733.

[11] Song, Z. et al. (2019) 'From sars to mers, thrusting coronaviruses into the spotlight', Viruses, 11(1), p. 59. doi:10.3390/v11010059.

[12] World Health Organization. (2003). WHO recommendations on SARS and blood safety. Website: http://www. who. int/csr/sars/guidelines/bloodsafety/en.

[13] Lu, H. (2020) 'Drug treatment options for the 2019-new coronavirus (2019-ncov)', BioScience Trends, 14(1), pp. 69–71. doi:10.5582/bst.2020.01020.

[14] Sheahan, T.P. et al. (2020) 'Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-COV', Nature Communications, 11(1). doi:10.1038/s41467-019-13940-6.

[15] Pillaiyar, T., Meenakshisundaram, S. and Manickam, M. (2020) 'Recent discovery and development of inhibitors targeting coronaviruses', Drug Discovery Today, 25(4), pp. 668–688. doi:10.1016/j.drudis.2020.01.015.

[16] Zhou, Y. et al. (2020) 'Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (<scp>covid</scp>   -19)', Diabetes/Metabolism Research and Reviews, 37(2). doi:10.1002/dmrr.3377.

[17] Dennison Himmelfarb, C.R. and Baptiste, D. (2020) 'Coronavirus disease (covid-19)', Journal of Cardiovascular Nursing, 35(4), pp. 318–321. doi:10.1097/jcn.0000000000000710.
[18] Pepera, G. et al. (2022) 'Epidemiology, risk factors and prognosis of cardiovascular disease in the coronavirus disease 2019 (covid-19) pandemic era: A systematic review', Reviews in Cardiovascular Medicine, 23(1), p. 1. doi:10.31083/j.rcm2301028.
[19] Goodman, K.E. et al. (2020) 'Impact of sex and metabolic comorbidities on coronavirus disease 2019 (covid-19) mortality risk across age groups: 66 646 inpatients across 613 U.S. hospitals', Clinical Infectious Diseases, 73(11). doi:10.1093/cid/ciaa1787.
[20] Pachtman Shetty, S.L. et al. (2021) 'Myocardial injury associated with coronavirus disease 2019 in pregnancy', American Journal of Obstetrics and Gynecology, 224(2), pp. 229–232. doi:10.1016/j.ajog.2020.10.014.
[21] Kaivola, J., Nyman, T.A. and Matikainen, S. (2021) 'Inflammasomes and SARS-COV-2 infection', Viruses, 13(12), p. 2513. doi:10.3390/v13122513.
[22] Clark, I.A. (2007) 'The advent of the cytokine storm', Immunology & Cell Biology, 85(4), pp. 271–273. doi:10.1038/sj.icb.7100062.
[23] Hu, B., Huang, S., & Yin, L. (2021). The cytokine storm and COVID-19. Journal of medical virology, 93(1), 250-256.
[24] Fajgenbaum, D. C., & June, C. H. (2020). Cytokine storm. New England Journal of Medicine, 383(23), 2255-2273.
[25] Sinha, P. and Linas, B.P. (2021) 'Combination therapy with tocilizumab and dexamethasone cost-effectively reduces coronavirus disease 2019 mortality', Clinical Infectious Diseases, 73(11), pp. 2116–2118. doi:10.1093/cid/ciab409.
[26] Kolilekas, L. et al. (2020) 'Can steroids reverse the severe covid-19 induced "Cytokine storm"?', Journal of Medical Virology, 92(11), pp. 2866–2869. doi:10.1002/jmv.26165.
[27] Águas, R., Mahdi, A., Shretta, R., Horby, P., Landray, M., & White, L. (2021). Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. Nature Communications, 12(1), 915.
[28] RECOVERY Collaborative Group. (2021). Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine, 384(8), 693-704.
[29] Ali, S. et al. (2021) 'Hyperimmune anti-covid-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial', EClinicalMedicine, 36, p. 100926. doi:10.1016/j.eclinm.2021.100926.
[30] Pourahmad, R., Moazzami, B. and Rezaei, N. (2020) 'Efficacy of plasmapheresis and immunoglobulin replacement therapy (IVIG) on patients with covid-19', SN Comprehensive Clinical Medicine, 2(9), pp. 1407–1411. doi:10.1007/s42399-020-00438-2.
[31] Moradimajd, P. et al. (2021) 'Administration of intravenous immunoglobulin in the treatment of COVID-19: A review of available evidence', Journal of Medical Virology, 93(5), pp. 2675–2682. doi:10.1002/jmv.26727.
[32] Nguyen, A.A. et al. (2020) 'Immunoglobulins in the treatment of covid-19 infection: Proceed with caution!', Clinical Immunology, 216, p. 108459. doi:10.1016/j.clim.2020.108459.
[33] Mohtadi, N., Ghaysouri, A., Shirazi, S., Shafiee, E., Bastani, E., Kokhazadeh, T., & Tavan, H. (2020). Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: A case series. Virology, 548, 1-5.
[34] Seok, J.K. et al. (2021) 'Therapeutic regulation of the NLRP3 inflammasome in chronic inflammatory diseases', Archives of Pharmacal Research, 44(1), pp. 16–35. doi:10.1007/s12272-021-01307-9.
[35] Xing, Y. et al. (2017) 'Cutting edge: TRAF6 mediates TLR/IL-1R signaling–induced nontranscriptional priming of the NLRP3 inflammasome', The Journal of Immunology, 199(5), pp. 1561–1566. doi:10.4049/jimmunol.1700175.
[36] Sun, C. et al. (2022) 'The role of inflammasomes in COVID-19: Potential therapeutic targets', Journal of Interferon & Cytokine Research, 42(8), pp. 406–420. doi:10.1089/jir.2022.0061.
[37] Rodrigues, T. S., de Sá, K. S., Ishimoto, A. Y., Becerra, A., Oliveira, S., Almeida, L., ... & Zamboni, D. S. (2021). Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. Journal of Experimental Medicine, 218(3).
[38] Kaivola, J., Nyman, T.A. and Matikainen, S. (2021a) 'Inflammasomes and SARS-COV-2 infection', Viruses, 13(12), p. 2513. doi:10.3390/v13122513.
[39] Zhao, N., Di, B. and Xu, L. (2021) 'The NLRP3 inflammasome and COVID-19: Activation, pathogenesis and therapeutic strategies', Cytokine & Growth Factor Reviews, 61, pp. 2–15. doi:10.1016/j.cytogfr.2021.06.002.
[40] Bonaventura, A. et al. (2022) 'Colchicine for covid-19: Targeting NLRP3 inflammasome to Blunt hyperinflammation', Inflammation Research, 71(3), pp. 293–307. doi:10.1007/s00011-022-01540-y.
[41] Sergi, C.M. and Chiu, B. (2020) 'Targeting NLRP3 inflammasome in an animal model for coronavirus disease 2019 (Covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)', Journal of Medical Virology, 93(2), pp. 669–670. doi:10.1002/jmv.26461.
[42] Paniri, A. and Akhavan-Niaki, H. (2020) 'Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in Cytokine storm modulation', Life Sciences, 257, p. 118114. doi:10.1016/j.lfs.2020.118114.
[43] Gupta, R. (2020) 'Anakinra: A silver lining in covid-19?', Critical Care, 24(1). doi:10.1186/s13054-020-03312-8.
[44] Khan, A.R. et al. (2020) 'Anakinra for severe forms of covid-19', The Lancet Rheumatology, 2(10). doi:10.1016/s2665-9913(20)30271-x.
[45] Navarro-Millán, I. et al. (2020) 'Use of anakinra to prevent mechanical ventilation in severe covid-19: A case series', Arthritis & Rheumatology, 72(12), pp. 1990–1997. doi:10.1002/art.41422.
[46] Radulescu, D. et al. (2021) 'Acute kidney injury in moderate and severe COVID-19 patients: Report of two University Hospitals', Experimental and Therapeutic Medicine, 23(1). doi:10.3892/etm.2021.10959.
[47] Cauchois, R. et al. (2020) 'Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19', Proceedings of the National Academy of Sciences, 117(32), pp. 18951–18953. doi:10.1073/pnas.2009017117.
[48] Tharaux, P.L. et al.(2021). Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. The Lancet Respiratory Medicine, 9(3), 295-304.
[49] Kyriazopoulou, E. et al. (2021). An open label trial of anakinra to prevent respiratory failure in COVID-19. Elife, 10, e66125.
[50] Ferreira, A.C. et al. (2021) 'SARS-COV-2 engages inflammasome and pyroptosis in human primary monocytes', Cell Death Discovery, 7(1). doi:10.1038/s41420-021-00428-w.

[51] Magupalli, V.G. et al. (2020) 'HDAC6 mediates an aggresome-like mechanism for NLRP3 and pyrin inflammasome activation', Science, 369(6510). doi:10.1126/science.aas8995.
[52] Tardif, J.C. et al. (2021). Efficacy of colchicine in non-hospitalized patients with COVID-19. Medrxiv, 2021-01.
[53] Li, J. et al. (2020). Metformin use in diabetes prior to hospitalization: effects on mortality in Covid-19. Endocrine Practice, 26(10), 1166-1172.
[54] Hughes, E.L. et al. (2017) 'Mast cells mediate early neutrophil recruitment and exhibit anti-inflammatory propertiesviathe Formyl peptide receptor 2/lipoxin a4receptor', British Journal of Pharmacology, 174(14), pp. 2393–2408. doi:10.1111/bph.13847.
[55] Das, U.N. (2021) 'Bioactive lipids in COVID-19-further evidence', Archives of Medical Research, 52(1), pp. 107–120. doi:10.1016/j.arcmed.2020.09.006.
[56] Batiha, G.E.-S. et al. (2022) 'Potential role of lipoxin in the management of COVID-19: A narrative review', Inflammopharmacology, 30(6), pp. 1993–2001. doi:10.1007/s10787-022-01070-3.
[57] Zhou, Y. et al. (2022) 'Lipoxin A4 attenuates MSU-crystal-induced NLRP3 inflammasome activation through suppressing NRF2 thereby increasing TXNRD2', Frontiers in Immunology, 13. doi:10.3389/fimmu.2022.1060441.
[58] Liu, H. et al. (2018) 'Lipoxin A4 receptor agonist BML-111 induces autophagy in alveolar macrophages and protects from acute lung injury by activating MAPK signaling', Respiratory Research, 19(1). doi:10.1186/s12931-018-0937-2.
[59] Attele, A.S. (1999). Ginseng pharmacology: multiple constituents and multiple actions. Biochemical pharmacology, 58(11), 1685-1693.
[60] Sun, Y.J. et al. (2014). Chemical constituents from fruit of Panax ginseng. Zhong yao cai= Zhongyaocai= Journal of Chinese Medicinal Materials, 37(8), 1387-1390.
[61] Yi, Y.-S. (2021) 'New mechanisms of ginseng saponin-mediated anti-inflammatory action via targeting canonical inflammasome signaling pathways', Journal of Ethnopharmacology, 278, p. 114292. doi:10.1016/j.jep.2021.114292.
[62] Yi, Y.-S. (2022) 'Potential benefits of ginseng against COVID-19 by targeting inflammasomes', Journal of Ginseng Research, 46(6), pp. 722–730. doi:10.1016/j.jgr.2022.03.008.