

## REFERENCES

- Abou-Ismaïl, M. Y., Diamond, A., Kapoor, S., Arafah, Y., & Nayak, L. (2020). The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thrombosis research*, *194*, 101–115. <https://doi.org/10.1016/j.thromres.2020.06.029>
- Abdallah, N., Zaki, A. M., & Abdel-Salam, S. A. (2020). Stability of MERS-CoV RNA on spin columns of RNA extraction kit at room temperature. *Diagnostic microbiology and infectious disease*, *98*(4), 115182. <https://doi.org/10.1016/j.diagmicrobio.2020.115182>
- Ahmed, M. H., & Hassan, A. (2020). Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review. *SN comprehensive clinical medicine*, 1–10. Advance online publication. <https://doi.org/10.1007/s42399-020-00610-8>
- Al-Harbi, N. O., Imam, F., Al-Harbi, M. M., Ansari, M. A., Zoheir, K. M. A., Korashy, H. M., ... Ahmad, S. F. (2016). Dexamethasone Attenuates LPS-induced Acute Lung Injury through Inhibition of NF- $\kappa$ B, COX-2, and Pro-inflammatory Mediators. *Immunological Investigations*, *45*(4), 349–369. doi:10.3109/08820139.2016.1157814
- Alzohairy M. A. (2016). Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. *Evidence-based complementary and alternative medicine : eCAM*, *2016*, 7382506. <https://doi.org/10.1155/2016/7382506>
- Arnaldez, F. I., O'Day, S. J., Drake, C. G., Fox, B. A., Fu, B., Urba, W. J., Montesarchio, V., Weber, J. S., Wei, H., Wigginton, J. M., & Ascierto, P. A. (2020). The Society for Immunotherapy of Cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response. *Journal for immunotherapy of cancer*, *8*(1), e000930. <https://doi.org/10.1136/jitc-2020-000930>
- Avadhanula V, Rodriguez CA, DeVincenzo JP, Wang Y, Webby RJ, Ulett GC, et al.(2006). Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. *J Virol*;80(4):1629–36
- Bascones-Martinez, A., Mattila, R., Gomez-Font, R., & Meurman, J. H. (2014). Immunomodulatory drugs: oral and systemic adverse effects. *Medicina oral, patologia oral y cirugia bucal*, *19*(1), e24–e31. <https://doi.org/10.4317/medoral.19087>
- Batista, F., Lima, L., Abrante, I., de Araújo, J., Batista, F., & Abrante, I. et al. (2018). Antinociceptive activity of ethanolic extract of Azadirachta indica A. Juss (Neem, Meliaceae) fruit through opioid, glutamatergic and acid-sensitive ion pathways in adult zebrafish (Danio rerio). *Biomedicine & Pharmacotherapy*, *108*, 408–416. doi: 10.1016/j.biopha.2018.08.160
- Bell, L., Meydan, C., Kim, J., Foux, J., Butler, D., Mason, C. E., Shapira, S. D., Noursadeghi, M., & Pollara, G. (2021). Transcriptional response modules characterize IL-1 $\beta$  and IL-6 activity in COVID-19. *iScience*, *24*(1), 101896. <https://doi.org/10.1016/j.isci.2020.101896>
- Bernhard W. Lung surfactant: function and composition in the context of development and respiratory physiology. *Ann Anat.* (2016) 208:146– 50. doi: 10.1016/j.aanat.2016.08.003
- Bonilla, F. A., and Oettgen, H. C. (2010). Adaptive immunity. *J. Allerg. Clin. Immunol.* 125, S33–S40. doi: 10.1016/j.jaci.2009.09.017
- Branchett, W. J., & Lloyd, C. M. (2019). Regulatory cytokine function in the respiratory tract. *Mucosal immunology*, *12*(3), 589–600. <https://doi.org/10.1038/s41385-019-0158-0>
- Bittencourt-Mernak, M. I., Pinheiro, N. M., da Silva, R. C., Ponci, V., Banzato, R., Pinheiro, A., Olivo, C. R., Tibério, I., Lima Neto, L. G., Santana, F., Lago, J., & Prado, C. M. (2021). Effects of Eugenol and

- Dehydrodieugenol B from *Nectandra leucantha* against Lipopolysaccharide (LPS)-Induced Experimental Acute Lung Inflammation. *Journal of natural products*, 84(8), 2282–2294. <https://doi.org/10.1021/acs.jnatprod.1c00386>
- Burrage, D. R., Koushesh, S., & Sofat, N. (2020). Immunomodulatory Drugs in the Management of SARS-CoV-2. *Frontiers in immunology*, 11, 1844. <https://doi.org/10.3389/fimmu.2020.01844>
- Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2022 Jan 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554776/>
- Catanzaro, M., Corsini, E., Rosini, M., Racchi, M., & Lanni, C. (2018). Immunomodulators Inspired by Nature: A Review on Curcumin and Echinacea. *Molecules (Basel, Switzerland)*, 23(11), 2778. <https://doi.org/10.3390/molecules23112778>
- Chattopadhyay. (1998). "Possible biochemical mode of antiinflammatory action of Azadirachta indica A. Juss. in rats," *Indian Journal of Experimental Biology*, vol. 36, no. 4, pp. 418– 420, 1998.
- Channappanavar R, Perlman S. (2017). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* Vol 39(5):529-539.
- Chen, J.-J., Chung, C.-Y., Hwang, T.-L., and Chen, J.-F. (2009). Amides and benzenoids from *Zanthoxylum ailanthoides* with inhibitory activity on superoxide generation and elastase release by neutrophils. *J. Nat. Prod.* 72, 107–111. doi: 10.1021/np800689b
- Choudhary, S., Sharma, K., Singh, H., & Silakari, O. (2020). The interplay between inflammatory pathways and COVID-19: A critical review on pathogenesis and therapeutic options. *Microbial Pathogenesis*, 104673. doi:10.1016/j.micpath.2020.104673
- Cilloniz, C., Martin-Loeches, I., Garcia-Vidal, C., San Jose, A., & Torres, A. (2016). Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns. *International journal of molecular sciences*, 17(12), 2120. <https://doi.org/10.3390/ijms17122120>
- Cleaves H.J.. (2015) Svedberg Unit. In: Gargaud M. et al. (eds) *Encyclopedia of Astrobiology*. Springer, Berlin, Heidelberg. [https://doi.org/10.1007/978-3-662-44185-5\\_5249](https://doi.org/10.1007/978-3-662-44185-5_5249)
- Courtine, E., Cagnard, N., Mazzolini, J., Antona, M., Pène, F., Fitting, C., Jacques, S., Rousseau, C., Niedergang, F., Gerondakis, S., Chiche, J.-D., Ouaz, F., & Mira, J.-P. (2012). Combined loss of cRel/p50 subunits of NF-κB leads to impaired innate host response in sepsis. *Innate Immunity*, 18(5), 753–763. <https://doi.org/10.1177/1753425912440296>
- Costela-Ruiz, V. J., Illescas-Montes, R., Puerta-Puerta, J. M., Ruiz, C., & Melguizo-Rodríguez, L. (2020). SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine & growth factor reviews*, 54, 62–75. <https://doi.org/10.1016/j.cytogfr.2020.06.001>
- Dai, M., Wahyuni, A., DK, I., Azizah, T., Suhendi, A., & Saifudin, A. (2016). Antioxidant activity of *Phyllanthus niruri* L. herbs: in vitro and in vivo models and isolation of active compound. *National Journal Of Physiology, Pharmacy And Pharmacology*, 6(1), 32. doi: 10.5455/njppp.2015.5.0510201575
- Da'i M, Wahyuni AS, Kusumowati ITD, Setiawan D, Dhi'fi HJ, Suhendi A, et al (2011).. The Correlation of Phenolic Content with Antioxidant Activity Five Types Indonesian Herbs International Seminar on Translational Research in Cancer Chemoprevention.
- Dapson, R. W., and Bain, C. L. (2015). Brazilwood, Sappanwood, Brazilin and the Red Dye Brazilin: From Textile Dyeing and Folk Medicine to Biological Staining and Musical Instruments. *Biotech. Histochem.* 90 (6), 401–423. doi:10.3109/10520295.2015.1021381

- D.E., S., I.M., B., U., S., S.M., M., & B., A. (2021). Potential Therapeutic Option used for the Cure of Covid-19 using Locally Available Indigenous Herbs (Nigeria) Containing Antioxidant, Vitamins, Minerals; thus, this will help to tackle Current Status, Challenges as well as Futuristic Perspective
- de Klerk, E., & 't Hoen, P. (2015). Alternative mRNA transcription, processing, and translation: insights from RNA sequencing. *Trends In Genetics*, 31(3), 128-139. doi: 10.1016/j.tig.2015.01.001 Globally.
- African Journal Of Biology And Medical Research*, 4(4), 53-117. doi: 10.52589/ajbmr-afsi6cxu
- Devaney, J., Curley, G. F., Hayes, M., Masterson, C., Ansari, B., O'Brien, T., O'Toole, D., & Laffey, J. G. (2013). Inhibition of pulmonary nuclear factor kappa-B decreases the severity of acute Escherichia coli pneumonia but worsens prolonged pneumonia. *Critical care (London, England)*, 17(2), R82. <https://doi.org/10.1186/cc12696>
- Dinareello C. A. (2018). Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological reviews*, 281(1), 8–27. <https://doi.org/10.1111/imr.12621>
- Dorrington, M. G., & Fraser, I. D. C. (2019). *NF- $\kappa$ B Signaling in Macrophages: Dynamics, Crosstalk, and Signal Integration*. *Frontiers in Immunology*, 10. doi:10.3389/fimmu.2019.00705
- Duh PD, Yen GC, Yen WJ, Chang LW. (2001). Antioxidant effects of water extracts from barley (*Hordeum vulgare* L.) prepared under different roasting temperatures. *J Agri Food Chem*; 49(3): 1455-1463
- Du Toit, K., Elgorashi, E. E., Malan, S. F., Drewes, S. E., van Staden, J., Crouch, N. R., & Mulholland, D. A. (2005). Anti-inflammatory activity and QSAR studies of compounds isolated from Hyacinthaceae species and *Tachiadenus longiflorus* Griseb.(Gentianaceae). *Bioorganic & medicinal chemistry*, 13(7), 2561-2568.
- El-Maati M F A, Mahgoub S A, Labib S M, Al-Gaby A M A and Ramadan M F. (2016). Phenolic extracts of clove (*Syzygium aromaticum*) with novel antioxidant and antibacterial activities. *European Journal of Integrative Medicine* 8(4): 494–504. <https://doi.org/10.1016/J.EUJIM.2016.02.006>
- Eze, M. O., Ejike, C., Ifeonu, P., Udeinya, I. J., Udenigwe, C. C., & Uzoegwu, P. N. (2022). Anti-COVID-19 potential of *Azadirachta indica* (Neem) leaf extract. *Scientific African*, 16, e01184. <https://doi.org/10.1016/j.sciaf.2022.e01184>
- Feuillet, V., Canard, B., & Trautmann, A. (2021). Combining Antivirals and Immunomodulators to Fight COVID-19. *Trends in immunology*, 42(1), 31–44. <https://doi.org/10.1016/j.it.2020.11.003>
- Fernandes-Brum CN, Garcia B, Moreira R, Sagio SA (2017) A panel of the most suitable reference genes for RT-qPCR expression studies of coffee: screening their stability
- Fleige, S., & Pfaffl, M. W. (2006). *RNA integrity and the effect on the real-time qRT-PCR performance*. *Molecular Aspects of Medicine*, 27(2-3), 126–139. doi:10.1016/j.mam.2005.12.003
- Fragoulis, A., Biller, K., Fragoulis, S., Lex, D., Uhlig, S., & Reiss, L. (2021). Reference Gene Selection for Gene Expression Analyses in Mouse Models of Acute Lung Injury. *International Journal Of Molecular Sciences*, 22(15), 7853. doi: 10.3390/ijms22157853
- Gadotti, A. C., de Castro Deus, M., Telles, J. P., Wind, R., Goes, M., Garcia Charello Ossoski, R., de Padua, A. M., de Noronha, L., Moreno-Amaral, A., Baena, C. P., & Tuon, F. F. (2020). IFN- $\gamma$  is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. *Virus research*, 289, 198171. <https://doi.org/10.1016/j.virusres.2020.198171>
- Garrido-Trigo, A. and Salas, A., 2019. Molecular Structure and Function of Janus Kinases: Implications for the Development of Inhibitors. *Journal of Crohn's and Colitis*, 14(Supplement\_2), pp.S713-S724.
- Ghimeray, A.K., Jin, C.W., Ghimire, B., & Cho, D.H. (2009). Antioxidant activity and quantitative estimation of azadirachtin and nimbin in *Azadirachta Indica* A. Juss grown in foothills of Nepal. *African Journal of Biotechnology*, 8, 3084-3091.

- Goker Bagca, B., & Biray Avci, C. (2020). The potential of JAK/STAT pathway inhibition by ruxolitinib in the treatment of COVID-19. *Cytokine & growth factor reviews*, 54, 51–62. <https://doi.org/10.1016/j.cytogfr.2020.06.013>
- Grzanka, A., Misiołek, M., Golusiński, W. *et al.* (2011). Molecular mechanisms of glucocorticoids action: implications for treatment of rhinosinusitis and nasal polyposis. *Eur Arch Otorhinolaryngol* 268, 247–253. <https://doi.org/10.1007/s00405-010-1330-z>
- Haji Abdolvahab, M., Moradi-kalbolandi, S., Zarei, M., Bose, D., Majidzadeh-A, K., & Farahmand, L. (2020). *Potential role of interferons in treating COVID-19 patients. International Immunopharmacology*, 107171. doi:10.1016/j.intimp.2020.107171
- Han, X., & Parker, T. L. (2017). Anti-inflammatory activity of clove (*Eugenia caryophyllata*) essential oil in human dermal fibroblasts. *Pharmaceutical biology*, 55(1), 1619–1622. <https://doi.org/10.1080/13880209.2017.1314513>
- Hao, Q., Shetty, S., Tucker, T. A., Idell, S., & Tang, H. (2022). Interferon- $\gamma$  Preferentially Promotes Necroptosis of Lung Epithelial Cells by Upregulating MLKL. *Cells*, 11(3), 563. <https://doi.org/10.3390/cells11030563>
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Hopkins, J. (2021). Mortality Analyses - Johns Hopkins Coronavirus Resource Center. Retrieved 29 November 2021, from <https://coronavirus.jhu.edu/data/mortality>
- Hu, X., Li, J., Fu, M., Zhao, X. and Wang, W., 2021. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduction and Targeted Therapy*, 6(1).
- Hu, Z.-J., Xu, J., Yin, J.-M., Li, L., Hou, W., Zhang, L.-L., ... Jin, R.-H. (2020). *Lower Circulating Interferon-Gamma Is a Risk Factor for Lung Fibrosis in COVID-19 Patients. Frontiers in Immunology*, 11. doi:10.3389/fimmu.2020.585647
- Huang, X., Liu, Y., Lu, Y., & Ma, C. (2015). *Anti-inflammatory effects of eugenol on lipopolysaccharide-induced inflammatory reaction in acute lung injury via regulating inflammation and redox status. International Immunopharmacology*, 26(1), 265–271. doi:10.1016/j.intimp.2015.03.026
- Ibrahim, D., Hong, L. S., & Kuppan, N. (2013). *Antimicrobial Activity of Crude Methanolic Extract from Phyllanthus niruri. Natural Product Communications*, 8(4), 1934578X1300800. doi:10.1177/1934578x1300800422
- Il Yun Jeong, Chang Hyun Jin, Yong Dae Park, Hyo Jung Lee, Dae Seong Choi, Myung Woo Byun, Yeung Ji Kim.(2008).Anti-inflammatory Activity of an Ethanol Extract of *Caesalpinia sappan* L. in LPS-induced RAW 264.7 Cells.Preventive Nutrition and Food Science,13(4),253-258.
- Ishiyama, T., Dharmarajan, S., Hayama, M., Moriya, H., Grapperhaus, K., & Patterson, G. A. (2005). Inhibition of nuclear factor kappaB by IkappaB superrepressor gene transfer ameliorates ischemia-reperfusion injury after experimental lung transplantation. *The Journal of thoracic and cardiovascular surgery*, 130(1), 194–201. <https://doi.org/10.1016/j.jtcvs.2005.02.040>
- Islas, J., Acosta, E., G-Buentello, Z., Delgado-Gallegos, J., Moreno-Treviño, M., Escalante, B., & Moreno-Cuevas, J. (2020). An overview of Neem (*Azadirachta indica*) and its potential impact on health. *Journal Of Functional Foods*, 74, 104171. doi: 10.1016/j.jff.2020.104171



- Ivashkiv L. B. (2018). IFN $\gamma$ : signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. *Nature reviews. Immunology*, 18(9), 545–558. <https://doi.org/10.1038/s41577-018-0029-z>
- Jantan, I., Haque, M. A., Ilangkovan, M., & Arshad, L. (2019). An Insight Into the Modulatory Effects and Mechanisms of Action of *Phyllanthus* Species and Their Bioactive Metabolites on the Immune System. *Frontiers in pharmacology*, 10, 878. <https://doi.org/10.3389/fphar.2019.00878>
- Kebaier, C., Chamberland, R. R., Allen, I. C., Gao, X., Broglie, P. M., Hall, J. D., Jania, C., Doerschuk, C. M., Tilley, S. L., & Duncan, J. A. (2012). Staphylococcus aureus  $\alpha$ -hemolysin mediates virulence in a murine model of severe pneumonia through activation of the NLRP3 inflammasome. *The Journal of infectious diseases*, 205(5), 807–817. <https://doi.org/10.1093/infdis/jir846>
- Klok, F. A., Kruijff, M. J. H. A., van der Meer, N. J. M., Arbous, M. S., Gommers, D. A. M. P. J., Kant, K. M., ... Endeman, H. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*. doi:10.1016/j.thromres.2020.04.01
- Kuang, J., Yan, X., Genders, A. J., Granata, C., & Bishop, D. J. (2018). An overview of technical considerations when using quantitative real-time PCR analysis of gene expression in human exercise research. *PloS one*, 13(5), e0196438. <https://doi.org/10.1371/journal.pone.0196438>
- Lalonde, L. F., Reyes, J., & Gajadhar, A. A. (2013). Application of a qPCR assay with melting curve analysis for detection and differentiation of protozoan oocysts in human fecal samples from Dominican Republic. *The American journal of tropical medicine and hygiene*, 89(5), 892–898. <https://doi.org/10.4269/ajtmh.13-0106>
- Li, N., Fan, X., Xu, M., Zhou, Y., & Wang, B. (2020). Flu Virus Attenuates Memory Clearance of *Pneumococcus* via IFN- $\gamma$ -Dependent Th17 and Independent Antibody Mechanisms. *iScience*, 23(12), 101767. <https://doi.org/10.1016/j.isci.2020.101767>
- Li, W., Moltedo, B., & Moran, T. M. (2012). Type I interferon induction during influenza virus infection increases susceptibility to secondary Streptococcus pneumoniae infection by negative regulation of  $\gamma\delta$  T cells. *Journal of virology*, 86(22), 12304–12312. <https://doi.org/10.1128/JVI.01269-12>
- Livak, K. J., Wills, Q. F., Tipping, A. J., Datta, K., Mittal, R., Goldson, A. J., Sexton, D. W., & Holmes, C. C. (2013). Methods for qPCR gene expression profiling applied to 1440 lymphoblastoid single cells. *Methods (San Diego, Calif.)*, 59(1), 71–79. <https://doi.org/10.1016/j.ymeth.2012.10.004>
- Maes, M., Higginson, E., Pereira-Dias, J., Curran, M. D., Parmar, S., Khokhar, F., Cuchet-Lourenço, D., Lux, J., Sharma-Hajela, S., Ravenhill, B., Hamed, I., Heales, L., Mahroof, R., Soderholm, A., Forrest, S., Sridhar, S., Brown, N. M., Baker, S., Navapurkar, V., Dougan, G., ... Conway Morris, A. (2021). Ventilator-associated pneumonia in critically ill patients with COVID-19. *Critical care (London, England)*, 25(1), 25. <https://doi.org/10.1186/s13054-021-03460-5>
- Magalhaes, C. B.; Casquilho, N. V.; Machado, M. N.; Riva, D. R.; Travassos, L. H.; Leal-Cardoso, J. H.; Fortunato, R. S.; Faffe, D. S.; Zin, W. A. *Respir. Physiol. Neurobiol.* 2019, 259, 30–36.
- Magalhaes, C. B.; Riva, D. R.; DePaula, L. J.; Brando-Lima, A.; Koatz, V. L.; Leal-Cardoso, J. H.; Zin, W. A.; Faffe, D. S. *J. Appl. Physiol.* 2010, 108 (4), 845–51
- Makoshi MS, Adanyeguh IM, Nwatu LI. (2013). Hepatoprotective effect of Phyllanthus niruri aqueous extract in acetaminophen sub-acute exposure rabbits. *J Vet Med Anim Health*. Vol 5(1):8–15.
- Mallikadevi, T., Paulsamy, S., Karthika, K., & Jamuna, S. (2012). In vitro and in vivo anti-inflammatory activity of whole plant methanolic extract of *Mukia maderaspatana*(L.) M. roem.(cucurbitaceae). *International Journal of Pharmacy & Pharmaceutical Sciences*, 5(4), 435.

- Manna, S., Baidara, P., & Mandal, S. M. (2020). Molecular pathogenesis of secondary bacterial infection associated to viral infections including SARS-CoV-2. *Journal of infection and public health*, 13(10), 1397–1404. <https://doi.org/10.1016/j.jiph.2020.07.003>
- Manohar, P., Loh, B., Nachimuthu, R., Hua, X., Welburn, S. C., & Leptihn, S. (2020). Secondary Bacterial Infections in Patients With Viral Pneumonia. *Frontiers in medicine*, 7, 420. <https://doi.org/10.3389/fmed.2020.00420>
- Mansour, F. H., & Pestov, D. G. (2013). Separation of long RNA by agarose-formaldehyde gel electrophoresis. *Analytical biochemistry*, 441(1), 18–20. <https://doi.org/10.1016/j.ab.2013.06.008>
- Makris, S., Paulsen, M., & Johansson, C. (2017). Type I Interferons as Regulators of Lung Inflammation. *Frontiers in immunology*, 8, 259. <https://doi.org/10.3389/fimmu.2017.00259>
- Mason RJ. (2020). Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J* 2020;55(4):2000607.
- Matsumura, T., & Takahashi, Y. (2020). The role of myeloid cells in prevention and control of group A streptococcal infections. *Biosafety And Health*, 2(3), 130-134. doi: 10.1016/j.bsheal.2020.05.006
- Matthay, M. A., McAuley, D. F., & Ware, L. B. (2017). Clinical trials in acute respiratory distress syndrome: challenges and opportunities. *The Lancet. Respiratory medicine*, 5(6), 524–534. [https://doi.org/10.1016/S2213-2600\(17\)30188-1](https://doi.org/10.1016/S2213-2600(17)30188-1)
- Magalhães CB, Riva DR, DePaula LJ, Brando-Lima AC, Koatz VLG, Leal-Cardoso JH, Zin WA, Faffe DS. (2010). In vivo anti-inflammatory action of eugenol on lipopolysaccharide-induced lung injury. *J Appl Physiol* 108: 845–851.
- Magalhães, C. B., Casquilho, N. V., Machado, M. N., Riva, D. R., Travassos, L. H., Leal-Cardoso, J. H., ... Zin, W. A. (2018). *The anti-inflammatory and anti-oxidative actions of eugenol improve lipopolysaccharide-induced lung injury. Respiratory Physiology & Neurobiology.* doi:10.1016/j.resp.2018.07.001
- Mehta, J., Rolta, R., Mehta, B. B., Kaushik, N., Choi, E. H., & Kaushik, N. K. (2022). Role of Dexamethasone and Methylprednisolone Corticosteroids in Coronavirus Disease 2019 Hospitalized Patients: A Review. *Frontiers in microbiology*, 13, 813358. <https://doi.org/10.3389/fmicb.2022.813358>
- Melehani, J. H., & Duncan, J. A. (2016). Inflammasome Activation Can Mediate Tissue-Specific Pathogenesis or Protection in Staphylococcus aureus Infection. *Current topics in microbiology and immunology*, 397, 257–282. [https://doi.org/10.1007/978-3-319-41171-2\\_13](https://doi.org/10.1007/978-3-319-41171-2_13)
- Mirastschijski, U., Dembinski, R., & Maedler, K. (2020). *Lung Surfactant for Pulmonary Barrier Restoration in Patients With COVID-19 Pneumonia. Frontiers in Medicine*, 7. doi:10.3389/fmed.2020.00254
- Mitchell, S., Mercado, E. L., Adelaja, A., Ho, J. Q., Cheng, Q. J., Ghosh, G., & Hoffmann, A. (2019). *An NFKB Activity Calculator to Delineate Signaling Crosstalk: Type I and II Interferons Enhance NFKB via Distinct Mechanisms. Frontiers in Immunology*, 10. doi:10.3389/fimmu.2019.01425
- Mosaddek, A., & Rashid, M. (2008). A comparative study of the anti-inflammatory effect of aqueous extract of neem leaf and dexamethasone. *Bangladesh Journal Of Pharmacology*, 3(1). doi: 10.3329/bjp.v3i1.836
- Netea, M. G., Kullberg, B. J., & Van der Meer, J. W. (2000). Circulating cytokines as mediators of fever. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 31 Suppl 5, S178–S184. <https://doi.org/10.1086/317513>

- Nirmal, N., & Benjakul, S. (2011). Inhibitory Effect of Mimosine on Polyphenoloxidase from Cephalothoraxes of Pacific White Shrimp (<i>Litopenaeus vannamei</i>). *Journal Of Agricultural And Food Chemistry*, 59(18), 10256-10260. doi: 10.1021/jf201603k
- Nirmal, N., Rajput, M., Prasad, R., & Ahmad, M. (2015). Brazilin from Caesalpinia sappan heartwood and its pharmacological activities: A review. *Asian Pacific Journal Of Tropical Medicine*, 8(6), 421-430. doi: 10.1016/j.apjtm.2015.05.014
- Nisar, M. F., Khadim, M., Rafiq, M., Chen, J., Yang, Y., & Wan, C. C. (2021). Pharmacological Properties and Health Benefits of Eugenol: A Comprehensive Review. *Oxidative medicine and cellular longevity*, 2021, 2497354. <https://doi.org/10.1155/2021/2497354>
- Noreen, S., Maqbool, I., & Madni, A. (2021). Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. *European journal of pharmacology*, 894, 173854. <https://doi.org/10.1016/j.ejphar.2021.173854>
- Patel, S. K., Saikumar, G., Rana, J., Dhama, J., Yatoo, M. I., Tiwari, R., Rodríguez-Morales, A. J., & Dhama, K. (2020). Dexamethasone: A boon for critically ill COVID-19 patients?. *Travel medicine and infectious disease*, 37, 101844. <https://doi.org/10.1016/j.tmaid.2020.101844>
- Parra Gordo, M. L., Buitrago Weiland, G., Grau García, M., & Arenaza Choperena, G. (2021). *Radiologic aspects of COVID-19 pneumonia: Outcomes and thoracic complications. Radiología (English Edition)*, 63(1), 74–88. doi:10.1016/j.rxeng.2020.11.002
- Pfizer, .., 2020. *Viral vs. Bacterial Pneumonia: Understanding the Difference | Pfizer*. [online] Pfizer.com. Available at: <[https://www.pfizer.com/news/hot-topics/viral\\_vs\\_bacterial\\_pneumonia\\_understanding\\_the\\_difference](https://www.pfizer.com/news/hot-topics/viral_vs_bacterial_pneumonia_understanding_the_difference)> [Accessed 13 October 2021].
- Pires, S., & Parker, D. (2018). IL-1 $\beta$  activation in response to Staphylococcus aureus lung infection requires inflammasome-dependent and independent mechanisms. *European journal of immunology*, 48(10), 1707–1716. <https://doi.org/10.1002/eji.201847556>
- Poojari, S., Alabi, O. J., Okubara, P. A., & Naidu, R. A. (2016). SYBR<sup>®</sup> Green-based real-time quantitative reverse-transcription PCR for detection and discrimination of grapevine viruses. *Journal of virological methods*, 235, 112–118. <https://doi.org/10.1016/j.jviromet.2016.05.013>
- Promptchara E, Ketloy C, Palaga T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 38(1):1-9.
- Quinton, L. J., Walkey, A. J., & Mizgerd, J. P. (2018). *Integrative Physiology of Pneumonia. Physiological Reviews*, 98(3), 1417–1464. doi:10.1152/physrev.00032.2017
- Rawson, T. M., Moore, L. S. P., Zhu, N., Ranganathan, N., Skolimowska, K., Gilchrist, M., ... Holmes, A. (2020). *Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clinical Infectious Diseases*. doi:10.1093/cid/ciaa530
- Read, B. E. (1930). The Chinese Pharmacopoeia. *Canadian Medical Association Journal*, 23(4), 568.
- Rizk, J. G., Kalantar-Zadeh, K., Mehra, M. R., Lavie, C. J., Rizk, Y., & Forthal, D. N. (2020). Pharmacological-Immunomodulatory Therapy in COVID-19. *Drugs*, 80(13), 1267–1292. <https://doi.org/10.1007/s40265-020-01367-z>
- Rosarior, V. L., Lim, P. S., Wong, W. K., Yue, C. S., Yam, H. C., & Tan, S. A. (2021). Antioxidant-rich Clove Extract, A Strong Antimicrobial Agent against Urinary Tract Infections-causing Bacteria *in vitro*. *Tropical life sciences research*, 32(2), 45–63. <https://doi.org/10.21315/tlsr2021.32.2.4>
- Roser M, Ritchie H, Ortiz-Ospina E, Hasell J.(2020). Coronavirus disease (COVID-19)–Statistics and research. Our World in data 2020

- Samadder S. (2021). Immunopathological Changes in SARS-CoV-2 Critical and Non-critical Pneumonia Patients: A Systematic Review to Determine the Cause of Co-infection. *Frontiers in public health*, 8, 544993. <https://doi.org/10.3389/fpubh.2020.544993>
- Santa Cruz, A., Mendes-Frias, A., Oliveira, A., Dias, L., Matos, A., & Carvalho, A. et al. (2021). Interleukin-6 Is a Biomarker for the Development of Fatal Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. *Frontiers In Immunology*, 12. doi: 10.3389/fimmu.2021.613422
- Sasaki, Y., Hosokawa, T., Nagai, M., & Nagumo, S. (2007). In Vitro Study for Inhibition of NO Production about Constituents of Sappan Lignum. *Biological And Pharmaceutical Bulletin*, 30(1), 193-196. doi: 10.1248/bpb.30.193
- Schicke, E., Cseresnyés, Z., Rennert, K., Vau, V., Haupt, K. F., Hornung, F., Nietzsche, S., Swiczak, F., Schmidtke, M., Glück, B., Koch, M., Schacke, M., Heller, R., Mosig, A. S., Figge, M. T., Ehrhardt, C., Löffler, B., & Deinhardt-Emmer, S. (2020). *Staphylococcus aureus* Lung Infection Results in Down-Regulation of Surfactant Protein-A Mainly Caused by Pro-Inflammatory Macrophages. *Microorganisms*, 8(4), 577. <https://doi.org/10.3390/microorganisms8040577>
- Schröfelbauer B, Polley S, Behar M, Ghosh G, Hoffmann A. (2012). NEMO ensures signaling specificity of the pleiotropic IKK $\beta$  by directing its kinase activity toward IKK $\alpha$ . *Mol Cell*. Vol 47:111–21. doi: 10.1016/j.molcel.2012.04.020
- Seif, F., Khoshmirsafa, M., Aazami, H., Mohsenzadegan, M., Sedighi, G. and Bahar, M., 2017. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Communication and Signaling*, 15(1).
- Sever-Chroneos, Z., Krupa, A., Davis, J., Hasan, M., Yang, C. H., Szeliga, J., Herrmann, M., Hussain, M., Geisbrecht, B. V., Kobzik, L., & Chroneos, Z. C. (2011). Surfactant protein A (SP-A)-mediated clearance of *Staphylococcus aureus* involves binding of SP-A to the staphylococcal adhesin eap and the macrophage receptors SP-A receptor 210 and scavenger receptor class A. *The Journal of biological chemistry*, 286(6), 4854–4870. <https://doi.org/10.1074/jbc.M110.125567>
- Sharifipour, E., Shams, S., Esmkhani, M., Khodadadi, J., Fotouhi-Ardakani, R., Koochpaei, A., Doosti, Z., & Ej Golzari, S. (2020). Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC infectious diseases*, 20(1), 646. <https://doi.org/10.1186/s12879-020-05374-z>
- Sharov K. S. (2020). SARS-CoV-2-related pneumonia cases in pneumonia picture in Russia in March-May 2020: Secondary bacterial pneumonia and viral co-infections. *Journal of global health*, 10(2), 020504. <https://doi.org/10.7189/jogh.10.-020504>
- Silas D.E., Bugaje I.M. , Suleman U., Mohammad S.M., Aliyu B. (2021), Potential Therapeutic Option used for the Cure of Covid-19 using Locally Available Indigenous Herbs (Nigeria) Containing Antioxidant, Vitamins, Minerals; thus, this will help to tackle Current Status, Challenges as well as Futuristic Perspective Globally. *African Journal of Biology and Medical Research* 4(4), 53-117. DOI: 10.52589/AJBMRAFSI6CXU.
- Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020;76:71-76
- Somanabandhu A, Nityangkuru S, Mahidol C. (1993) <sup>1</sup>H and <sup>13</sup>C NMR assignments of phyllanthin and hypophyllanthin lignans that enhance cytotoxic responses with cultured multidrug-resistant cells. *Journal of Natural Products*, 56, 233-239.
- Sreedharan, S. P., Kumar, A., & Giridhar, P. (2018). Primer design and amplification efficiencies are crucial for reliability of quantitative PCR studies of caffeine biosynthetic *N*-methyltransferases in coffee. *3 Biotech*, 8(11), 467. <https://doi.org/10.1007/s13205-018-1487-5>

- Srinivasan, R., selvam, G., Karthik, S., Mathivanan, K., Baskaran, R., & Karthikeyan, M. et al. (2012). In vitro antimicrobial activity of *Caesalpinia sappan* L. *Asian Pacific Journal Of Tropical Biomedicine*, 2(1), S136-S139. doi: 10.1016/s2221-1691(12)60144-0
- Stefova, Marina & Stafilov, Trajce & Kulevanova, Svetlana. (2003). HPLC analysis of flavonoids.
- Suraya, A. A., Misran, A., & Hakiman, M. (2021). The Efficient and Easy Micropropagation Protocol of *Phyllanthus niruri*. *Plants (Basel, Switzerland)*, 10(10), 2141. <https://doi.org/10.3390/plants10102141>
- Sunitha, J., Krishna, S., Ananthalakshmi, R., Jeeva, J. S., Girija, A. S., & Jeddy, N. (2017). Antimicrobial Effect of Leaves of *Phyllanthus niruri* and *Solanum nigrum* on Caries Causing Bacteria: An In vitro Study. *Journal of clinical and diagnostic research : JCDR*, 11(6), KC01–KC04. <https://doi.org/10.7860/JCDR/2017/23602.10066>
- Suwan, T., Wanachantararak, P., Khongkhunthian, S., & Okonogi, S. (2018). *Antioxidant activity and potential of Caesalpinia sappan aqueous extract on synthesis of silver nanoparticles*. *Drug Discoveries & Therapeutics*, 12(5), 259–266. doi:10.5582/ddt.2018.01059
- Svec, D., Tichopad, A., Novosadova, V., Pfaffl, M. W., & Kubista, M. (2015). How good is a PCR efficiency estimate: Recommendations for precise and robust qPCR efficiency assessments. *Biomolecular detection and quantification*, 3, 9–16. <https://doi.org/10.1016/j.bdq.2015.01.005>
- Syamsunarno MRAA, Safitri R and Kamisah Y (2021) Protective Effects of *Caesalpinia sappan* Linn. and Its Bioactive Compounds on Cardiovascular Organs. *Front. Pharmacol.* 12:725745. doi: 10.3389/fphar.2021.725745
- ThermoFisher. (2022). The Purpose of ROX Reference Dye in Real-Time PCR (qPCR). Retrieved 24 May 2022, from <https://www.thermofisher.com/blog/behindthebench/the-purpose-of-rox-reference-dye-in-real-time-pcr-qpcr/>
- Tjandrawinata, Raymond & Nofiarny, Dwi & Maat, Suprpto. (2005). Effects of standardized *Phyllanthus Niruri* extract on changes in immunological parameters: correlation between pre-clinical and clinical studies.. *Medika*. 31. 367-371.
- Tomson L, Kruma Z, Galoburda R. (2012) Screening of *Phyllanthus* species for antimicrobial properties. *Chemical Sciences Journal*, 2012, csj 56.
- Troeger, C., Blacker, B., Khalil, I. A., Rao, P. C., Cao, J., Zimsen, S. R. M., ... Abebe, Z. (2018). *Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016*. *The Lancet Infectious Diseases*. doi:10.1016/s1473-3099(18)30310-4
- Wang, L. C., Liao, L. X., Zhao, M. B., Dong, X., Zeng, K. W., & Tu, P. F. (2017). Protosappanin A exerts anti-neuroinflammatory effect by inhibiting JAK2-STAT3 pathway in lipopolysaccharide-induced BV2 microglia. *Chinese journal of natural medicines*, 15(9), 674–679. [https://doi.org/10.1016/S1875-5364\(17\)30096-1](https://doi.org/10.1016/S1875-5364(17)30096-1)
- Wang, M., Ji, X., Wang, B., Li, Q., & Zhou, J. (2018). Simultaneous Evaluation of the Preservative Effect of RNA later on Different Tissues by Biomolecular and Histological Analysis. *Biopreservation and biobanking*, 16(6), 426–433. <https://doi.org/10.1089/bio.2018.0055>
- Washiyama, M., Sasaki, Y., Hosokawa, T., & Nagumo, S. (2009). Anti-inflammatory Constituents of *Sappan Lignum*. *Biological And Pharmaceutical Bulletin*, 32(5), 941-944. doi: 10.1248/bpb.32.941
- Weiser, J. N., Ferreira, D. M., & Paton, J. C. (2018). *Streptococcus pneumoniae*: transmission, colonization and invasion. *Nature reviews. Microbiology*, 16(6), 355–367. <https://doi.org/10.1038/s41579-018-0001-8>

- WHO, I., 2019. *Pneumonia*. [online] Who.int. Available at: <<https://www.who.int/news-room/fact-sheets/detail/pneumonia>> [Accessed 13 October 2021].
- Wright JR. (2006). The “wisdom” of lung surfactant: balancing host defense and surface tension-reducing functions. *Am J Physiol Lung Cell Mol Physiol*. (2006) 291:L847–50. doi: 10.1152/ajplung.00261.
- Wong Fok Lung, T., & Prince, A. (2020). *Consequences of Metabolic Interactions during Staphylococcus aureus Infection*. *Toxins*, 12(9), 581. doi:10.3390/toxins12090581
- Wu, C. P., Adhi, F., & Highland, K. (2020). Recognition and management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19. *Cleveland Clinic journal of medicine*, 87(11), 659–663. <https://doi.org/10.3949/ccjm.87a.ccc015>
- Xu HX, Lee SF. (2004) The antibacterial principle of *Caesalpinia sappan*. *Phytother Res*; 18(8): 647-651
- Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *The Journal of infection*, 80(6), 607–613. <https://doi.org/10.1016/j.jinf.2020.03.037>
- Yeh, J. L., Hsu, J. H., Hong, Y. S., Wu, J. R., Liang, J. C., Wu, B. N., Chen, I. J., & Liou, S. F. (2011). Eugenolol and Glyceryl-Isoeugenol Suppress LPS-Induced INOS Expression by Down-Regulating NF- $\kappa$ B and AP-1 through Inhibition of Mapks and AKT/I $\kappa$ B $\alpha$  Signaling Pathways in Macrophages. *International Journal of Immunopathology and Pharmacology*, 345–356. <https://doi.org/10.1177/039463201102400208>
- Yingkun, N., Zhenyu, W., Jing, L., Xiuyun, L., & Huimin, Y. (2012). *Stevioside Protects LPS-Induced Acute Lung Injury in Mice*. *Inflammation*, 36(1), 242–250. doi:10.1007/s10753-012-9540-8
- Ylmaz, M., Ozic, C., & Gok, Ihami. (2012). *Principles of Nucleic Acid Separation by Agarose Gel Electrophoresis*. *Gel Electrophoresis - Principles and Basics*. doi:10.5772/38654
- Youssef, J., Novosad, S. A., & Winthrop, K. L. (2016). *Infection Risk and Safety of Corticosteroid Use*. *Rheumatic Disease Clinics of North America*, 42(1), 157–176. doi:10.1016/j.rdc.2015.08.004
- Zhang, Y., Chen, Y., & Meng, Z. (2020). Immunomodulation for Severe COVID-19 Pneumonia: The State of the Art. *Frontiers in immunology*, 11, 577442. <https://doi.org/10.3389/fimmu.2020.577442>
- Zhang, W., Zhao, Y., Zhang, F., Wang, Q., Li, T., Liu, Z., Wang, J., Qin, Y., Zhang, X., Yan, X., Zeng, X. and Zhang, S., 2020. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clinical Immunology*, 214, p.108393.
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... Cao, B. (2020). *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study*. *The Lancet*, 395(10229), 1054–1062. doi:10.1016/s0140-6736(20)30566-3
- Zin, W. A., Silva, A. G., Magalhães, C. B., Carvalho, G. M., Riva, D. R., Lima, C. C., Leal-Cardoso, J. H., Takiya, C. M., Valença, S. S., Saldiva, P. H., & Faffe, D. S. (2012). Eugenol attenuates pulmonary damage induced by diesel exhaust particles. *Journal of applied physiology (Bethesda, Md. : 1985)*, 112(5), 911–917. <https://doi.org/10.1152/jappphysiol.00764.2011>