

## Potential herbal-based treatment for COVID-19, a case for papaya leaves extract

M.S. Shukor<sup>1</sup> and M.Y. Shukor<sup>2</sup>

<sup>1</sup>Snoc International Sdn Bhd, Lot 343, Jalan 7/16 Kawasan Perindustrian Nilai 7, Inland Port, 71800, Negeri Sembilan, Malaysia.

<sup>2</sup>Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, UPM 43400 Serdang, Selangor, Malaysia.

### Abstract

COVID-19 is caused by the coronavirus SARS-CoV-2 and is now a pandemic affecting humans at the global scale. Researchers are still trying to find a cure and a vaccine to fight the pandemic. Drug-based cure and vaccines are overwhelmingly virus-specific and newer drugs and vaccines are needed to resist new novel viral infections and resistant strains. The use of natural-based therapies including herbal remedies and plant-based extracts to fight viral infections is an ongoing work which has accelerated to a fast pace due to the severity of the current pandemic. Several approaches have been carried out including the use of traditional Chinese herbal medicines. Papaya leaves extract (PLE) has been intensively studied for its antiviral, immunomodulatory and cytokine storm-alleviating properties in dengue-afflicted patients. These properties, especially PLE ability to inhibit TNF-alpha, hold promise for its capability as a possible weapon to fight COVID-19. This work attempts to put up a case for PLE as a conceivable weapon to fight COVID-19.

### 1. Introduction

The global pandemic of COVID-19 has infected more than 50 million people and caused the deaths of more than one million people worldwide with grim projection of future cases (Aisami and Shukor 2020; Aisami *et al.* 2020; Shukor *et al.* 2020; Uba *et al.* 2020; Yahuza *et al.* 2020). Recent data has shown that survivors of COVID-19 exhibit serious degeneration in terms of cognitive deficits termed 'long COVID' (Hampshire *et al.* 2020) with conditions of 'brain fog' that can cause mental deficit or the lowering of IQ akin to the mind aging by a decade (Leatham 2020) prompting calls for the search of COVID-19 vaccine or drugs to be expedited. Even without this new information, the current race for vaccine production and drug testing have already been beset by issues such as safety and efficacy (Khuroo *et al.* 2020). As the pandemic progresses, more mutations have been reported with some mutations changing the amino acids of the spike protein (Saha *et al.* 2020; Korber *et al.* 2020). The spike protein is responsible for the virus entry and *in silico* model has shown that one mutation has increased the binding efficiency of the virus to its target receptor protein (ACE-2) (Korber *et al.* 2020). Whether this mutation would enhance the virulence *in vivo* needs further confirmatory studies. Antigenic drift of the virus can lead to accumulation of immunologically relevant mutations such as the one mentioned and over time this will complicate vaccines efficacy. To date, vaccines for SARS, MERS and the other human coronaviruses have not been developed due to many issues including the waning of the viral infections for SARS and MERS. This and the mutations discovered is likely to compound the hindrance to the development of an effective vaccine in the near future (Koyama *et al.* 2020). Due to this, the use of other approaches including natural-based therapy concurrent to vaccine research

is needed. To complement current and future pharmaceuticals-based approach, there has been an increasing call to mobilize the use of antioxidants, functional foods and herbal-based antivirals to combat COVID-19 (Rastmanesh *et al.* 2020). In the early stages of the pandemic where China was the hardest hit by the virus, the use of traditional Chinese medicine (TCM) has already been initiated, understandably, by the failure of available medicines to treat infected patients (Law *et al.* 2020a; b). For instance, a press conference of the joint prevention and control mechanism of state council on the 17<sup>th</sup> of February, 2020 by the Publicity Department of the People's Republic of China reported that the use of TCM in 102 COVID-19 patients with mild cases leads to the disappearance time for the clinical symptom shortened by 2 days, body temperature recovery time shortened by 1.7 days and a shortening of 2.2 days for the average length of stay in hospital. In addition, it was also found that CT image improvement increases by 22%, a 33% increase in the clinical cure rate, a reduction in the rate of common to severe cases by 27.4% and an increase in lymphocyte count by 70%. In addition, a shortening of more than 2 days from the average length of stay in hospital in severe patients receiving TCM (Ren *et al.* 2020). In the SARS and H1N1 outbreak, Chinese herbal formula was utilized to combat the outbreak with reasonable success. This was based on historical records and human evidence and this has prompted researchers to suggest TCM as an alternative method to combat COVID-19 in combination with a rigorous population studies (Luo *et al.* 2020).

## **2. Plants as sources of antivirals**

The use of bioactive compounds from plant in antiviral research including COVID-19 is not new and has been competing with other research to discover new anticancer and antibiotics sources from plants (Bisen 2018). Plant active compounds from trees belonging to the family Calophyllaceae, for instance, contain compounds such as inophyllum, calanolide A and coumarins. Of these compounds, Calanolide A is a potent inhibitor to the non-nucleoside reverse transcriptase of HIV virus. This drug prevents the entry of HIV into healthy T-cells nucleus (Currens *et al.* 1996). Sarawak MediChem Pharmaceuticals (USA) was a company that attempted to further develop the drug for human use (Currens *et al.* 1996; Kp *et al.* 2015). The plant extracts from the Phyllanthus family; *P. urinaria* and *P. niruri* (locally known as “dukung anak”) are used in the clinical trials conducted at the Henan Institute of Medical Sciences, in China on 123 chronic Hepatitis B patients. It was observed that patients receiving *P. urinaria* plant extracts resulted in the seroconversion for the HBe-antibody status from negative to positive and undetectable Hbs antigen in the sera sample receiving the plant extracts (Wang *et al.* 1995). One of the top virus death cases in Malaysia is caused by the dengue virus. More than 80,000 cases were reported in 2019 with more than 100 deaths (Lee 2019). One of the top herbal remedies that emerges as a prime weapon for the dengue viral infection is *Carica papaya*, where the leaves extract or PLE has been tested in clinical environment in patients infected by the dengue virus. PLE safety records is well known as it is traditionally used for the treatment of diarrhea (Amzad Hossain *et al.* 2020). In two studies, platelets, white blood cells and neutrophils counts are back to normal after the administration of papaya leaves aqueous extract leading to the recovery of infected patients (Ahmad *et al.* 2011; Kumar *et al.* 2015). Further research has demonstrated that PLE decreases dengue complication through another route by inhibiting the viral production. A study suggests that PLE significantly lowers the expression of NS1 and envelope proteins in dengue virus-infected THP-1 cells. A significant lowering of the intracellular viral load supports PLE antiviral activity (Sharma *et al.* 2019). In addition, papaya extracts and papaya-associated phytochemicals possibly

enhance recovery in dengue infected patients through their anti-inflammatory and immunomodulatory properties (Pandey *et al.* 2016). A study shows that nine selected ligands from papaya (*Carica papaya*) leaves show good binding to viral proteins from dengue, influenza A (H1N9) and chikungunya (Narayanaswamy *et al.* 2017) indicating their potential development as drug candidates in the future. A large-scale pilot study involving 51 subjects in India receiving placebo and papaya leaves extract (PLE) show an improved platelet counts and viral clearance kinetics (Sathyapalan *et al.* 2020). In Malaysia, 228 patients afflicted with dengue fever and dengue hemorrhagic fever were subjected to an open-labeled randomized controlled trial using PLE as a potential cure. The results show that after 40 and 48 hours of admission there was a significantly higher increase in the mean platelet count in the intervention group compared to the control group (Subenthiran *et al.* 2013). The health benefits of papaya leaves juice in combating dengue is even acknowledged by the current Director General of Health of the Malaysian Ministry of Health (Anon 2014).

### **3. Papaya leaves extract as anti-inflammatory agent**

Further scrutiny of the literature including patents reveals more information regarding the potential role of PLE in disease treatment. For instance, in 2005, a Japanese pharmaceutical company filed a patent entitled “Compositions for cancer prevention, treatment, or amelioration comprising papaya extract”. The patent claims that the PLE can be used with few side effects for the treatment or prevention of many kinds of cancer such as stomach, lung, colon, pancreatic, leukemia or other kinds of blood cancers (Morimoto and Dang 2006). In 2009, a patent was filed by a French pharmaceutical company entitled “TNF-alpha inhibitor”. The gist of this patent is the use of PLE as an anti-inflammatory agent through inhibiting the secretion of the cytokine tumor necrosis factor-alpha or TNF-alpha (Binachon 2012). What is remarkable about these patents is that the papaya tree does not grow in these countries, but its remarkable properties have reached far and wide. The papaya tree originates from South America and is now widely grown in all tropical countries. It has numerous uses in fighting many illnesses. It is interesting to note that the patent holders above are relatively well-known pharmaceutical companies till this day and had spent tens of thousands of dollars to secure the patent in numerous countries. Another patent from India covers the usage of PLE to increase the blood platelet counts often seen in diseases including dengue infection (Alva and Thapar 2010). This patent is based on the numerous works available in the literature on the usage of PLE to fight dengue infection as mentioned above.

### **4. Potential role of Papaya leaves extract in severe COVID-19 treatment**

COVID-19 has not benefit from the usage of papaya extract to date, not yet, but there is a growing body of evidences that suggests its probable usage to combat COVID-19. In severe COVID-19 patients, cytokine storm is one of the most important mechanisms that lead to deaths of COVID-19-infected patients (Chen *et al.* 2020). Cytokine storm occurs when the lungs of infected patients become severely inflamed due to the massive overproduction of a host of mediators such as interleukins, interferons, TNF-alpha, macrophage and other factors which are lumped together as cytokines or chemokines. Cytokine storms often lead to infected cells dying through apoptosis and necrosis leading to severe tissue damage and hemorrhages triggering multiple organ failure (Tetro 2020; Chen *et al.* 2020; Yao *et al.* 2020; Ruscitti *et al.* 2020). Cytokine storms are dominantly characterized by the overproduction of cytokines such as IL-6 (interleukin-6) and TNF- $\alpha$  and are

involved in the pathogenesis and disease courses such as COVID-19 (Ragab *et al.* 2020; Robinson *et al.* 2020) and other afflictions such as asthma (Inam *et al.* 2017), leptospirosis leukemia (Kuo 2019) Actinobacteria-related diseases caused by *Mycobacterium leprae*, *M. tuberculosis* and *Tropheryma whipplei* (Lagier and Raoult 2014), sepsis caused by exotoxins and endotoxins (Cavaillon 2018) and the clinical severity of dengue infection (Masood *et al.* 2018). The current therapeutic strategy involves blocking the production of IL-6 and TNF-alpha, with several pharmaceutical companies running clinical trials on blocking the Interleukin IL-6 receptors (Sanofi, Regeneron and Roche) and Eusa Pharma with siltuximab that binds to interleukin IL-6. The results of the trials show limited success (Anon 2020). The role of PLE as an inhibitor to TNF-alpha may play a bigger role than its ability to inhibit IL-6 as it is more upstream than IL-6 in the inflammation pathway cascade (Tisoncik *et al.* 2012). The most current suggestion based on accumulated pieces of evidence has suggested that the focus should be on the use of anti-TNF therapy (Feldmann *et al.* 2020; Robinson *et al.* 2020). The possible use of PLE in alleviating cytokine storm has been demonstrated in dengue infection in mice model (Norahmad *et al.* 2019). Whether this is due to the inhibition of IL-6 or TNF-alpha or both deserve further studies but its usage to alleviate cytokine storm in COVID-19 in severe cases should be taken seriously by the medical community.

Other possible routes that bioactive compound from PLE can fight COVID-19 are through its rich antioxidant property and increasing the white blood, hemoglobin, lymphocyte and platelet counts. In one study, patients having virus-induced lung damage were given fermented papaya preparation for one month. The researchers observed an increase in salivary IgA and increase in phase II and superoxide dismutase enzyme expression levels, which are essential antioxidants in the respiratory tract (Marotta *et al.* 2012). In a more recent meta-analysis study, a pooled analysis in patients suffering of severe COVID-19 revealed a significantly lower platelet count while an even lower platelet count was observed with mortality in a study on the subgroup analysis which compare patients by their survival. In addition, a fivefold enhanced risk of severe COVID-19 is associated to a low platelet count based on four studies (n = 1427) that reported the data on the rate of thrombocytopenia (Lippi *et al.* 2020). In another study, COVID-19 patients exhibit lymphocytopenia, leukopenia and eosinophil cytopenia than those in non- COVID-19 patients (Li *et al.* 2020) which is very similar to what were observed in patients with dengue fever with significantly lower total white blood cells, neutrophil, and platelet counts (Ralapanawa *et al.* 2018).

More recent data has concluded that the hemoglobin level in COVID-19 patients is dangerously low (Lippi and Mattiuzzi). As PLE enhances the production of the white blood, hemoglobin, lymphocyte and platelet in humans, rabbit and rats (Sarala and Paknikar 2014; Ansari 2016; Khaliq *et al.* 2016; Hamidah *et al.* 2017), its application in these cases can probably help to alleviate the severity of the disease. COVID 19 patients also suffer from a lower level of the regulatory T cells to severely damaged cells in severe case (Qin *et al.* 2020). The severity of COVID-19 disease can be evaluated through monitoring the progress of lymphopenia or lymphocytopenia (Huang *et al.* 2020; Yang *et al.* 2020; Li *et al.* 2020). Intensive Care Unit (ICU) patients exhibit a marked reduction in CD4<sup>+</sup> and CD8<sup>+</sup> T cells with elevated levels of serum IL-6, IL-10, and TNF- $\alpha$  (Diao *et al.* 2020). At first, it was thought that the SARS-CoV-2 virus enter the T cells using the spike protein CD147 (Wang, Chen, *et al.* 2020; Wang, Xu, *et al.* 2020a), however this information was deemed premature (Wang, Xu, *et al.* 2020b) and more studies are needed to understand the

mechanism of T cells reduction in severe COVID-19. It has been demonstrated that PLE upregulates the Th1 (T Helper type 1, a subset of CD4<sup>+</sup> T cell) (Otsuki *et al.* 2010; Jayasinghe *et al.* 2017). The mature leaves papaya extract is also found to increase the lymphocyte counts on a rat model (Jayasinghe *et al.* 2017). A study on healthy human subjects show that the papaya fruit increases the regulatory T cells level (Abdullah *et al.* 2011) indicating another avenue for the bioactive compounds from papaya to improve the severity of COVID-19 in patients.

More recently, clinical studies have shown that coagulopathy is one of the pathogenesises of COVID-19. The major pathogenic mechanism based on a series of autopsy studies is coined 'Pulmonary Intravascular Coagulopathy-PIC' (McGonagle *et al.* 2020). In this phenomenon, the lungs become edematous exhibiting patchy hemorrhage with diffuse alveolar damage and the distended small vessels and capillaries become extensively inundated with fibrin thrombi (Belen-Apak and Sarialioğlu 2020) leading to the authors to recommendation on the use of anticoagulant/thrombolytic therapy. This study is interesting as it opens up the possibility of PLE and papaya bioactive compounds as a therapeutic agent for COVID-19 as far as anticoagulant/thrombolytic aspect is concerned. This is because PLE and papaya bioactive compounds from papaya latex contained cysteine proteases which displayed fibrinogenolytic and fibrinolytic activities. In one study, thrombus induced in the ear of hairless mice was treated with the latex fraction from the mountain papaya (*Carica candamarcensis*) and the major antithrombotic action of the latex fraction is suggested by the author through the mechanism of proteolytic cleavage of fibrinogen and fibrin (Bilheiro *et al.* 2013).

## 5. Conclusion

In conclusion, herbal medicine and plant-based extracts are natural-based therapy that can possibly complement drug-based treatment of COVID-19. As novel viruses continue to cause global concern including the current COVID-19 pandemic, more and more efforts are needed to combat virus-based afflictions in current and future scenarios. PLE has shown good records against the dengue virus with its immunomodulatory and cytokine storm-alleviating properties, a trait shared by COVID-19 complications and hence, PLE can possibly be harnessed to fight COVID-19 through similar routes.

### Author statement

Shukor, M.S. and Shukor, M.Y: Conceptualization, Shukor, M.S. Writing- Original draft preparation, Shukor M.Y.: Writing- Reviewing and Editing.

**Funding:** This research received no external funding

**Conflict of interest:** The authors declare that there is no conflict of interest

### Abbreviation

HBe	hepatitis B envelope protein
HBs	hepatitis B surface protein
IL-6	Interleukin-6
TNF-alpha	Tumor Necrosis Factor alpha

COVID-19	Coronavirus disease 2019
SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
PLE	Papaya leaves extract
ACE-2	Angiotensin-converting enzyme 2

## Reference

- Abdullah M, Chai P-S, Loh C-Y, Chong M-Y, Quay H-W, Vidyadaran S, Seman Z, Kandiah M, Seow H-F (2011) *Carica papaya* increases regulatory T cells and reduces IFN- $\gamma$ +CD4+ T cells in healthy human subjects. *Molecular Nutrition & Food Research* **55**, 803–806. doi:10.1002/mnfr.201100087.
- Ahmad N, Fazal H, Ayaz M, Abbasi BH, Mohammad I, Fazal L (2011) Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pacific Journal of Tropical Biomedicine* **1**, 330–333. doi:10.1016/S2221-1691(11)60055-5.
- Aisami A, Shukor MYA (2020) Predictive Mathematical Modelling of the Total Number of COVID-19 Cases for the Kingdom of Saudi Arabia. *Journal of Environmental Microbiology and Toxicology* **8**, 11–15.
- Aisami AB, Umar AM, Shukor MYA (2020) Prediction of Cumulative Death Cases in Indonesia Due to COVID-19 Using Mathematical Models. *Bioremediation Science and Technology Research* **8**, 32–36.
- Alva J, Thapar M (2010) Increasing low platelets instantly.  
<https://patents.google.com/patent/WO2010041263A1/en?q=%22papaya+leaves%22+dengue&oq=%22papaya+leaves%22+dengue&sort=old>.
- Amzad Hossain M, Hitam S, Hadidja Ibrahim Ahmed S (2020) Pharmacological and toxicological activities of the extracts of papaya leaves used traditionally for the treatment of diarrhea. *Journal of King Saud University - Science* **32**, 962–969. doi:10.1016/j.jksus.2019.07.006.
- Anon (2014) Papaya leaf juice can help in recovery from dengue fever. *The Star Online*.  
<https://www.thestar.com.my/News/Nation/2014/07/05/Papaya-leaf-juice-can-help-in-recovery-from-dengue-fever/>.
- Anon . (2020) Interleukin-6 Inhibitors. *COVID-19 Treatment Guidelines*.  
<https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/interleukin-6-inhibitors/>.
- Ansari RM (2016) Extract of *Carica papaya* L. leaves: Standardising its use in dengue fever. *Indian Journal of Pharmacology* **48**, 338–339. doi:10.4103/0253-7613.182892.
- Belen-Apak FB, Sarialioğlu F (2020) Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy. *Journal of Thrombosis and Thrombolysis* 1–3. doi:10.1007/s11239-020-02129-0.

- Bilheiro RP, Braga AD, Filho ML, Carvalho-Tavares J, Agero U, Carvalho M das G, Sanchez EF, Salas CE, Lopes MTP (2013) The thrombolytic action of a proteolytic fraction (PIG10) from *Carica candamarcensis*. *Thrombosis Research* **131**, e175–e182. doi:10.1016/j.thromres.2013.01.028.
- Binachon C (2012) Inhibiteur de TNF-alpha. <https://patents.google.com/patent/FR2973705A1/en?q=%22papaya+leaves%22+virus+-mosaic&oq=%22papaya+leaves%22+virus+-mosaic&sort=old>.
- Bisen P (2018) Therapeutic and Preventive Potential of Functional Food and Cancer. *Journal of Cancer Science and Research* **01**,. doi:10.4172/2576-1447.1000e101.
- Cavaillon J-M (2018) Exotoxins and endotoxins: Inducers of inflammatory cytokines. *Toxicon: Official Journal of the International Society on Toxinology* **149**, 45–53. doi:10.1016/j.toxicon.2017.10.016.
- Chen C, Zhang XR, Ju ZY, He WF (2020) [Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies]. *Zhonghua Shao Shang Za Zhi = Zhonghua Shaoshang Zazhi = Chinese Journal of Burns* **36**, E005. doi:10.3760/cma.j.cn501120-20200224-00088.
- Currens MJ, Mariner JM, McMahon JB, Boyd MR (1996) Kinetic analysis of inhibition of human immunodeficiency virus type-1 reverse transcriptase by calanolide A. *The Journal of Pharmacology and Experimental Therapeutics* **279**, 652–661.
- Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z, Feng Z, Zhang Y, Wu Y, Chen Y (2020) Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Frontiers in Immunology* **11**,. doi:10.3389/fimmu.2020.00827.
- Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T (2020) Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *The Lancet* **395**, 1407–1409. doi:10.1016/S0140-6736(20)30858-8.
- Hamidah A, Anggereini, E, Nurjanah . (2017) Effect of *Carica papaya* Leaf Juice on Hematology of Mice (*Mus musculus*) with Anemia. *Biosaintifika* **9**, 417–412.
- Hampshire A, Trender W, Chamberlain SR, Jolly A, Grant JE, Patrick F, Mazibuko N, Williams S, Barnby JM, Hellyer P, Mehta MA (2020) Cognitive deficits in people who have recovered from COVID-19 relative to controls: An N=84,285 online study. *medRxiv* 2020.10.20.20215863. doi:10.1101/2020.10.20.20215863.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* **395**, 497–506. doi:10.1016/S0140-6736(20)30183-5.

- Inam A, Shahzad M, Shabbir A, Shahid H, Shahid K, Javeed A (2017) *Carica papaya* ameliorates allergic asthma via down regulation of IL-4, IL-5, eotaxin, TNF- $\alpha$ , NF- $\kappa$ B, and iNOS levels. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* **32**, 1–7. doi:10.1016/j.phymed.2017.04.009.
- Jayasinghe CD, Gunasekera DS, De Silva N, Jayawardena KKM, Udagama PV (2017) Mature leaf concentrate of Sri Lankan wild type *Carica papaya* Linn. modulates nonfunctional and functional immune responses of rats. *BMC complementary and alternative medicine* **17**, 230. doi:10.1186/s12906-017-1742-z.
- Khaliq A, Asadullah, Ahmed A, Jehan F (2016) Hematopoietic potential of *Carica papaya* leaves in healthy rabbits. *Medical Channel* **22**, 51–56.
- Khuroo MS, Khuroo M, Khuroo MS, Sofi AA, Khuroo NS (2020) COVID-19 Vaccines: A Race Against Time in the Middle of Death and Devastation! *Journal of Clinical and Experimental Hepatology*. doi:10.1016/j.jceh.2020.06.003.
- Korber B, Fischer W, Gnanakaran SG, Yoon H, Theiler J, Abfalterer W, Foley B, Giorgi EE, Bhattacharya T, Parker MD, Partridge DG, Evans CM, Silva T de, LaBranche CC, Montefiori DC, Group SC-19 G (2020) Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. *bioRxiv* 2020.04.29.069054. doi:10.1101/2020.04.29.069054.
- Koyama T, Weeraratne D, Snowdon JL, Parida L (2020) Emergence of Drift Variants That May Affect COVID-19 Vaccine Development and Antibody Treatment. *Pathogens* **9**, 324. doi:10.3390/pathogens9050324.
- Kp M, Sharma N, Diwaker D, Ganju L, Sb S (2015) Plant Derived Antivirals: A Potential Source of Drug Development. *Virology & Antiviral Research* **2013**,. doi:10.4172/2324-8955.1000109.
- Kumar DrCVMN, Vadlamudi T, Venkatamuni A, Vardhan V, Prasad Y, Ravi U, D.V.R. S (2015) Therapeutic potential of *Carica papaya* l. leaf extract in treatment of dengue patients. *International Journal of Applied Biology and Pharmaceutical Technology* **6**, 93–98.
- Kuo D-M (2019) Pharmaceutical Composition for Decreasing The Side Effects of Pancreatic Cancer Drug, and Manufacturing Method and Uses Thereof. <https://patents.google.com/patent/US20190099424A1/en?q=%22papaya+leaf%22+%22interleukin-6%22+inhibitor&oq=%22papaya+leaf%22+%22interleukin-6%22+inhibitor&sort=old>.
- Lagier J-C, Raoult D (2014) Immune reconstitution inflammatory syndrome associated with bacterial infections. *Expert Opinion on Drug Safety* **13**, 341–350. doi:10.1517/14740338.2014.887677.



- Law S, Leung A, Chuanshan X (2020a) Is the traditional Chinese herb “Artemisia annua” possible to fight against COVID-19? *Integrative Medicine Research* **9**, 100474. doi:10.1016/j.imr.2020.100474.
- Law S, Leung A, Chuanshan X (2020b) Is the traditional Chinese herb, ‘Celastrol’ effective to combat COVID-19? *Journal of Materials and Environmental Science* **11**, 1205–1208.
- Leatham X (2020) Coronavirus causes ‘brain fog’, research suggests. *Mail Online*. <https://www.dailymail.co.uk/news/article-8882221/Coronavirus-causes-brain-fog-knock-eight-points-IQ-research-suggests.html>.
- Lee L (2019) Dengue death toll rises in Malaysia, number of cases close to double. *Reuters*. <https://www.reuters.com/article/us-malaysia-dengue-idUSKCN1V00D6>.
- Li YX, Wu W, Yang T, Zhou W, Fu YM, Feng QM, Ye JM (2020) [Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19]. *Zhonghua Nei Ke Za Zhi* **59**, E003. doi:3760.10/cma.j.cn112138-20200221-00114.
- Lippi G, Mattiuzzi C Hemoglobin value may be decreased in patients with severe coronavirus disease 2019. *Hematology, Transfusion and Cell Therapy*. doi:10.1016/j.htct.2020.03.001. Accessed 13 April 2020.
- Lippi G, Plebani M, Henry BM (2020) Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clinica Chimica Acta; International Journal of Clinical Chemistry* **506**, 145–148. doi:10.1016/j.cca.2020.03.022.
- Luo H, Tang Q, Shang Y, Liang S, Yang M, Robinson N, Liu J (2020) Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chinese Journal of Integrative Medicine* **26**, 243–250. doi:10.1007/s11655-020-3192-6.
- Marotta F, Naito Y, Jain S, Lorenzetti A, Soresi V, Kumari A, Carrera Bastos P, Tomella C, Yadav H (2012) Is there a potential application of a fermented nutraceutical in acute respiratory illnesses? An in-vivo placebo-controlled, cross-over clinical study in different age groups of healthy subjects. *Journal of Biological Regulators and Homeostatic Agents* **26**, 285–294.
- Masood KI, Jamil B, Rahim M, Islam M, Farhan M, Hasan Z (2018) Role of TNF  $\alpha$ , IL-6 and CXCL10 in Dengue disease severity. *Iranian Journal of Microbiology* **10**, 202–207.
- McGonagle D, Sharif K, O’Regan A, Bridgewood C (2020) Re: Patiently waiting for the results of anti-IL 6 therapy in severe COVID-19 infection. *Autoimmunity Reviews*. doi:10.1016/j.autrev.2020.102560.
- Morimoto C, Dang NH (2006) Compositions for cancer prevention, treatment, or amelioration comprising papaya extract. <https://patents.google.com/patent/WO2006004226A1/en?q=papaya+il-6>.

- Narayanaswamy R, KW L, ME N (2017) Molecular docking analysis of *Carica papaya* Linn constituents as antiviral agent. *International Food Research Journal* **24**, 1819–1825.
- Norahmad NA, Mohd Abd Razak MR, Mohamad Misnan N, Md Jelas NH, Sastu UR, Muhammad A, Ho TCD, Jusoh B, Zolkifli NA, Thayan R, Mat Ripen A, Zainol M, Syed Mohamed AF (2019) Effect of freeze-dried *Carica papaya* leaf juice on inflammatory cytokines production during dengue virus infection in AG129 mice. *BMC Complementary and Alternative Medicine* **19**,. doi:10.1186/s12906-019-2438-3.
- Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C (2010) Aqueous extract of *Carica papaya* leaves exhibits anti-tumor activity and immunomodulatory effects. *Journal of Ethnopharmacology* **127**, 760–767. doi:10.1016/j.jep.2009.11.024.
- Pandey S, Cabot PJ, Shaw PN, Hewavitharana AK (2016) Anti-inflammatory and immunomodulatory properties of *Carica papaya*. *Journal of Immunotoxicology* **13**, 590–602. doi:10.3109/1547691X.2016.1149528.
- Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian D (2020) Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. doi:10.1093/cid/ciaa248.
- Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R (2020) The COVID-19 Cytokine Storm; What We Know So Far. *Frontiers in Immunology* **11**,. doi:10.3389/fimmu.2020.01446.
- Ralapanawa U, Alawattagama ATM, Gunrathne M, Tennakoon S, Kularatne SAM, Jayalath T (2018) Value of peripheral blood count for dengue severity prediction. *BMC Research Notes* **11**,. doi:10.1186/s13104-018-3505-4.
- Rastmanesh R, Marotta F, Tekin I (2020) Call for mobilization of functional foods, antioxidants, and herbal antivirals in support of international campaign to control coronavirus. *Bioactive Compounds in Health and Disease* **3**, 90–94–94. doi:10.31989/bchd.v3i5.717.
- Ren J-L, Zhang A-H, Wang X-J (2020) Traditional Chinese medicine for COVID-19 treatment. *Pharmacological Research* **155**, 104743. doi:10.1016/j.phrs.2020.104743.
- Robinson PC, Richards D, Tanner HL, Feldmann M (2020) Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. *The Lancet Rheumatology* **2**, e653–e655. doi:10.1016/S2665-9913(20)30309-X.
- Ruscitti P, Berardicurti O, Iagnocco A, Giacomelli R (2020) Cytokine storm syndrome in severe COVID-19. *Autoimmunity Reviews* 102562. doi:10.1016/j.autrev.2020.102562.
- Saha P, Banerjee AK, Tripathi PP, Srivastava AK, Ray U (2020) A virus that has gone viral: Amino acid mutation in S protein of Indian isolate of Coronavirus COVID-19 might impact receptor binding and thus infectivity. *bioRxiv* 2020.04.07.029132. doi:10.1101/2020.04.07.029132.

- Sarala N, Paknikar S (2014) Papaya Extract to Treat Dengue: A Novel Therapeutic Option? *Annals of Medical and Health Sciences Research* **4**, 320–324. doi:10.4103/2141-9248.133452.
- Sathyapalan DT, Padmanabhan A, Moni M, P-Prabhu B, Prasanna P, Balachandran S, Trikkur SP, Jose S, Edathadathil F, Anilkumar JO, Jayaprasad R, Koramparambil G, Kamath RC, Menon V, Menon V (2020) Efficacy & safety of *Carica papaya* leaf extract (CPL) in severe thrombocytopenia ( $\leq 30,000/\mu\text{l}$ ) in adult dengue – Results of a pilot study. *PLoS ONE* **15**,. doi:10.1371/journal.pone.0228699.
- Sharma N, Mishra KP, Chanda S, Bhardwaj V, Tanwar H, Ganju L, Kumar B, Singh SB (2019) Evaluation of anti-dengue activity of *Carica papaya* aqueous leaf extract and its role in platelet augmentation. *Archives of Virology* **164**, 1095–1110. doi:10.1007/s00705-019-04179-z.
- Shukor MYA, Sabo IA, Yahuza S, Dan-Iya BI, Wada SA (2020) Prediction of Cumulative Death Cases in The United States Due to COVID-19 Using Mathematical Models. *Journal of Environmental Microbiology and Toxicology* **8**, 37–41.
- Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, Afzan A, Abdullah NR, Ismail Z (2013) *Carica papaya* leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. *Evidence-Based Complementary and Alternative Medicine: eCAM* **2013**, 616737. doi:10.1155/2013/616737.
- Tetro JA (2020) Is COVID-19 receiving ADE from other coronaviruses? *Microbes and Infection*. doi:10.1016/j.micinf.2020.02.006.
- Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG (2012) Into the Eye of the Cytokine Storm. *Microbiology and Molecular Biology Reviews : MMBR* **76**, 16–32. doi:10.1128/MMBR.05015-11.
- Uba G, Yakasai HM, Abubakar A, Shukor MYY (2020) Prediction of Cumulative Death Cases in Brazil Due to Covid-19 Using Mathematical Models. *Bulletin of Environmental Science and Sustainable Management (e-ISSN 2716-5353)* **4**, 13–19.
- Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, Gong L, Zhang Y, Cui H-Y, Geng J-J, Wang B, Sun X-X, Wang C-F, Yang X, Lin P, Deng Y-Q, Wei D, Yang X-M, Zhu Y-M, Zhang K, Zheng Z-H, Miao J-L, Guo T, Shi Y, Zhang J, Fu L, Wang Q-Y, Bian H, Zhu P, Chen Z-N (2020) SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *bioRxiv* 2020.03.14.988345. doi:10.1101/2020.03.14.988345.
- Wang M, Cheng H, Li Y, Meng L, Zhao G, Mai K (1995) Herbs of the genus *Phyllanthus* in the treatment of chronic hepatitis B: observations with three preparations from different geographic sites. *The Journal of Laboratory and Clinical Medicine* **126**, 350–352.

- Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S, Lu L (2020a) SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cellular & Molecular Immunology* 1–3. doi:10.1038/s41423-020-0424-9.
- Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S, Lu L (2020b) Retraction Note to: SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cellular and Molecular Immunology* 1. doi:10.1038/s41423-020-0498-4.
- Yahuza S, Sabo IA, Dan-Iya BI, Shukor MYY (2020) Prediction of Cumulative Death Cases in Nigeria Due to COVID-19 Using Mathematical Models. *Bulletin of Environmental Science and Sustainable Management (e-ISSN 2716-5353)* 4, 20–24.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine* 0,. doi:10.1016/S2213-2600(20)30079-5.
- Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D (2020) In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. doi:10.1093/cid/ciaa237.