

## Papaya leaves extract; a possible weapon against COVID-19?

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 a global scale. Researchers are still trying to find a cure and the vaccine to fight this disease. 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 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 Chinese herbal medicines and plant extracts which show good potential as inhibitors to several viruses including coronaviruses. Papaya leaves extract has been intensively studied for its antiviral, immunomodulatory and cytokine storm alleviating properties in dengue afflicted patients. These properties, especially the last two, hold promise for its capability as a possible weapon to fight COVID-19. This work attempts to put up a case for papaya leaves extract as a conceivable weapon to fight COVID-19.

### Introduction

Numerous plant extracts have yielded critical bioactive compounds that have been explored for their antiviral activities. Plant active compounds trees belonging to the family Calophyllaceae, for instance, contain bioactive compounds including 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. Sarawak MediChem Pharmaceuticals (USA) attempts 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 are reported in 2019 with more than 100 deaths reported (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 has been tested in clinical environment in patients infected by the dengue virus. 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 papaya leaves extract decreases dengue complication through another route by inhibiting the viral production. A study suggests that papaya leaves extract 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 papaya leaves extract 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 *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 show an improved platelet counts and viral clearance kinetics (Sathyapalan *et al.* 2020). In Malaysia, 228 patients afflicted with dengue fever and dengue haemorrhagic fever (DHF) were subjected to an open-labeled randomized controlled trial. 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 was even mentioned by the current Director General of Health of the Malaysian Ministry of Health in a newspaper article (Anon 2014).

As more and more wonderful properties of papaya leaves extract are reported in the literature, researchers began to use the extracted phytochemicals from the plant to combat other viral infections either *in vivo*, *in vitro* or *in silico*. The current global affliction caused by the SARS-CoV-2 virus is the novel virus that causes COVID-19. The use of herbal medicine to combat COVID-19 to complement drug and vaccine-based approach is understandable due to the severity and rather abrupt properties of the pandemic. In 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, it was reported that the use of traditional Chinese medicine (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).

COVID-19 has not benefited from the usage of papaya extract to date, not yet, but there is a growing body of evidences that suggest its probable usage to combat COVID-19. For a start, the anti-inflammatory and immunomodulatory properties of papaya leaves extract exhibited in dengue infection studies can probably increase the chances of COVID-19 patients in recovering from the infection. For instance, the papaya leaves extract is able to reduce the severity of cytokine storm in dengue infection in mice model (Norahmad *et al.* 2019). In addition, clinical trial on the papaya leaves extract on dengue fever found a decrease of 18% on the Interleukin IL-6 level of papaya leaves extract-treated patients and an increase of 13% in the placebos of the subgroup (Dipu T.

Sathyapalan *et al.* 2020). Therefore, papaya leaves extract is probably useful as an inhibitor candidate for the Interleukin IL-6 in reducing cytokine storm in COVID-19. 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, tumour necrosis factor, 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 haemorrhages triggering multiple organ failure (Tetro 2020; Chen *et al.* 2020; Yao *et al.* 2020). The inflammation of the lungs in the COVID 19 patient is due to Interleukin IL-6, an several companies are beginning clinical trials with the sole aim to inhibit IL-6. For example, the partnership of two companies— Sanofi and Regeneron leads to the running of a clinical trial using Kevzara, a fully-human monoclonal antibody to block the Interleukin IL-6 receptors (Anon 2020). Roche also uses the same strategy with Actemra, another Interleukin IL-6 receptors' blocker and anti-inflammatory. Furthermore, Eusa Pharma has developed siltuximab; a monoclonal antibody targeting interleukin IL-6 (Shah *et al.* 2020).

Other routes that bioactive compound from papaya leaves extract 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 SOD 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 are 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 papaya leaves extract 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 C *et al.*) due to the ability of the SARS-CoV-2 virus to enter T cells using the spike protein CD147 (Wang, Chen, *et al.* 2020; Wang, Xu, *et al.* 2020). A study on healthy human subjects show that papaya leaves extract increases the regulatory T cells level (Abdullah *et al.* 2011) indicating another avenue for the papaya leaves extract to improve the severity of COVID-19 in patients.

In conclusion, herbal medicine and plant-based extracts can complement drug-based treatment of viral diseases. As novel viruses continue to cause global concern including the current COVID-19 pandemic, more and more efforts are needed to be carried out to combat virus-based afflictions. The screening of more and more plant bioactive compounds has resulted in the development of potential treatments for HIV, HBV and even COVID-19. The bioactive compounds found can be further developed through combinatorial chemical approaches. Papaya leaves extract has shown good records against the dengue virus with its immunomodulatory and cytokine storm alleviating properties can possibly be harnessed to fight COVID-19. Consumption of papain leaf extract can probably help in fighting COVID-19 infection, but more studies are needed to support this premise. An important step for a start is the *in silico* docking behavior of potential ligands from papaya leaves extract to the papain-like COVID-19 protease; one of the main targets of COVID-19 antiviral drug screening strategy (Arya *et al.* 2020; Zhang *et al.* 2020).

### Conflict of interest

The authors declare that there is no conflict of interest

### 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.
- 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) Kevzara to be assessed by Sanofi and Regeneron to treat Covid-19. <https://www.pharmaceutical-technology.com/news/sanofi-regeneron-kevzara-covid-19/>.
- 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.
- Arya R, Das A, Prashar V, Kumar M (2020) Potential inhibitors against papain-like protease of novel coronavirus (SARS-CoV-2) from FDA approved drugs. doi:10.26434/chemrxiv.11860011.v2.
- 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.
- Hamidah A, Anggereini, E, Nurjanah . (2017) Effect of *Carica papaya* Leaf Juice on Hematology of Mice (*Mus musculus*) with Anemia. *Biosaintifika* **9**, 417–412.
- Khaliq A, Asadullah, Ahmed A, Jehan F (2016) Hematopoietic potential of *Carica papaya* leaves in healthy rabbits. *Medical Channel* **22**, 51–56.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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 (CPLE) 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.
- Shah GL, Murata K, Holder J, Marcello L, Cho S, Hoover E, Chung DJ, Dahi PB, Lahoud OB, Scordo M, Landau HJ, Giralt SA (2020) Improved Quality of Life with Interleukin-6 (IL-6) Blockade with Siltuximab Peri-Autologous Hematopoietic Stem Cell Transplantation (AHCT) in Older Patients with Multiple Myeloma (MM). *Biology of Blood and Marrow Transplantation* **26**, S129–S130. doi:10.1016/j.bbmt.2019.12.648.
- 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.
- 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.

- 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 (2020) 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.
- 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.
- Zhang D, Wu K, Zhang X, Deng S, Peng B (2020) In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *Journal of Integrative Medicine* **18**, 152–158. doi:10.1016/j.joim.2020.02.005.