

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

M.S. Shukor¹ and M.Y. Shukor²

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

²Department 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 vaccine are overwhelmingly virus-specific and newer drugs and vaccines are needed to resist new novel viral infections. The use of herbal remedies and plant-based extract 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 shows strong potential 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 and these properties, especially the last two holds promise for its possible weapon to fight COVID-19. This work attempts to put up a case for papaya leaves extract as a possible weapon to fight COVID-19.

Introduction

Numerous plant extracts have yielded important 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) began 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 viral. 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 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 were back to normal after the administration of papaya leaves aqueous extract and the infected patients recovered (Ahmad *et al.* 2011; Kumar *et*

et al. 2015). Further research has demonstrated that papaya leaf extract decrease dengue complication through another route by inhibiting viral production. A study suggests that papaya leaves extract significantly cause the expression of NS1 and envelope proteins to be lowered in DENV-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). A larger 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).

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 also known as 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 17th of February, 2020 by the Publicity Department of the People's Republic of China, a reported use of Chinese traditional medicine in 102 COVID-19 patients with mild cases, it was found that the disappearance time for the clinical symptom was shortened by 2 days, body temperature recovery time shortened by 1.7 days, a shortening of 2.2 days for the average length of stay in hospital. In addition, it was also found that CT image improvement was increased 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 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 prompt researchers to suggest Chinese herbal formula as an alternative method to combat COVID-19 combine with a rigorous population studies (Luo *et al.* 2020).

It has not benefit from the usage of papaya extract to fight its infection, 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 can increase an infected person chance of recovering from the infection. The papaya leaves extract is able to reduce the severity of cytokine storm in dengue infection in mice model (Norahmad *et al.* 2019). 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, and Sanofi and Regeneron are running a Clinical trial named Kevzara a fully-

human monoclonal antibody to block the Interleukin IL-6 receptors (Anon 2020). Clinical trial on the carica papaya leaf extract (CPLE) on the dengue fever found a decrease of 18% on the Interleukin IL-6 of the treated patients with (CPLE) and an increase of 13% in the placebos of the subgroup (Dipu T. Sathyapalan et al. 2020). Therefore (CPLE) is probably useful as an inhibitor candidate for the Interleukin IL-6 in reducing cytokine storm in COVID-19. Several pharmaceutical companies are running clinical trials on the possibility in combating COVID-19 by targeting the interleukin IL-6 inhibitors, they are Sanofi and Regeneron with a Clinical trial named Kevzara, a fully human monoclonal antibody to block the Interleukin IL-6 receptors. (Sanofil and Regeneron), Roche with Actemra, it acts as Interleukin IL-6 receptors' blocker and anti-inflammatory (Roche), Eusa Pharma with siltuximab a monoclonal antibody targeting interleukin IL-6 (Eusa Pharma). Clinical trial on the carica papaya leaf extract (CPLE) on the dengue fever found a decrease of 18% on the Interleukin IL-6 of the treated patients with (CPLE) and an increase of 13% in the placebo's subgroup (Dipu T. Sathyapalan et al. 2020). Therefore (CPLE) is probably useful as an inhibitor candidate for the Interleukin IL-6 in reducing the COVID 19 Cytokine Storm.

In another 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). 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).

In conclusion, herbal medicine and plant-based extracts can complement drug-based treatment of viral diseases. As virus continue to cause global concern including the current pandemic caused by COVID-19, more and more efforts need to be carried out to combat this affliction. The screening of more and more plant bioactive compounds has resulted in the development of potential treatment for HIV, HBV and even COVID-19. The bioactive compounds found can be further developed as other compound through combinatorial chemical approaches. Papaya leaves extract has shown good records against the dengue viral with its immunomodulatory and cytokine storm alleviating properties can possibly be harnessed to fight COVID-19.

Reference

- 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 (2020) Kevzara to be assessed by Sanofi and Regeneron to treat COVID-19. <https://www.pharmaceutical-technology.com/news/sanofi-regeneron-kevzara-COVID-19/>.

- 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.
- 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>.
- 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.

- 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.
- 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.
- 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.
- Tetro JA (2020) Is COVID-19 receiving ADE from other coronaviruses? *Microbes and Infection*. doi:10.1016/j.micinf.2020.02.006.
- 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.
- 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.

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

M.S. Shukor¹ and M.Y. Shukor²

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

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

COVID-19 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 vaccine are overwhelmingly virus-specific and newer drugs and vaccines are needed to resist new novel viral infections. A shift towards herbal remedies to fight viral infections is an approach that can be explored especially in poorer countries or when drugs and vaccines are still not available. One of the top herbal remedies that emerges as a prime weapon for 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 were back to normal after the administration of papaya leaves aqueous extract and the infected patients recovered (Ahmad et al. 2011; Kumar et al. 2015). Further research has demonstrated that papaya leaf extract decrease dengue complication through another route by inhibiting viral production. A study suggests that papaya leaves extract significantly cause the expression of NS1 and envelope proteins to be lowered in DENV-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).

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. SARS-CoV-2 is the novel virus that causes COVID-

19. It has not benefit from the usage of papaya extract to fight its infection, 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 can increase an infected person chance of recovering from the infection. The papaya leaves extract is able to reduce the severity of cytokine storm in dengue infection in mice model (Norahmad et al. 2019). 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 the Interleukin IL-6, Sanofi and Regeneron is running a Clinical trial named Kevzara a fully-human monoclonal antibody to block the Interleukin IL-6 receptors. (Sanofil and Regeneron). Clinical trial on the carica papaya leaf extract (CPLE) on the dengue fever found a decrease of 18% on the Interleukin IL-6 of the treated patients with (CPLE) and an increase of 13% in the placebos subgroup (Dipu T. Sathyapalan et al. 2020). Therefore (CPLE) can be used as an inhibitor candidate for the Interleukin IL-6 in reducing the COVID 16 Cytokine Storm.

In another 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). 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).

Reference

- 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.
- 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.
- 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.
- 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.
- Sanofi & Regeneron <https://www.pharmaceutical-technology.com/news/sanofi-regeneron-kevzara-COVID-19/>
- 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.
- Tetro JA (2020) Is COVID-19 receiving ADE from other coronaviruses? *Microbes and Infection*. doi:10.1016/j.micinf.2020.02.006.
- 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.

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 Dipu T. Sathyapalan et al 2020, plosone)