

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

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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 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. 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 (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 using papaya leaves extract 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 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*.

COVID-19 is the current global affliction caused by the SARS-CoV-2 virus. The use of herbal medicine to combat COVID-19 in complementing drug and vaccine-based approaches 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, 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).

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 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 development of an effective vaccine in the near future. Hence, the use of other approaches including plant-based extracts is not something to be dismissed.

COVID-19 has not benefit 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; Ruscitti *et al.* 2020). The inflammation of the lungs in the COVID 19 patient is due to sustained level of interleukin IL-6 (McGonagle *et al.* 2020b), and it is one of the targets for reducing the severity of COVID-19 (McGonagle *et al.* 2020a). Currently, 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 *et al.* 2020) 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). 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). In another clinical study in Shanghai, China, COVID-19 patients show a decline in the lymphocyte count and CD4⁺ Th1 (Cao *et al.* 2020) (Min *et al.* 2020). It has been demonstrated that papaya leaves extract upregulates the Th1 (T Helper type 1, a subset of CD4⁺ 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.* 2020a). In this phenomenon, the lungs become oedematous exhibiting patchy haemorrhage with diffuse alveolar damage and the distended small vessels and capillaries become extensively inundated with fibrin thrombi (Belen-Apak and Saralioğlu 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 papaya leaves extract and papaya bioactive compounds as a therapeutic agent for COVID-19 as far as anticoagulant/thrombolytic aspect is concerned. This is because papaya leaves extract 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).

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

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