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**EVIDENCE OF COMPLEMENTARY AND PROPHETIC MEDICINE IN THE
MANAGEMENT OF DENGUE INFECTION*****Dapatan Kajian Perubatan Komplimentari dan Sunnah dalam Perawatan Jangkitan Demam
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Abstract

Dengue fever is a viral infection caused by dengue virus that is transmitted via mosquitoes. Increased mortality from the infection also shows that the threat is real. Definitive treatment such as antiviral therapy has not been established and anti-dengue vaccination development was hampered by unprecedented issues. Therefore, alternative treatments have to be sought out. With the cultural diversity and the availability of various tropical plants and food, people in this region have tried and studied various complementary ailments for the infection. People also are looking towards a prophetic approach in preventing and treating dengue infection. This paper illustrates dengue infection from the epidemiological point of view, the standard therapy and issues pertaining to the infection. This paper also discusses complementary treatments of dengue infection such as *Carica papaya* leaf, coconut juice, *Euphorbia hirta* and *Psidium guajava* leaf. Scientific evidence of the effectiveness of these treatments is explained in detail. This paper also looks at the scientific evidence and literatures by Islamic scholars with regards to the use of prophetic methods in the treatment of dengue infection. Dates were shown to be effective in increasing platelet counts. In conclusion, complementary and prophetic medicine may benefit patients with dengue fever infection as an adjunct therapy.

Keywords: Dengue fever, Complimentary, Prophetic, *Carica papaya*, *Euphorbia hirta*, *Psidium guajava*, dates.

Abstrak

Demam denggi adalah jangkitan virus denggi yang disebarkan melalui gigitan nyamuk. Peningkatan kematian akibat jangkitan juga menunjukkan keseriusan jangkitannya. Rawatan khusus seperti terapi antiviral belum lagi wujud dan penggunaan vaksin anti-denggi terhalang oleh kesan buruk. Oleh itu, rawatan alternatif telah dikaji dan dicari. Dengan kepelbagaian budaya dan pelbagai tumbuhan tropika dan makanan, pengkaji di rantau ini telah mencuba dan mempelajari pelbagai penawar untuk jangkitan denggi. Pengkaji juga meninjau pendekatan

sunnah dalam mencegah dan merawat jangkitan denggi. Kertas ini menerangkan jangkitan denggi dari sudut pandang epidemiologi, terapi standard dan isu berkaitan dengan jangkitan. Kertas ini juga membincangkan rawatan sampingan denggi seperti daun betik, jus kelapa, *tawatawa* dan daun jambu batu. Bukti saintifik mengenai keberkesanan rawatan ini diterangkan secara terperinci. Kertas ini juga melihat bukti saintifik dan literatur oleh sarjana Islam berkaitan dengan penggunaan kaedah sunnah dalam rawatan jangkitan denggi. Kurma didapati berkesan untuk meningkatkan bilangan platelet. Sebagai kesimpulan, terapi sampingan dan terapi sunnah boleh memberi manfaat kepada pesakit dengan jangkitan demam denggi sebagai terapi tambahan.

Kata kunci: Demam denggi, terapi sampingan, kaedah sunnah, *Carica papaya*, *Euphorbia hirta*, *Psidium guajava*, kurma.

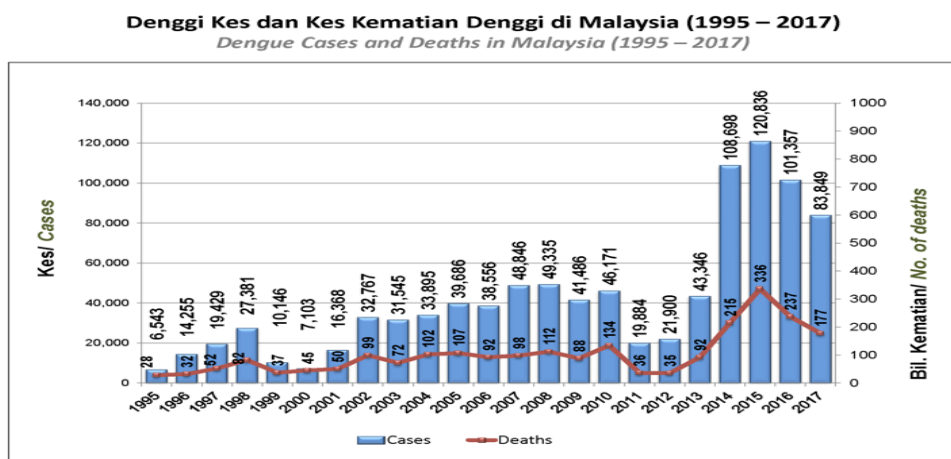
INTRODUCTION

Dengue fever is an arthropod-borne disease caused by a family of viruses known as flaviviridae genus flavivirus (also referred as arbovirus)(Gould and Solomon 2008) It is transmitted by mosquitoes of *Aedes* species particularly *Aedes aegypti* and *Aedes albopictus* (WHO 2012). A person can contract dengue virus when he or she was bitten by a female *Aedes* mosquito which carries the viruses inside its gut. With a single bite, it transmits the viruses through its saliva into the human blood circulation. The mosquito itself would not be affected by the virus and the virus would remain inside its body for life. Hence, they can spread the virus to others with another bite.

The prevalence of dengue fever has increased tremendously since the 1960s, with around 50 to 528 million people are infected annually (Bhatt et al. 2013). Nowadays, it is endemic in more than 100 countries including Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. It affects globally but mainly in tropical and subtropical climate region and affects mostly urban rather than the suburban areas. In these regions, about a third of the population is at risk of the dengue infection (CDC 2012).

Dengue fever is a serious concern in Malaysia with escalating number of cases. Although the incidence decreased in 2011 and 2012, the number surged back up in 2014 as the reported cases reached six-figures (108,698 cases). The highest incidence was in 2015 with 120, 836 cases and 336 deaths.

Figure 1: Statistics on dengue cases and dengue deaths in Malaysia from 1995-2017



Note: (Adapted from Agensi Remote Sensing Malaysia (ARSM) at <http://idengue.remotesensing.gov.my/idengue/page2.php?kandungan=content/statistik.pdf>. (Malaysia 2018)

Despite increasing incidence and mortality rate in dengue cases, to date, there is neither curative nor preventive therapies. Management are mainly supportive and symptomatic. Early recognition and diagnosis are crucial to substantially lower the risk of severe complications. These severe complications include dengue hemorrhagic fever, dengue shock syndrome and eventually death.

Scientists and researchers all over the world have done tremendous efforts to find the cure and prevent dengue infection. This includes the invention of dengue vaccines which commenced since as early as 1929 but had been hindered by incomplete understanding of the disease pathogenesis. Apart from that, difficulty of developing vaccines are also due to the presence of multiple dengue serotypes. To date, the most advanced vaccine is a live attenuated chimeric vaccine (Thisyakorn and Thisyakorn 2013). The vaccines are available in the market since 2016. However, it is found to pose an increasing risk of severe virologically confirmed dengue in those who had never been exposed to dengue prior to vaccination (Sridhar et al. 2018).

Other than the vaccine development, people in certain dengue endemic areas have started to acknowledge the natural treatment for dengue. In Malaysia, among the common and popular traditional practice for dengue are the use of papaya leaves, crab soup and coconut water. Many reports from articles, newspapers and magazines had suggested and showed the benefits of the use of these natural treatments for patients with dengue. It is believed that many dengue patients experienced rapid recovery with the use of these alternative treatments. Hence, in this report, we analyze the literature reviews with regards to the advancement in dengue treatment through the use of complementary medicine. Do they really work or are speedy recovery just a coincidence?

Current Standard Management of Dengue Fever

There is no specific antiviral treatment for dengue. It is a self-limiting illness and in most cases, patients usually recover within 2 weeks if there is no complication. Hospitalization is required when there is a need for fluid replacement under close supervision or if the platelets level is low which need further monitoring for bleeding tendencies. Otherwise, it can be managed as outpatient especially if the patient is able to drink lots of fluids and attend the nearby health facility for daily blood monitoring from the third day of illness until 1-2 days after recovery phase (World Health Organization (WHO) 2016).

In general, supportive and symptomatic management with the aim to prevent complications remain the mainstay of dengue treatment. Supportive treatments include bed rest with fluid replacement therapy or in severe cases, packed cells or platelet transfusion maybe needed. For symptomatic treatment, mild analgesic-antipyretic therapy can be used to relieve lethargy, malaise, and fever. However, aspirin, other salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided as this increase the tendency of bleeding. The role of antiviral medication is questionable and is still under research (Wiwanitkit 2010).

COMPLEMENTARY MEDICINE FOR DENGUE

Dengue is not a new disease to the world unlike emerging diseases like H1N1 or severe acute respiratory syndrome (SARS). However, in comparison with other viral diseases, there is still no available approved antiviral drug or vaccine for dengue. This could be the main reason for some people to start focusing on complementary medicine especially those derived from plants

and other natural sources which are considered to be safe and non-toxic. To date, there are about 31 different species of plants have been found to have the potential to treat dengue. Among them, about ten phytochemicals have been isolated from 11 species of plants. Research and investigations have been carried out on these different plant extracts which showed some evidence of anti-viral activity on dengue virus and help to improve the dengue patient's condition (Idrees and Ashfaq 2012; Patil et al. 2014).

In Malaysia, among the popular natural treatment used in dengue management are papaya leaf juices, crab soup and coconut water (Ching et al. 2016). Among all, the use of papaya leaf extract is perhaps the most renowned alternative treatment for dengue and multiple studies have been carried out in dengue endemic countries looking towards the benefits of this herbal remedy. In this writing, we discussed on several complementary treatments for dengue fever which includes papaya leaf, crab soup, young coconut, tawa-tawa and guava leaf.

Dengue and Use of Papaya Leaf

Papaya or botanically known as *Carica papaya* is the plant of species in the genus *Carica* of the plant family *Caricaceae*. It is a well-known tropical plant which originated in Central America but is currently grown and cultivated in many other tropical areas worldwide (van Wyk, 2005). The fruit contains a rich source of vitamins such as Vitamin C, A, B, and E and other nutrients and minerals. The plant is popular not only due to its delicious and healthy fruit, but the whole parts of the plant like roots, bark, leaves, seeds and pulp are also known to have medicinal properties (Aravind et al. 2013).

As for dengue, the leave of *C. papaya* was found to exhibit potent inhibitory activity against dengue fever. This is because in dengue infection, thrombocytopenia is the main problem that leads to complication like dengue hemorrhagic fever, and *C. papaya* leaves have been believed to have beneficial effect on the increment of platelet count.

The first study of *C. papaya* leaf extracts in patients suffering from dengue fever was reported in the Sri Lanka in 2008 by Dr Hettige who did the pilot study on 12 dengue fever patients found that papaya leaf juice helps to increase the total white cell counts, platelet counts and patients gain recovery without hospital admission (Hettige 2008). In 2009, another study has been done in which the *C. papaya* leaf suspension was administered into mice and it showed significantly increased in mean platelet counts after certain hours compared to placebo group (Sathasivam et al. 2009). Then, a case report by Ahmad et al. (2011), have showed that aqueous leaf extracts of *C. papaya* can help to increase the platelets count, white blood cells (WBC) and neutrophils in a patient infected with severe dengue fever.

However, a study done in 2011 showed that *C. papaya* leaf extract did not show any effect on platelet count in dengue fever patient and it emphasized that the previous three studies done which showed that platelet increased after the use of papaya leaf extract may be a consequence of natural course of illness and nothing more than a placebo effect (Assir et al. 2011).

In 2012, several studies have been done on effects of *C. papaya* leaf towards dengue. In India, one study showed increased in platelets count in 5 patients after 24 hours of administration of *C. papaya* leaves extract (Prakash Kala 2012). In Indonesia, a randomized control trial done showing that *C. papaya* leaf extract capsule can be used as complementary medicine in dengue patients as it caused significant increase in platelet count, maintaining the stability of haematocrit level and shortens the hospitalization period (Yunita, Hanani, and Kristianto 2012). In Sri Lanka, an in vivo study on rats, revealed that oral administration of freshly prepared and mature concentrated *C. papaya* leaf had increased the platelets, WBC and red blood cells

(RBC) counts and also inhibit oedema and vascular permeability and showing maximum membrane stabilizing activity of the rat's RBCs (Gammulle et al. 2012). Then, there was an in vitro study first reported also in Sri Lanka which showed that *C. papaya* leaf extracts have biological membrane stabilization properties which can inhibit stress-induced hemolysis (Ranasinghe et al. 2012).

There are many more research and studies done after that and most of it focused on determining the active metabolites and components in *C. papaya* leaf that have anti-dengue effects. In 2013, a group of Malaysian researchers have conducted an open-label randomized controlled trial which revealed that juice extracted from papaya leaves helps increase the platelet count in patients with dengue fever. They have reported that the genes, ALOX 12 and PTAFR were highly expressed among those administered with the juice and these genes could inhibit the growth of dengue virus and have maximum activity against DENV-2 replication plus involving in the mutation of the virus which is said to be common in Malaysia (Subenthiran et al. 2013). Further study by Senthilvel et al. (2013), suggested that the flavonoid quercetin from *C. papaya* leaf have significant anti-dengue activities by blocking the viral assembly mechanism of DENV2 virus. Joseph et al. (2015), in their in vitro study proposed that both methanolic and chloroform extracts taken from *C. papaya* leaf have anti-dengue effects. However, the methanolic extracts, containing triterpenoids and flavonoids, showed more cytotoxic effects compared to chloroform extract which contained alkaloids, tannin and saponin. There are a few studies which suggest that the *C. papaya* leaf extract possess anti-oxidant activity which can help to improve the condition of patients infected with dengue. This strong antioxidant property is associated with the high content of phenolics, flavonoids, proteins and vitamin C in the *C. papaya* leaf preparation (Begum 2014; Joseph et al. 2015). There is also a study which claimed that *C. papaya* had a stimulatory effect on haemopoiesis in the bone marrow thus helps to increase platelet production (Tham et al. 2013).

Other than in vivo study done on mice by Dharmarathna et al. (2013) and Tahir et al. (2014), showing positive evidence of increased platelets and RBC counts in dengue patients. This findings further supported by Arya and Agarwal (2014; Deepak, Girish, and Lakshmiprasad (2013); and Siddique, Sundus, and Faisal Ibrahim (2014). One of the study demonstrated that the improvement is better in younger age patient as compared to elderly (Rehman 2014).

Meanwhile in terms of adverse effect, the *C. papaya* leaf extract is said to be non-toxic and safe to be used. Toxicity study conducted on rats administered with *Carica papaya* leaves juice revealed that it is safe for oral consumption (Afzan et al. 2012; Halim et al. 2011). Based on the clinical study on human, there is no reported adverse effects occurred in the dengue patients after consumption of the leaf extract. Nevertheless, there is one study done on mice showing that consumption of *Carica papaya* leaf extract for longer period might be associated with hepatotoxicity and risk for cardiovascular disease (Sheikh, Younas, and Akhtar 2014).

In summary, papaya leaf extract has shown many positive effects in increasing the platelet level either in human or animal model experiment. It also helps to increase WBC, stimulate hemopoiesis and have antiviral properties towards dengue virus. However, there is need for more research and study to determine the optimal dose and preparation of papaya leaf for use in hospital settings.

Dengue and Use of Coconut Water

Young coconut water has been suggested by old folks to manage dengue fever. Dengue patients are also advised to consume lots of fluid to restore the body fluid losses through sweat, vomiting and diarrhea (Lum, Ng, and Khoo 2014). It is believed that the electrolytes and minerals content in coconut water is preferable for the body ion replacement as the component

is similar to the body's fluid (Evo, 2013). There is also an article stating that coconut oil contains antibacterial, antiviral and antifungal properties and this can be attributed to the presence of lauric acid. Our body will convert lauric acid into another compound called monolaurin which is responsible for the antiviral and antibacterial properties of coconut oil (Shaun Damon n.d.).

Dengue and Use of *Tawa-Tawa (Euphorbia Hirta)*

Euphorbia hirta is a type of herbal weed belonging to the family of Euphorbiaceae. It is native in India but can also be found throughout Java, Sunda, Sumatra, Peninsular Malaysia, the Philippines and Vietnam (Sarangi, 2014; SM et al. 2009). It is known as *tawa-tawa/gatas-gatas* in Philippines, *gelang susu* in Malaysia or asthma plant/snakeweed in English (Kritikar, 2012). *E. hirta* is popular in traditional old folk's medicine for respiratory and gastrointestinal and female disorder and also used for worm infestation in children and tumors (Kumar, Malhotra, and Kumar 2010).

In the Philippines, this hairy plant is commonly used to treat dengue by people living in rural areas as it is believed to be able to reverse the viral infection and prevent the fever from progressing into critical phase (Sarangi, 2014). There is an in vivo study done on rats in 2012 by a student from University of Santo Tomas (UST), Philippine showing that tawa- tawa is able to promote cell production, prevents platelet destruction and preserve and promote the hemostatic function of platelets of rats with induced-thrombocytopenia (Raynes et al. 2012). Another study done showing that the anti-thrombocytopenic effect of *E. hirta* is attributable to its polyphenolic antioxidant constituent which contributes to the protective effect on platelets (Apostol et al. 2012).

These findings are supported by evidence from one study done in Nigeria showing that *E. hirta* can help to arrest bleeding and modulate homeostasis (Omeje et al. 2007). Then, there is another clinical study done in Pakistan which showed that majority of dengue patients had improvement on their platelet count and leukopenia after use of aqueous extracts of *E. hirta* (Munazza et al. 2012). However, the mechanism of action of this plant is still unknown and the antiviral and anti-thrombocytopenic properties are currently under investigation. In terms of adverse effect, there is not enough information available to know whether this plant is safe or not but based on a study done showed that *E. hirta* extract is non-toxic in all the doses studied and did not cause any lethality or produce any remarkable histopathological signs or serum chemical alteration in rats (Yuet Ping et al. 2013).

A systematic review by Jayasinghe and Jayawardena (2018), concluded that available evidence conclusively demonstrates the potential of *E. hirta* against dengue as it holds significant antiviral and platelet increasing activities. However, the number of studies conducted to validate its anti-dengue activity was found to be inadequate.

Dengue and Use of Guava (*Psidium Guajava*)

Psidium guajava or commonly known as guava belong to family Myrtaceae. It is commonly being cultivated in tropical and subtropical country (Abd Kadir, Yaakob, and Mohamed Zulkifli 2013). Several studies had been done mostly in Indonesia which showed that both guava juice and leaf extract has positive effect on dengue patients. Quercetin (tannin and flavonoid) which is found in the leaf extract of guava has been shown to demonstrate anti-viral properties and was able to reduce viral replication of the dengue virus (Muharni, Martini, and Dinda, 2013).

Then, for the in vivo studies, there is one research done revealed that combinations of red yeast rice, and guava fruit give significant enhancement of platelet count in mice while another study

showed guava juice help to improve platelets count and decrease hematocrit in dengue patients (Agustinus,2009 ; Rosary, 2012). Most recently, Prasetio (2015) in his study proved that the red guava contains vitamin C, tannins, and flavonoids that can enhance the immune system and thus inhibit the replication of dengue virus and increased platelet levels in patient with dengue fever. In terms of toxicity, it is shown that based on toxicity studies done in mice and other animal models as well as controlled human studies proved that both guava leaf and fruit are safe to be use without producing any side effects. Conversely, it was shown to have good hepatoprotective effect (Kamath et al. 2008; Roy, Kamath, and Asad 2006).

PROPHETIC DIET IN DENGUE TREATMENT

In Islam, our main guidance in life is Quran and Sunnah (prophetic tradition) and it is obligatory for us to follow and to rely on these two sources in performing our daily activities. In terms of food, there are numerous Quranic verses and Hadith which recommended us on certain foods to be taken due to their healing properties. As for the prophetic food (the food that our prophet liked and suggested), there are about 12 foods which our beloved prophet Muhammad PBUH regularly mentioned in his sayings. These include Habbatus sauda, melon, figs, barley, milk, pomegranate, honey, dates, vinegar, pumpkin, mushroom and olive.

Dates or scientifically known as *Phoenix dactylifera*, is one of the popular prophetic foods which is currently being commercialized into many health products. It is claimed to be the emerging medicinal food and many studies has been done to prove its potential health benefits. In the Holy Quran, dates have been mentioned for about twenty times. In fact, in Surah Maryam verse 25 (Ali ,2011), it is the food advised to be eaten by Maryam (a.s.) at the time of her delivery to Prophet Isa (a.s.).

Regarding the use of dates in treating dengue fever, there is one study done in Indonesia which investigates the effects of giving dates juice in increasing the thrombocyte count in dengue haemorrhagic fever patients (Giyatmo, 2013). From the study, the result revealed that *P. dactylifera* juice help to improve the trombocytes count significantly. Then, another study done showed that the extract from date palm cause increased in thrombocyte and megakaryocyte trend in induced- thrombocytopenic rats (Wiyasihati, Wigati, and Wardani 2013). The mechanism of action is unknown but it is believed to be due to the strong anti-oxidant properties from carotenoids and phenolics which are found in *P. dactylifera* (Al-Farsi and Lee 2008).

CONCLUSION & SUGGESTION

To date, there is no exact cure for dengue or any available vaccine despite the rising number of cases. Each day, more people are getting infected by this flavivirus. Scientists and several research teams are still working on perfecting the vaccine and finding its cure.. Till now, the only way to control this disease is mainly via preventing the spread of virus through mosquitoes. The examples would be by destroying the breeding place for the mosquitoes, fogging, usage of mosquito nets and insect repellent, and enhancing personal protection such as wearing long sleeves or staying indoors during times which the Aedes mosquitoes are most active. Since dengue is becoming a widespread global infection and is one of the leading health problems not only in Malaysia but also in other countries as well, the focus to find cure for it has attracted the concerns of many. While waiting for the perfect vaccine, people started to exhibit their interest towards alternative or complementary medicine. With no clear- cut treatment from modern medicine, it is not surprising that the absolute cure might actually lie in nature.

There are numerous plants has been reported to exhibit anti-dengue activities and several researches have been done on these plants to dissect the active component of these plants. Some did show promising result in terms of efficacy to treat dengue either by increasing platelet counts, restoring body nutrients and electrolytes, or by preventing hemolysis.. However, most of the studies and research on these complementary medicines are still limited in terms of their study design, sample size and standardized preparation and dose. Most of the studies were unable to determine the active curative components from the plant extract. Hence, there is a need to conduct more studies as the information is still inadequate. Further studies in the future should focus more on the active components and their mechanism of actions, doses, adverse effects and toxicity and should include large scale of clinical trial in human.

In conclusion, the use of complementary medicine in treating dengue is an acceptable practice as it showed positive impact in many studies. Furthermore, it is also shown to have no adverse effect on the patient. However, this should not refrain the patients who contract dengue fever from seeking the treatment at their nearest health care provider as soon as possible as the main management for dengue patient is to maintain the body's fluid and relieve the symptoms.

Based on the findings, local film industry is in the process to revive itself to its former glory. After the slowdown process of the Malaysian film industry in 70's and 80's, with the help of Malaysian government through Economy Transformation Programme, National Film Policy and National Creative Industry Policy, impetus was to the industry. The consistent assistance by the Malaysian government is needed to nurture and spur the industry...

REFERENCES

- Abd Kadir, S. L., Yaakob, H., & Mohamed Zulkifli, R. (2013). Potential anti-dengue medicinal plants: A review. *Journal of Natural Medicines*. <https://doi.org/10.1007/s11418-013-0767-y>.
- Afzan, A., Abdullah, N. R., Halim, S. Z., Rashid, B. A., Semail, R. H. R., Abdullah, N., . Ismail, Z. (2012). Repeated dose 28-days oral toxicity study of *Carica papaya* L. Leaf extract in Sprague Dawley rats. *Molecules*. <https://doi.org/10.3390/molecules17044326>
- Agustinus, A. (n.d.). Hematologic Study of Metabolic Potention Red Guava (*Psidium guajava* L.) on Dengue Hemorrhagic Fever (DHF) Patient.
- Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B. H., Mohammad, I., & Fazal, L. (2011). Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pacific Journal of Tropical Biomedicine*. [https://doi.org/10.1016/S2221-1691\(11\)60055-5](https://doi.org/10.1016/S2221-1691(11)60055-5).
- Al-Farsi*, M. A., & Lee, C. Y. (2008). Nutritional and functional properties of dates: a review. *Critical Reviews in Food Science and Nutrition*, 48(10), 877–887.
- Ali, M. M. (2011). *Holy Quran*. Ahmadiyya Anjuman Ishaat Islam Lahore USA.
- Apostol, J. G., Gan, J. V. A., Raynes, R. J. B., S, A. A., Carigma, A. Q., Santiago, L. A., & Ysrael, M. C. (2012). Platelet-Increasing Effects of *Euphorbia hirta* Linn. (*Euphorbiaceae*) in Ethanol-Induced Thrombocytopenic Rat Models. *International Journal of Pharmaceutical Frontier Research*.
- Aravind, G., Bhowmik, D., Duraivel, S., & Harish, G. (2013). Traditional and Medicinal Uses of *Carica papaya*. *Journal of Medicinal Plants Studies*.
- Arya, S. C., & Agarwal, N. (2014, August). Apropos: effects of papaya leaves on thrombocyte counts in dengue--a case report. *JPMA. The Journal of the Pakistan Medical Association*. Pakistan.
- Assir, M. Z. K., un Nasir, N., Mansoor, H., Waseem, T., Ijaz Ahmed, H., Riaz, F., Akram, J. (2011). *Effect of carica papaya leaf extract on platelet count in dengue fever: A*

- randomized controlled trial (plead trial)*. *Journal of Allama Iqbal Medical College* (Vol. 9).
- Begum, M. (2014). *Phytochemical and Pharmacological Investigation of Carica papaya Leaf*. East West University.
- Bhatt, S., Gething, P. W., Brady, O. J., Messina, J. P., Farlow, A. W., Moyes, C. L., ... Hay, S. I. (2013). The global distribution and burden of dengue. *Nature*, 496(7446), 504–507. <https://doi.org/10.1038/nature12060>.
- CDC. (2012). Dengue and the Aedes aegypti mosquito. *Aegypti Fact Sheet*. [https://doi.org/10.1016/S0965-1748\(03\)00124-3](https://doi.org/10.1016/S0965-1748(03)00124-3).
- Ching, S., Ramachandran, V., Gew, L. T., Lim, S. M. S., Sulaiman, W. A. W., Foo, Y. L., ... Hoo, F. (2016). Complementary alternative medicine use among patients with dengue fever in the hospital setting: a cross-sectional study in Malaysia. *BMC Complementary and Alternative Medicine*. London. <https://doi.org/10.1186/s12906-016-1017-0>.
- Cogan, J. E. (2018). Dengue and severe dengue Key facts Global burden of dengue, (February), 1–7. Retrieved from <http://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue>.
- Deepak, B., Girish, K., & Lakshmi Prasad, L. J. (2013). Effect of papaya leaf juice on platelet and WBC count in dengue fever: a case report. *Journal of Ayurveda and Holistic Medicine*.
- Dharmarathna, S. L. C. A., Wickramasinghe, S., Waduge, R. N., Rajapakse, R. P. V. J., & Kularatne, S. A. M. (2013). Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. *Asian Pacific Journal of Tropical Biomedicine*. [https://doi.org/10.1016/S2221-1691\(13\)60145-8](https://doi.org/10.1016/S2221-1691(13)60145-8).
- EVO, H. (2013). Dengue Fever, Eat Only These Foods.
- Gammulle, A., Ratnasooriya, W., Jayakody, J., Fernando, C., Kanatiwela, C., & Udagama, P. V. (2012). Thrombocytosis and Anti-inflammatory Properties, and Toxicological Evaluation of Carica papaya Mature Leaf Concentrate in a Murine Model. *Online International Journal of Medicinal Plants Research* ©2012 Online Research Journals Full Length Research.
- Giyatmo, G. (2013). Efektifitas Pemberian Jus Kurma Dalam Meningkatkan Trombosit Pada Pasien Demam Berdarah Dengue Di RSUD Bunda Purwokerto. *Soedirman Journal of Nursing*, 8(1), 32–37.
- Gould, E., & Solomon, T. (2008). Pathogenic flaviviruses. *The Lancet*. [https://doi.org/10.1016/S0140-6736\(08\)60238-X](https://doi.org/10.1016/S0140-6736(08)60238-X).
- Halim, S. Z., Abdullah, N. R., Afzan, A., Rashid, B. A. A., Jantan, I., & Ismail, Z. (2011). Acute toxicity study of Carica papaya leaf extract in Sprague Dawley rats. *Journal of Medicinal Plants Research*.
- Hettige, S. (2008). Salutory effects of carica papaya leaf extract in dengue fever patients—a pilot study.
- Idrees, S., & Ashfaq, U. A. (2012). A brief review on dengue molecular virology, diagnosis, treatment and prevalence in Pakistan. *Genetic Vaccines and Therapy*, 10(1), 6. <https://doi.org/10.1186/1479-0556-10-6>.
- Jayasinghe, C., & Jayawardena, U. (2018). *Potential Use of Euphorbia hirta for Dengue: A Systematic Review of Scientific Evidence*. *The Journal of tropical medicine* (Vol. 2018). <https://doi.org/10.1155/2018/2048530>.
- Joseph, B., Sankarganesh, P., Ichiyama, K., & Yamamoto, N. (2015). In vitro study on cytotoxic effect and anti-DENV2 activity of Carica papaya L. leaf. *Frontiers in Life Science*. <https://doi.org/10.1080/21553769.2014.924080>.
- Kamath, J. V., Rahul, N., Kumar, C. K. A., & Lakshmi, S. M. (2008). Psidium guajava L: A review. *International Journal of Green Pharmacy (IJGP)*, 2(1).
- Kritikar, B. D. B. K. R. (2012). *Indian Medicinal Plants*. (B. D. B. K. R. Kritikar, Ed.) (8th ed.). MISC.

- Kumar, S., Malhotra, R., & Kumar, D. (2010). Euphorbia hirta: Its chemistry, traditional and medicinal uses, and pharmacological activities. *Pharmacognosy Reviews*. <https://doi.org/10.4103/0973-7847.65327>.
- Lum, L., Ng, C. J., & Khoo, E. M. (2014). Managing dengue fever in primary care: A practical approach. *Malaysian Family Physician: The Official Journal of the Academy of Family Physicians of Malaysia*.
- Malaysia, M. of H. of. (2018). MALAYSIA DENGUE INCIDENCE RATE & CASE FATALITY RATE FOR YEAR 2000-2017.
- Muharni, S., Martini, A., & Dinda, R. (2013). Efek Penggunaan Suplemen Ekstrak Daun Jambu Biji (*Psidium guajava* Linn.) dan Angkak (*Monascus purpureus*) dalam Meningkatkan Trombosit pada Demam Berdarah Dengue (DBD) di Instalasi Rawat Inap Ilmu Penyakit Dalam RSUP. DR. M. Djamil Padang. *Jurnal Penelitian Farmasi Indonesia*, 1(2), 57–61.
- Munazza, M., Rukhsan, K., Roohi, A., Mir, M., Khurshid, R., & Aftab, R. (2012). Management of thrombocytopenia and flu-like symptoms in dengue patients with herbal water of *Euphorbia hirta*. *Journal of Ayub Medical College, Abbottabad: JAMC*.
- Omeje, E. O., Amayo, L., Adikwu, M. U., Osadebe, P. O., & Ibezim, E. (2007). Platelet Response To Methanolic And Aqueous Extracts Of *Euphorbia hirta*. *Nigerian Journal of Natural Products and Medicine*, 11(1), 44–47.
- Patil, T., Patil, S., Patil, A., & Patil, S. (2014). Carica papaya leaf extracts—An Ethnomedicinal boon. *International Journal of Pharmacognosy and Phytochemical Research*, 6(2), 260–265.
- Prakash Kala, C. (2012). Leaf Juice of *Carica papaya* L.: A Remedy of Dengue Fever. *Medicinal & Aromatic Plants*. <https://doi.org/10.4172/2167-0412.1000109>
- Prasetio, J. N. (2015). Potential Red Guava Juice in Patients With Dengue Hemorrhagic Fever. *J Majority*.
- Ranasinghe, P., Ranasinghe, P., Abeysekera, W. P. K. M., Premakumara, G. a S., Perera, Y. S., Gurugama, P., & Gunatilake, S. B. (2012). In vitro erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts. *Pharmacognosy Research*. <https://doi.org/10.4103/0974-8490.102261>.
- Raynes, R. J., Sabado, A. A., Teh, L. C., Santiago, C. D., Oliver, M., Armeña, E., ... Barrosa, A. (2012). Investigation of the anti-thrombocytopenic property of *euphorbia hirta* linn (Tawa-Tawa) decoction in rat models. In *Philippine Council for Health Research and Development*. Retrieved from <http://www.pchrd.dost.gov.ph/phocadownload/userupload/publications/pub-newsletter-julsept2012.pdf>.
- Rehman, A. U. (2014). *Enhancing Platelet counts in patient of Dengue fever by administering extract of leaves of Carica Papaya*.
- Rosary, F. (n.d.). Hematologi Darah Tikus sebagai Model Demam Berdarah untuk Uji Khasiat Angkak dan Jambu Biji Merah (*Psidium guajava* Linn).
- Roy, C. K., Kamath, J. V., & Asad, M. (2006). Hepatoprotective activity of *Psidium guajava* Linn. leaf extract. *Indian Journal of Experimental Biology*.
- Sarangi, M. (2014). *Dengue and Its Phytotherapy: A review*. *International Journal of Pharmaceutical & Phyto pharmacological Research*.
- Sathasivam, K., Ramanathan, S., Mansor, S. M., Haris, M. R. M. H., & Wernsdorfer, W. H. (2009). Thrombocyte counts in mice after the administration of papaya leaf suspension. *Wiener Klinische Wochenschrift*. <https://doi.org/10.1007/s00508-009-1229-0>.
- Senthilvel, P., Lavanya, P., Kumar, K. M., Swetha, R., Anitha, P., Bag, S., ... Anbarasu, A. (2013). Flavonoid from *Carica papaya* inhibits NS2B-NS3 protease and prevents Dengue 2 viral assembly. *Bioinformation*. <https://doi.org/10.6026/97320630009889>.
- Shaun Damon. (n.d.). Coconut Oil: A Natural Antibacterial, Antiviral & Antifungal Medicine.

- Sheikh, N., Younas, N., & Akhtar, T. (2014). *Effect of Carica papaya leaf formulation on Hematology and Serology of normal. Biologia (Lahore, Pakistan)* (Vol. 60).
- Siddique, O., Sundus, A., & Faisal Ibrahim, M. (2014). Effects of papaya leaves on thrombocyte counts in dengue - A case report. *Journal of the Pakistan Medical Association*.
- SM, N., Patil, S. B., Naikwade, N. S., & Magdum, C. S. (2009). Review on phytochemistry and pharmacological aspects of *Euphorbia hirta* Linn. *Jprhc*.
- Sridhar, S., Luedtke, A., Langevin, E., Zhu, M., Bonaparte, M., Machabert, T., ... Khromava, A. (2018). Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *New England Journal of Medicine*.
- Subenthiran, S., Choon, T. C., Cheong, K. C., Thayan, R., Teck, M. B., Muniandy, P. K., ... 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*. <https://doi.org/10.1155/2013/616737>.
- Tahir, N., Zaheer, Z., Kausar, S., & Chiragh, S. (2014). Prevention of fall in platelet count by carica papaya leaf juice in carboplatin induced thrombocytopenia in mice. *Biomedica*, 30(1).
- Tham, C. S., Chakravarthi, S., Haleagrahara, N., & de Alwis, R. (2013). Morphological study of bone marrow to assess the effects of lead acetate on haemopoiesis and aplasia and the ameliorating role of *Carica papaya* extract. *Experimental and Therapeutic Medicine*. <https://doi.org/10.3892/etm.2012.851>.
- Thisyakorn, U., & Thisyakorn, C. (2013). Latest developments and future directions in dengue vaccines. *Therapeutic Advances in Vaccines*. <https://doi.org/10.1177/2051013613507862>.
- WHO. (2012). Global Strategy for Dengue Prevention and Control 2012–2020. *World Health Organization*. Retrieved at <https://doi.org/10.11812/201204034/en/index.html>.
- Wiwanitkit, V. (2010). Dengue fever: diagnosis and treatment. *Expert review of anti-infective therapy*, 8(7), 841-845.
- Wiyasihati, S. I., Wigati, K. W., & Wardani, T. (2013). Comparing the Effect of Red Yeast Rice, Date Palm, and Guava Leaf Extract on Thrombocyte and Megakaryocyte Count in Thrombocytopenic White Rats. *Folia Medica Indonesiana*, 49(2), 82.
- Yuet Ping, K., Darah, I., Chen, Y., Sreeramanan, S., & Sasidharan, S. (2013). Acute and subchronic toxicity study of *Euphorbia hirta* L. methanol extract in rats. *BioMed research international*, 2013.
- Yunita, F., Hanani, E., & Kristianto, J. (2012). The effect of *Carica papaya* L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient. *Int J Med Aromat Plants*, 2(4), 573-8.