Carica papaya Leaf Juice for Dengue

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Dengue, an *Aedes* mosquito-borne viral infection, has become a public health risk that demands the world's focus, especially in tropical countries. Despite of the life-threatening complication, there are still no specific antiviral medications for dengue infection. This situation highlight the research need in identifying potent compounds with promising anti-dengue activities. Therefore, a scoping review was conducted to gather and highlight the available scientific evidence for the use of *C. papaya* leaf, particularly using juice form, as a complementary method in treating dengue infection.

Carica papaya | papaya | leaf | juice | dengue

1. Introduction

The use of medicinal plants in disease prevention and treatment has been around for many generations worldwide and some of them have been scientifically proven. Various medicinal plants, especially those with antiviral activity have drawn interest from researchers to formulate new medicinal drugs for infectious diseases around the world [1]. Like other plants, *Carica papaya* L. has a high content of phytochemicals that not only have beneficial food nutritional values but also medicinal potential. Its leaves contain alkaloids [2][3][4][5], flavonoids [3][6][7][8], phenolic acids [6][7][8], saponin [9], amino acids [6], organic acids [6], vitamins [8][10], minerals [10], carbohydrates [6] and carotenoids [8]. Traditionally, this plant is used to lower blood pressure and blood sugar levels by ingesting boiled young leaves [11]. Infusion or decoction of the leaves taken orally not only regulate blood pressure but can also treat overweight condition. This plant is very famous for its edible fruit to relieve constipation. Its seeds can be pounded and then ingested to treat intestinal worms. Toothache, corns and warts can be treated by topically applying its sap [12]. Recently, the *C. papaya*, particularly its leaf part, has attracted wide attention for its potential use in dengue treatment.

Dengue, an Aedes mosquito-borne viral infection, has become a public health risk that demands the world's focus, especially in tropical countries [13]. This infection is one of the crucial health concerns in Malaysia because of its worrying statistical value. There were more than 900,000 dengue cases with over a thousand deaths reported in Malaysia from the year 2009 to present and more than 125,000 dengue cases were reported in 2019 alone [14]. The dengue virus (DENV) belongs to the virus family Flaviviridae and consists of five serotypes (DENV-1 to 5). Compared to other serotypes, the fifth serotype has only been circulated between non-human primates and mosquitoes (also known as the sylvatic cycle) with only one new human infected case reported in 2013 [15][16]. The ideal vector for DENV-5 is mosquito Aedes niveus, whilst the female Aedes aegypti mosquito is the common vector

in DENV transmission [16][17]. Compared to the male type, the female mosquito requires external blood as a nutrient supply, particularly iron mineral, for its eggs production and development [18]. Due to the very low transmission rate of the DENV-5 and a lack of scientific information, at present the World Health Organization upholds that the dengue disease is a public health concern mainly caused by the other four serotypes [19].

There are primary and secondary dengue infections. Individuals who have recovered from primary infection of a serotype have lifelong immunity against the same serotype but the risk of developing severe dengue would be higher following infection by any other of the three serotypes (secondary infection) [20][21]. Severe dengue, also known as dengue hemorrhagic fever, is potentially fatal. Despite of the life-threatening complication, there are still no specific antiviral medications for dengue infection [22]. Nevertheless, scientists are persistently striving to find the cure by diverging their attentions to develop a therapeutic drug that can disrupt or cease targeted DENV proteins' functions [23]. A licensed dengue vaccine commercially available in some countries is not effective against all four common serotypes of DENV, and it can cause individuals unexposed to DENV to be at greater risk of developing severe disease [24][25]. These situations highlight the research need in identifying potent compounds with promising anti-dengue activities via in depth understanding of dengue pathogenesis. There are currently no systematic scoping reviews focused on *C. papaya* leaf juice.

2. *Carica papaya* Leaf Juice for Dengue

Juice form of *C. papaya* leaf consisting of 28 included studies that focused on efficacy of this herbal preparation on dengue related parameters. The doses of juice used and treatment duration were varied. Interestingly, the findings from the included studies seemed to be associated with the use of *C. papaya* leaf juice. Therefore, regardless of variation in dose and treatment duration, this suggests the potential use of the leaf juice in treating dengue manifestation.

The *C. papaya* leaf juice does not demonstrate a linear dose-response relationship in the measured study parameters [26][27][28][29][30]. Nevertheless, s hormesis dose-response relationship was observed where beneficial effects were observed at low doses instead of high dose. Such a dose-response model has been reported to occur in some therapeutic agents such as antiviral drugs [31]. The DENV replication in a host's body would only be successful by inhibiting the signals of interferon in the body. In conjunction with this factor, a reliable mouse research model in dengue research was established. The AG129 mouse used in dengue research lacks α-, β- and γ-interferon receptors making the introduced DENV unable to communicate with the host's interferon and therefore the DENV can successfully replicate in the host's body [32][33]. The use of such a laboratory model could mimic clinical manifestation of human dengue infection. Another team of scientist also discovered the association between endothelial permeability of liver tissue and DENV and suggested that the liver can be the virus replication site [34]. Despite the efforts investigating larvicide(s) in reducing the number of mosquitoes as a disease vector, there was very few studies pertaining to the larvicidal effect of the leaf juice.

The choice of efficacy studies for medicinal plants is commonly determined by the ethnobotanical information. Ethnobotany is a field of study related to traditional knowledge on use of plants such as for medicinal use. This

type of valuable information is mostly based on years of belief and observation; and richer in countries with big ethnic diversity as these regions would have more communities, such as indigenous people, who used or tried alternative healthcare treatment, such as using plants to heal health conditions. Several drugs prescribed in conventional medicine originated from naturally occurring substances and are plant-based such as digoxin extracted from Digitalis lanata for heart problem and morphine (from Papaver somniferum) for pain control. Despite the credit of ethnobotany in drug discovery and development, consumers should always keep in mind that not all traditional knowledge of medicinal plants has been therapeutically investigated to establish a safe dose and therefore they should be more cautious in using it [35].

Lately, an extensive review about the safe use of different formulations of *C. papaya* leaves highlighted some safety concerns. Apart from the mild gastrointestinal side effects, interaction with co-administered drugs, such as certain hypoglycemic agents, anti-malarial, cardiovascular drugs, and antibiotics, has either increased or decreased the efficacy of the drugs. It revealed that consumption of *C. papaya* leaves (up to 21 days) affected the reproductivity in both male and female animals. The possibility of consuming products containing *C. papaya* leaves which cause dysregulation of liver enzymes and lesions on the liver, was suggested from three in vivo studies with long treatment duration (up to 35 days). However, no liver function-related side effect was reported in the appraised clinical data, except there were two case reports that documented a plausible association between consumption of *C. papaya* leaf extract and irregular level of liver enzymes but the impact from confounding factors, such as any concomitant drug and/or underlying health condition of the patients, was not described in the reports and therefore such association is still questionable [36].

Despite these unfavorable findings reported in the safety review, there are other aspects that shall be addressed too. Firstly, there is no clinical evidence that reports the adverse effect of *C. papaya* leaves on the human reproductive system, either long or short term. Secondly, as compared to a long consumption period, neither hepatoxicity nor other toxic-related effects were found on the animals treated with a single dose of the leaves aqueous extract within a 14-day study duration [37]. In addition, the safety findings from this research imply protective role of *C. papaya* leaf juice on the organs of dengue infected subjects. Thirdly, the type of solvents used in plant extraction is a key factor that may influence the efficacy and/or level of toxicity observed, especially when toxic chemical solvents are used [38][39].

A series of rodent toxicity studies using freeze-dried *C. papaya* leaf juice, from 14 days of single dosing up to 90 days of daily dosing over a range of doses, showed minimal toxicity findings and the no-observed-adverse-level was 2000 mg/kg body weight [37][40][41]. Hence, a human equivalent dose for the 2000 mg/kg body weight by considering a safety factor of 10 is 32.26 mg/kg body weight, which is equivalent to 2.26 g of the freeze-dried *C. papaya* leaf juice taken by a 70 kg human. The treatment regime prescribed in the included RCTs was 5–30 mL of the juice for adult consumption (vs. children: 2.5–5 mL) for one to six days [42][43][44][45][46].

Flavonoids have already been studied for their antiviral effect on human viruses, such as herpes simplex, polio, parainfluenza and respiratory syncytial viruses [47]. Flavonoids derived from plants have been shown to inhibit dengue viral replication where the in vitro inhibitory effect was observed using plaque assay [48]. Flavanones

isolated from Boesenbergia rotunda (L.) Mansf. Kulturpfl. showed competitive inhibition towards NS3 protease [49]. Using inhibition kinetics study, docking and protease assay, certain flavonoids were found to inhibit one of DENV enzymes non-structural proteins (NS2B/NS3 protease) at an allosteric site [50]. Other than the protease complex, a few studies also showed commercial flavonoids and flavonoids isolated from different plants inhibited another DENV enzyme (NS5-RNA-dependent RNA polymerase) activity [51][52][53][54]. Other quercetin and kaempferol analogues showed potential for inhibition on DENV enzymatic activities. Both structures, respectively, formed multi-hydrogen bonds with amino acid residues, which enhanced the binding strength of the compounds at the target site [55][56][57][58][59].

The ability of flavonoids to interact with the cell membrane surface that protects the lipid bilayer against harmful agents, such as free radicals, has been discovered [60][61]. Therefore, the reported erythrocyte membrane stabilizing effect could correlate to the high content of flavonoids in the *C. papaya* leaf juice. Similarly, scientists also found an association between flavonoid and immunomodulation activity, such as T helper cell differentiation into inflammatory and regulatory cells via mTOR pathway [62]. Interestingly, here, the *C. papaya* leaf juice was also found to be modulating the functional and non-functional immune responses.

As one of the biggest phenolic groups [63] and also the most abundant content found in *C. papaya* leaf juice, flavonoids have also been reported to modulate platelet aggregation (a clinical manifestation that could happen to dengue patients) through few pathways such as inhibition of arachidonic acid, suppression of cytoplasmic calcium ion, blockage of degranulation and integrin signaling mediated by αIIbβ3 integrin, inhibition of platelet granule secretion, and inhibition of thromboxane formation [64]. One study shows the protecting role of bone marrow by *C. papaya* leaf extract in regulating protein carbonyl and glutathione contents within bone marrow, less severity of histology lesion found on the lead-induced oxidative damage bone marrow and promotes production of blood cells and platelet in the bone marrow [65]. Similar prominent findings were also reported by the included studies in protecting or enhancing the production of bone marrow cells and splenocytes.

In Malaysia, *C. papaya* trees are planted for food consumption and commercial purposes. Two papaya varieties are popular in Malaysia, i.e., ‘eksotika’ and ‘sekaki’. Both varieties can be commonly found as hermaphrodite and there are slight differences in their physical appearance [66]. Currently, only one metabolite profiling analysis was conducted on the fruit part of both varieties and a distinct metabolite profile was found between the ‘eksotika’ and ‘sekaki’ [67]. Similar extensive profiling on the leaf part to investigate content difference for both varieties is still lacking.

The phytochemicals detected in the *C. papaya* leaf juice, such as the flavonoids, should be given attention to as they could be potential DENV inhibitors. These points of discussion provided insights on the potential of the *C. papaya* leaf found in this review; for example, recovery of platelet count to minimize risk of bleeding among thrombocytopenic dengue patients. Compared to the three plausible mechanisms of action of *C. papaya* leaf on dengue infection (anti-thrombocytopenic effect, immunomodulatory effect and antiviral effect) suggested by Bok et al., (2020) [68], the findings from this research focusing on leaf juice, emphasize the effect of larvicidal activity, anti-thrombocytopenia and immunomodulation.

Based on the gathered scientific evidence in this entry, not only the larvicidal effect, but the *C. papaya* leaf juice also has the potential in relieving dengue manifestations (anti-thrombocytopenic effect and immunomodulatory effect), which are preferable for only a short consumption period, such as the short treatment regime in treating dengue patients.

References

1. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J. Nat. Prod. 2020, 83, 770–803.
2. Zunjar, V.; Dash, R.; Jivrajani, M.; Trivedi, B.; Nivsarkar, M. Antithrombocytopenic activity of carpaine and alkaloidal extract of Carica papaya Linn. leaves in busulfan induced thrombocytopenic Wistar rats. J. Ethnopharmacol. 2016, 181, 20–25.
3. Julianti, T.; De Mieri, M.; Zimmermann, S.; Ebrahimi, S.N.; Kaiser, M.; Neuburger, M.; Raith, M.; Brun, R.; Hamburger, M. HPLC-based activity profiling for antiplasmodial compounds in the traditional Indonesian medicinal plant Carica papaya L. J. Ethnopharmacol. 2014, 155, 426–434.
4. Ogan, A.U. The basic constituents of the leaves of Carica papaya. Phytochemistry 1971, 10, 2544–2547.
5. Tang, C.S. New macrocylic, Δ1-piperideine alkaloids from papaya leaves: Dehydrocarpaine I and II. Phytochemistry 1979, 18, 651–652.
6. Gogna, N.; Hamid, N.; Dorai, K. Metabolomic profiling of the phytomedicinal constituents of Carica papaya L. leaves and seeds by 1H NMR spectroscopy and multivariate statistical analysis. J. Pharm. Biomed. Anal. 2015, 115, 74–85.
7. Canini, A.; Alesiani, D.; D'Arcangelo, G.; Tagliatesta, P. Gas chromatography-mass spectrometry analysis of phenolic compounds from Carica papaya L. leaf. J. Food Compos. Anal. 2007, 20, 584–590.
8. Andarwulan, N.; Kurniasih, D.; Apriady, R.A.; Rahmat, H.; Roto, A.V.; Bolling, B.W. Polyphenols, carotenoids, and ascorbic acid in underutilized medicinal vegetables. J. Funct. Foods 2012, 4, 339–347.
9. Vuong, Q.V.; Hirun, S.; Roach, P.D.; Bowyer, M.C.; Phillips, P.A.; Scarlett, C.J. Effect of extraction conditions on total phenolic compounds and antioxidant activities of Carica papaya leaf aqueous extracts. J. Herb. Med. 2013, 3, 104–111.
10. Ayoola, P.B.; Adeyeye, A. Phytochemical and nutrient evaluation Carica papaya (pawpaw) leaves. Int. J. Recent Res. Appl. Stud. 2010, 5, 325–328.

11. Ong, H.C.; Norzalina, J. Malay herbal medicine in Gemencheh, Negri Sembilan, Malaysia. Fitoterapia 1999, 70, 10–14.
12. Ong, H.C.; Ruzaila, B.N.; Milow, P. Traditional knowledge of medicinal plants among the Malay villagers in Kampung Tanjung Sabtu, Terengganu, Malaysia. Indian J. Tradit. Knowl. 2011, 10, 460–465.
13. Bhatt, S.; Gething, P.W.; Brady, O.J.; Messina, J.P.; Farlow, A.W.; Moyes, C.L.; Drake, J.M.; Brownstein, J.S.; Hoen, A.G.; Sankoh, O.; et al. The global distribution and burden of dengue. Nature 2013, 496, 504–507.
14. Kementerian Kesihatan Malaysia. Kenyataan Akhbar Ketua Pengarah Kesihatan Malaysia mengenai Situasi Semasa Demam Denggi, Zika dan Chikungunya di Malaysia Tahun 2009–2020. Available online: https://www.moh.gov.my/index.php/database_stores/store_view/17 (accessed on 14 February 2022).
15. Westaway, E.G.; Brinton, M.A.; Gaidamovich, S.; Horzinek, M.C.; Igarashi, A.; Kääriäinen, L.; Lvov, D.K.; Porterfield, J.S.; Russell, P.K.; Trent, D.W. Flaviviridae. Intervirology 1985, 24, 183–192.
16. Mustafa, M.; Rasotgi, V.; Jain, S.; Gupta, V. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. Med. J. Armed Forces India 2015, 71, 67–70.
17. Henchal, E.A.; Putnak, J.R. The dengue viruses. Clin. Microbiol. Rev. 1990, 3, 376–396.
18. Zhou, G.; Kohlhepp, P.; Geiser, D.; Frasquillo Mdel, C.; Vazquez-Moreno, L.; Winzerling, J.J. Fate of blood meal iron in mosquitoes. J. Insect Physiol. 2007, 53, 1169–1178.
19. World Health Organisation. Dengue and Severe Dengue. Available online: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (accessed on 14 February 2022).
20. Alvarez, M.; Rodriguez-Roche, R.; Bernardo, L.; Vazquez, S.; Morier, L.; Gonzalez, D.; Castro, O.; Kouri, G.; Halstead, S.B.; Guzman, M.G. Dengue hemorrhagic Fever caused by sequential dengue 1–3 virus infections over a long time interval: Havana epidemic, 2001–2002. Am. Soc. Trop. Med. Hyg. 2006, 75, 1113–1117.
21. Halstead, S.B. Neutralization and antibody-dependent enhancement of dengue viruses. Adv. Virus Res. 2003, 60, 421–467.
22. World Health Organisation. Dengue Control: The human. Available online: http://www.who.int/denguecontrol/human/en/ (accessed on 14 February 2022).
23. Dighe, S.N.; Ekwudu, O.m.; Dua, K.; Chellappan, D.K.; Katavic, P.L.; Collet, T.A. Recent update on anti-dengue drug discovery. Eur. J. Med. Chem. 2019, 176, 431–455.

24. World Health Organisation. Dengue vaccine: WHO position paper, September 2018–recommendations. Vaccine 2019, 37, 4848–4849.
25. World Health Organisation. Immunization, Vaccines and Biologicals: Questions and Answers on Dengue Vaccines. Available online: http://www.who.int/immunization/research/development/dengue_q_and_a/en/ (accessed on 14 February 2022).
26. Jayasinghe, C.D.; Gunasekera, D.S.; De Silva, N.; Jayawardena, K.K.M.; Udagama, P.V. Mature leaf concentrate of Sri Lankan wild type Carica papaya Linn. modulates nonfunctional and functional immune responses of rats. BMC Complement. Altern. Med. 2017, 17, 230.
27. Santosh Kumar, M.; Geetha, M.; Mansi, J.S.; Malvika, G.; Srinivas, L.D. Evaluation of efficacy of Carica papaya leaf extracts to increase platelet count in hydroxyurea induced thrombocytopenia in albino rats. Int. J. Basic Clin. Pharmacol. 2017, 7, 173–174.
28. Nandini, C.; Madhunapantula, S.V.; Bovilla, V.R.; Ali, M.; Mruthunjaya, K.; Santhepete, M.N.; Jayashree, K. Platelet enhancement by Carica papaya L. leaf fractions in cyclophosphamide induced thrombocytopenic rats is due to elevated expression of CD110 receptor on megakaryocytes. J. Ethnopharmacol. 2021, 275, 114074.
29. Anjum, V.; Arora, P.; Ansari, S.H.; Najmi, A.K.; Ahmad, S. Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of Carica papaya leaves. Pharm. Biol. 2017, 55, 2043–2056.
30. Mohd Abd Razak, M.R.; Norahmad, N.A.; Md Jelas, N.H.; Afzan, A.; Mohmad Misnan, N.; Mat Ripen, A.; Thayan, R.; Zainol, M.; Syed Mohamed, A.F. Immunomodulatory activities of Carica papaya L. leaf juice in a non-lethal, symptomatic dengue mouse model. Pathogens 2021, 10, 501.
31. Calabrese, E.J.; Baldwin, L.A. Chemotherapeutics and hormesis. Crit. Rev. Toxicol. 2003, 33, 305–353.
32. Zellweger, R.M.; Shresta, S. Mouse models to study dengue virus immunology and pathogenesis. Front. Immunol. 2014, 5, 151.
33. Johnson, A.J.; Roehrig, J.T. New mouse model for dengue virus vaccine testing. J. Virol. 1999, 73, 783.
34. Smith, D.R.; Khakpoor, A. Involvement of the liver in dengue infections. Dengue Bull. 2009, 3, 75–86.
35. McClatchey, W.C.; Mahady, G.B.; Bennett, B.C.; Shiels, L.; Savo, V. Ethnobotany as a pharmacological research tool and recent developments in CNS-active natural products from ethnobotanical sources. Pharmacol. Ther. 2009, 123, 239–254.

36. Lim, X.Y.; Chan, J.S.W.; Japri, N.; Lee, J.C.; Tan, T.Y.C. Carica papaya L. leaf: A systematic scoping review on biological safety and herb-drug interactions. Evid.-Based Complement. Altern. Med. 2021, 2021, 5511221.
37. Halim, S.Z.; Abdullah, N.; Afzan, A.; Abd Rashid, B.; Jantan, I.; Ismail, Z. Acute toxicity study of Carica papaya leaf extract in Sprague Dawley rats. J. Med. Plants Res. 2011, 5, 1867–1872.
38. World Health Organisation. Annex 1 WHO Guidelines on Good Herbal Processing Practices for Herbal Medicines. Available online: https://www.who.int/traditional-complementary-integrative-medicine/publications/trs1010_annex1.pdf (accessed on 14 February 2022).
39. Joshi, D.; Adhikari, N. An overview on common organic solvents and their toxicity. J. Pharm. Res. 2019, 28, 1–18.
40. Afzan, A.; Abdullah, N.R.; Halim, S.Z.; Rashid, B.A.; Semail, R.H.; Abdullah, N.; Jantan, I.; Muhammad, H.; Abdullah, N.R.; Halim, S.Z.; et al. Repeated dose 28-days oral toxicity study of Carica papaya L. leaf extract in Sprague Dawley rats. Molecules 2012, 17, 4326–4342.
41. Ismail, Z.; Halim, S.Z.; Abdullah, N.R.; Afzan, A.; Abdul Rashid, B.A.; Jantan, I. Safety evaluation of oral toxicity of Carica papaya Linn. leaves: A subchronic toxicity study in Sprague Dawley rats. Evid.-Based Complement. Altern. Med. 2014, 2014, 741470.
42. Hettige, S. Salutary effects of Carica papaya leaf extract in dengue fever patients–a pilot study. Sri Lankan Fam. Physician 2008, 29, 17–19.
43. Prakash Kala, C. Leaf juice of Carica papaya L.: A remedy of dengue fever. Med. Aromat. Plants 2012, 1, 109.
44. Solanki, S.G.; Trivedi, P. Evaluation of the efficacy of Carica papaya leaf extract on platelet counts in dengue patients. J. Adv. Sci. Res. 2020, 11, 62–65.
45. Naresh Kumar, C.V.M.; Taranath, V.; Venkatamuni, A.; Vishnu Vardhan, R.; Siva Prasad, Y.; Ravi, U.; Sai Gopal, D.V.R. Therapeutic potential of Carica papaya L. leaf extract in treatment of dengue patients. Int. J. Appl. Biol. Pharm. Technol. 2015, 6, 93–98.
46. Hettige, S.; Pushpakumara, J.; Wanigabadu, L.U.; Ransirini Hettige, E.M.; Kottege, A.; Jayaratne, S.D.; Saman, G. Controlled clinical trial on effect of ‘Carica papaya’ leaf extract on patients with dengue fever. J. Clin. Res. Med. 2020, 3, 1–7.
47. Kaul, T.N.; Middleton, E.J.; Ogra, P.L. Antiviral effect of flavonoids on human viruses. J. Med. Virol. 1985, 15, 71–79.
48. Sánchez, I.; Gómez-Garibay, F.; Taboada, J.; Ruiz, B.H. Antiviral effect of flavonoids on the dengue virus. Phytother. Res. 2000, 14, 89–92.
49. Kiat, T.S.; Pippen, R.; Yusof, R.; Ibrahim, H.; Khalid, N.; Rahman, N.A. Inhibitory activity of cyclohexenyl chalcone derivatives and flavonoids of fingerroot, Boesenbergia rotunda (L.),

towards dengue-2 virus NS3 protease. Bioorganic Med. Chem. Lett. 2006, 16, 3337–3340.

50. De Sousa, L.R.; Wu, H.; Nebo, L.; Fernandes, J.B.; da Silva, M.F.; Kiefer, W.; Kanitz, M.; Bodem, J.; Diederich, W.E.; Schirmeister, T.; et al. Flavonoids as noncompetitive inhibitors of dengue virus NS2B-NS3 protease: Inhibition kinetics and docking studies. Bioorganic Med. Chem. 2015, 23, 466–470.
51. Coulerie, P.; Maciuk, A.; Eydoux, C.; Hnawia, E.; Lebouvier, N.; Figadere, B.; Guillemot, J.C.; Nour, M. New inhibitors of the DENV-NS5 RdRp from Carpolepis laurifolia as potential antiviral drugs for dengue treatment. Rec. Nat. Prod. 2014, 8, 286–289.
52. Allard, P.-M.; Dau, E.T.H.; Eydoux, C.; Guillemot, J.-C.; Dumontet, V.; Poullain, C.; Canard, B.; Guéritte, F.; Litaudon, M. Alkylated flavanones from the bark of Cryptocarya chartacea as dengue virus NS5 polymerase inhibitors. J. Nat. Prod. 2011, 74, 2446–2453.
53. Coulerie, P.; Eydoux, C.; Hnawia, E.; Stuhl, L.; Maciuk, A.; Lebouvier, N.; Canard, B.; Figadère, B.; Guillemot, J.C.; Nour, M. Biflavonoids of Dacrydium balansae with potent inhibitory activity on dengue 2 NS5 polymerase. Planta Med. 2012, 78, 672–677.
54. Coulerie, P.; Nour, M.; Maciuk, A.; Eydoux, C.; Guillemot, J.C.; Lebouvier, N.; Hnawia, E.; Leblanc, K.; Lewin, G.; Canard, B.; et al. Structure-activity relationship study of biflavonoids on the dengue virus polymerase DENV-NS5 RdRp. Planta Med. 2013, 79, 1313–1318.
55. Senthilvel, P.; Lavanya, P.; Kumar, K.M.; Swetha, R.; Anitha, P.; Bag, S.; Sarveswari, S.; Vijayakumar, V.; Ramaiah, S.; Anbarasu, A. Flavonoid from Carica papaya inhibits NS2B-NS3 protease and prevents dengue 2 viral assembly. Bioinformation 2013, 9, 889–895.
56. Mir, A.; Ismatullah, H.; Rauf, S.; Niazi, U.H.K. Identification of bioflavonoid as fusion inhibitor of dengue virus using molecular docking approach. Inform. Med. Unlocked 2016, 3, 1–6.
57. Anju Krishnan, K.; Latha, M.S.; Sruthy, B. A computational analysis of the therapeutic effect of Carica papaya leaves against dengue fever. Indian J. Sci. Res. 2018, 18, 55–61.
58. Keramagi, A.R.; Skariyachan, S. Prediction of binding potential of natural leads against the prioritized drug targets of chikungunya and dengue viruses by computational screening. 3 Biotech 2018, 8, 274.
59. Qamar, M.T.; Ashfaq, U.A.; Tusleem, K.; Mumtaz, A.; Tariq, Q.; Goheer, A.; Ahmed, B. In-silico identification and evaluation of plant flavonoids as dengue NS2B/NS3 protease inhibitors using molecular docking and simulation approach. Pak. J. Pharm. Sci. 2017, 30, 2119–2137.
60. Oteiza, P.I.; Erlejman, A.G.; Verstraeten, S.V.; Keen, C.L.; Fraga, C.G. Flavonoid-membrane interactions: A protective role of flavonoids at the membrane surface? Clin. Dev. Immunol. 2005, 12, 592035.

61. Hendrich, A.B. Flavonoid-membrane interactions: Possible consequences for biological effects of some polyphenolic compounds. Acta Pharmacol. Sin. 2006, 27, 27–40.
62. Hosseinzade, A.; Sadeghi, O.; Naghdipour Biregani, A.; Soukhtehzari, S.; Brandt, G.S.; Esmaillzadeh, A. Immunomodulatory effects of flavonoids: Possible Induction of T CD4+ regulatory cells through suppression of mTOR pathway signaling activity. Front. Immunol. 2019, 10, 51.
63. De la Rosa, L.A.; Moreno-Escamilla, J.O.; Rodrigo-García, J.; Alvarez-Parrilla, E. Chapter 12-Phenolic Compounds. In Postharvest Physiology and Biochemistry of Fruits and Vegetables; Yahia, E.M., Ed.; Woodhead Publishing: Sawston, UK, 2019; pp. 253–271.
64. Faggio, C.; Sureda, A.; Morabito, S.; Sanches-Silva, A.; Mocan, A.; Nabavi, S.F.; Nabavi, S.M. Flavonoids and platelet aggregation: A brief review. Eur. J. Pharmacol. 2017, 807, 91–101.
65. Tham, C.S.; Chakravarthi, S.; Haleagrahara, N.; De Alwis, R. Morphological study of bone marrow to assess the effects of lead acetate on haemopoiesis and aplasia and the ameliorating role of Carica papaya extract. Exp. Ther. Med. 2013, 5, 648–652.
66. Chan, Y.K. Breeding the papaya–Carica papaya. UTAR Agric. Sci. J. 2015, 1, 32–42.
67. Sanimah, S.; Sarip, J. Metabolomic analysis of Carica papaya variety eksotika and sekaki. J. Trop. Agric. Food Sci. 2015, 43, 103–117.
68. Bok, Z.K.; Balakrishnan, M.; Jong, Y.X.; Kong, Y.R.; Khaw, K.Y.; Ong, Y.S. The plausible mechanisms of action of Carica papaya on dengue infection: A comprehensive review. Prog. Drug Discov. Diomedical Sci. 2020, 3, a0000097.