



E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2020; 8(6): 50-56
Received: 23-09-2020
Accepted: 29-10-2020

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Anti-dengue effects of medicinal plants: A review

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Abstract

Dengue viral infections have shown to infect 390 million individuals annually, causing severe clinical disease in the form of dengue hemorrhagic fever (DHF). The World Health Organization (WHO) has identified dengue as one of the top ten global health threats in year 2019. There is currently no specific drug for treatment of this potentially fatal disease. Although a vaccine was recently licensed to prevent infection, it was found to have poor efficacy against some dengue virus (DENV) serotypes. Therefore, researchers are now seeking herbal treatments for the dengue based on ethno medical usage. This review provides information on herbal plants commonly found in tropical countries which documented for anti-dengue properties by enough scientific experimental details. We hope to encourage more studies on plants described in this review for the development of new therapeutic targets for the management of dengue fever.

Keywords: Dengue, pathogenesis, treatment, herbal plants, validated targets

1. Introduction

Dengue viral infection is currently one of the most significant mosquito-borne infection in humans ^[1]. Dengue has been considered as the serious cause of morbidity and mortality in most tropical and subtropical areas, including Southeast and South Asia, Central and South America ^[2]. As stated by World Health Organization, 2.5 billion people of the world's population in tropical and subtropical areas are thought to be at risk of being infected with the Dengue virus (DENV) with 50 million of them been infected annually ^[3].

Aedes aegypti and *Aedes albopictus* are the two principal vectors of dengue. Dengue is circulated all over the world rapidly since *Aedes* mosquitoes are well adapted to the human habitat.

Dengue fever is endemic in Sri Lanka. The first serologically confirmed dengue fever (DF) patient was reported in Sri Lanka in 1962 ^[4]. DHF has become endemic in Sri Lanka from 1989 onwards ^[4]. From 1989 the number of DF/ DHF cases has markedly increased with each epidemic.

Dengue epidemics mainly occur during rainy seasons when there is a warm and humid climate, following south-west and northeast monsoon rains ^[2, 5]. A massive upsurge in the number of dengue patients in Sri Lanka was seen in the year 2017. Epidemiology Unit of the Ministry of Health had reported 186101 suspected dengue cases over 320 deaths for the year 2017 ^[6].

Up to date there is no effective drug for dengue fever. Therefore, Scientific community now seeking the new herbal treatments for the treatment of dengue fever.

2. Materials and methods

Information for this review were obtained from previous research findings regarding phytochemical and anti-viral and anti-dengue pharmacological aspects of medicinal plants from available literatures published in scientific databases such as Web of Science, Science Direct, PubMed, JSTOR and Google Scholar with inclusion criteria of full length published articles on anti-dengue activity studies of various medicinal plants conducted in numerous countries. primary search terms like, dengue fever, anti-dengue activities, herbal plants, invitro *in vivo* studies are used to collect the information.

3. Clinical manifestation of dengue

Those who are infected with the DENV can show a wide range of clinical symptoms ranging from asymptomatic infection to symptomatic illness. Symptomatic infection may manifest as undifferentiated fever, DF, DHF. DHF is further classified into four severity grades, namely grade I, II, III and IV. Among them, grade III and IV are considered to have dengue shock syndrome (DSS) ^[7].

There are four serotypes of DENVs, namely DENV-1, DENV - 2, DENV -3 and DENV- 4. Mainly serotype 1 and 4 existed in Sri Lanka during the year 2009 to 2015 ^[8].

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Serotype 2 and 3 are more virulent and cause of massive dengue epidemics [2]. During 2017 epidemic, DENV 2 was the predominant circulating strain [9]. Other than that in 2010 also massive dengue outbreak had been reported, and PCR studies of DHF patients had revealed that DENV 1 serotype is predominant during that period [10].

It had been revealed that infection with one serotype leads to develop protective immunity against that serotype but not against other serotypes [2, 3]. Some studies have shown that there is a 500-fold risk of development of DHF as a result of DENV 1/DENV 2 subsequent infections compared with primary infection [3]. That risk was 150-fold when the sequence is DENV 3/DENV 2. For the DENV 4/ DENV 2 had a 50-fold chance of having DHF [3].

4. Pathogenesis of dengue fever

When infected mosquito had a bite, dengue virus infects Langerhans cells in the epidermis and keratinocytes [11]. Consequently, it infects many other cell types, monocytes, dendritic cells, macrophages, endothelial cells, and hepatocytes. Infected monocytes and dendritic cells lead to produce a greater amount of pro-inflammatory cytokines and chemokines [10].

Once a person is infected with DENV, after an initial incubation period of 3-7 days manifest with sudden onset of fever accompanied by high viremia. Among them, some individuals proceed to the critical phase associated with plasma leakage. This vascular leakage is the hallmark of DHF, and it is due to increase of vascular permeability because of endothelial dysfunction.

Experiments in dengue mouse models show that the lipid mediator platelet-activating factor (PAF) and the chemokine receptors play a significant role in the development of DHF [12]. It has been recently found that PAF is the predominant mediator for the vascular leak [13].

5. Validated targets for the treatment of dengue

The disease outcome of the dengue virus is controlled by both viral and host factors. So in order to develop the therapeutic for dengue, both factors should be encountered. Theoretically, cellular proteins, which are involved in the replication of the DENV, can be used as potential target for the antiviral therapy by inhibition of the protein. Other than that, inhibition of cellular proteins which involved in the pathogenesis of DF also can use as an alternative approach for the treatment. Some recent researches are carried based on cholesterol metabolism since cholesterol is involved in DENV entry and replication [14]. Since it was found that PAF is responsible for the vascular leak of DF patients [13], it is worthwhile to seek platelet activating factor receptor (PAFR) antagonists towards the therapeutic for DF.

Moreover, secretory phospholipase A2 (sPLA2) enzyme is required for the synthesis of PAF through the formation of lyso PAF [14]. Recently Sri Lankan research group had found that sPLA2 enzyme level is significantly increased in patients with DHF when compared to those with DF during the 1st 120h of illness [15]. Therefore, sPLA2 inhibitors also will play an important role as an effective therapeutic target for minimizing vascular leakage in DHF patients.

6. Current treatments for dengue

There is no effective drug or vaccine for the treatment of this potentially fatal disease. In 2015, the vaccine called Dengvaxia was developed and licensed for use in 11 countries. However, it is not effective for the protection from infection of all the four serotypes of dengue [16].

There are multiple anti-DENV agents in various stages of development. Some are direct-acting antivirals namely RNA polymerase inhibitors, nucleoside analogues and protease inhibitors. Some anti-dengue agents are developing that target host-mediated translational modifications such as α glucosidase inhibitors [17]. Moreover, the Sri Lankan research group was found that Rupatadine, PAFR blocker had shown safety and dose-dependent significant benefits in reducing dengue complications and shortening the duration of illness using a randomized, placebo-controlled trial in 183 adult patients in Sri Lanka with acute dengue [18].

7. Use of medicinal plants for the treatment of dengue

Traditional Ayurveda medicine has a wide therapeutic window with rare side effects with compare to modern synthetic medicines which possess irreversible adverse events to human beings. Today nearly 51 % approved drugs are directly or indirectly derived from the herbal plants [16].

Sri Lanka is enriched with an assortment of medicinal plants, which are widely used for a variety of diseases in a traditional medical system known as Ayurveda [19]. Currently, it is urgent to seek new compounds having anti-viral activity from herbs based on traditional medicinal practices. Hence, the scientific community is now seeking new drugs and treatments for dengue in traditional Ayurvedic medicine since it is non-toxic and inexpensive.

There are reported compounds with a natural origin which have anti-viral activity, including Flavones, tannins, and alkaloids [20, 21]. Moreover, phenolic compounds were showed to possess antiviral properties against herpes viruses and adenoviruses. Caffeic acid was inhibited HSV-1 with EC₅₀ 15.3 g/mL, and at 40 g/mL it showed 100 % inhibition [22]. Furthermore, caffeic acid and chlorogenic acid were reported as having a broad spectrum of antiviral activity [22].

According to the previous literature plant-based, antiviral compounds can block or inhibit dengue virus replication cycle by interfering with virus attachment to cells, interfering with viral enzymes or suspending dengue viral genome replication [16]. However, still, it was not able to address much of those mechanisms through herbal medicine.

This review paper highlighted the published research work on the use of herbal medicine for the treatments of dengue fever, which having enough scientific evidence for future needs (Table 1).

In addition to specific crude extracts of medicinal plants, some isolated compounds also showed anti dengue properties. Such as phaeophorbide a, Cyclohexenyl chalcone derivatives (4-hydroxypanduratin A and Panduratin A), Andrographalide, Gallic acid, quercetin, catechin, naringin, Pectolarin, acacetin -7-O-rutinoside, methyl gallate, Baicalein, Eugenin, Cyclododecane, n-hexadecanoic acid and carrophyllene (Figure 1 and 2). However, there are no evidence for the use of those isolated compounds for further clinical studies.

Table 1: Anti dengue properties of some medicinal plants

Medicinal plant	Family	Type of extract/ isolated compound	Anti-dengue activity	Ref
<i>Carica papaya</i>	Caricaceae	Leaf juice	An open-labelled randomized controlled trial was carried out on 228 patients with DF and DHF. C. papaya juice was given for 3 consecutive days to the test group. Control group having only the standard management. Significant increase in mean platelet count was observed in the test group ($P < 0.001$) but not in the control	[23]

			group	
<i>Carica papaya</i>	Caricaceae	Leaf juice	<i>In-vitro</i> study was reported the membrane-stabilizing effect of <i>C. papaya</i> leaf juice using membrane-stabilizing assay and hypotonicity induced hemolysis assay. They suggest that <i>C. papaya</i> leaf juice is able to protect blood cells against stress-induced destruction	[24]
<i>Carica papaya</i>	Caricaceae	Suspension of crude papaya leaves	One study was found that the increase of thrombocyte count in mice between 1h-12h time interval after the administration of suspension of crude papaya leaves at 15 mg/ kg of body weight [26]. Another study was carried out by using the cyclophosphamide-induced thrombocytopenic rat model, and they have observed the increase of platelet count at concentrations of 400 and 800 mg/kg of <i>C. papaya</i> leaf aqueous extract	[25]
<i>Carica papaya</i>	Caricaceae	<i>C. papaya</i> leaf extract capsule which containing 70 % ethanol extract of <i>C. papaya</i> .	An open-labelled randomized controlled trial was carried out on 80 patients with DF including both the control group (n=40) and test group (n= 40). The test group was treated with two capsules 3 times daily. They had found the significant increase ($P < 0.01$) of the platelet count while maintaining the hematocrit in the normal level	[26]
<i>Hippophae rhamnoides</i>	Elaeagnaceae	Ethanol extract	Evaluated for anti-dengue activity in human macrophage cell line U-937 which infected with DENV 2. Significant anti dengue activity revealed.	[27]
<i>Cryptonamia crenulata</i>	Halymeniaceae	DL galactan hybrid C2S-3	Potent and selective inhibitor of multiflication of diverse strains of DENV 2 in vero cells with higher effectiveness	[28]
<i>Clinacanthus nutans</i>	Acanthaceae	Isolated compound-phaeophorbide a	Inhibit production of viral RNA and viral protein upon infection of DENV 2 virus with C6/36 cells	[29]
<i>Phyllanthus phillyreifolius</i>	Phyllanthaceae	Aqueous and ethanolic extract	Showed potent antiviral activity in Huh7.5 cells at 250 µg/mL concentration against four serotypes.	[30]
Cocktail extract of four <i>phyllantus sp. (Phyllanthus amarus, P.niruri, P.urinaria, P.watsonii)</i>	Phyllanthaceae	Aqueous and methanolic extracts	Showed strongest inhibitory activity against DENV 2 with more than 90% of virus reduction	[31]
<i>Curcuma longa, Zingiber zerumbet, Curcuma manga</i>	Zingiberaceae	Methanol fraction	<i>Curcuma longa</i> methanol fraction exhibited the strongest inhibitory activity (91.3%, 300 ppm) and <i>Zingiber zerumbet</i> (89%, 300 ppm)	[32]
<i>Bosenbergia rotunda</i>	Zingiberaceae	Isolated compounds- Cyclohexenyl chalcone derivatives. 4-hydroxyanduratin A and Panduratin A	Show good competitive inhibitory activity towards DENV 2 virus NS3 protease	[33]
<i>Ocimum sanctum</i>	Lamiaceae	Methanol extract	Exhibit antiviral properties toward DENV 1 through inhibition of cytopathic formation and viral replication	[34]
<i>Lippia alba</i>	Verbanaceae	Essential oil	Inhibition was observed by treatment of virus before adsorption on cell, IC50 =0.4-32.6 µg/mL	[35]
<i>Lippia citriodora</i>	Verbanaceae	Essential oil	Inhibition was observed by treatment of virus before adsorption on cell IC50 =1.9-33.7 µg/mL	[35]
<i>Andrographis paniculata</i>	Acanthaceae	Isolated compound - Andrographalide	Showed significant anti DENV activity in both cell lines with EC50 for DENV 2 is 21.3 µM and 22.73 µM for HepG2 and HeLa respectively.	[36]
<i>Andrographis paniculata</i>	Acanthaceae	Methanolic extract	Showed 75 % inhibition of Vero cells that infected with DENV I based on cytopathic effect.	[37]
<i>Mormordica Charantia</i>	Curcubitaceae	Methanolic extract	Showed 50 % inhibition of Vero cells that infected with DENV I based on cytopathic effect.	[37]
<i>Psidium gujava</i>	Myrtaceae	Ethanol extract	Significantly increase platelet number of thrombocytopenic mice model through enhancement of stem cell factor expression	[38]
<i>Psidium gujava</i>	Myrtaceae	Isolated compounds, Gallic acid, quercetin, catechin, naringin	All four compounds selectively inhibited DENV 2 replication with EC50 values Gallic acid (28.8 µg/mL), quercetin(19.2 µg/mL), catechin (33.7 µg/mL), naringin (47.9 µg/mL)	[39]
<i>Distictella elongata</i>	Bignoniaceae	Ethanol extract	Presented antiviral activity against DENV 2	[40]
<i>Distictella elongata</i>	Bignoniaceae	Isolated compounds- Pectolinarin (1)and acacetin -7-O-rutinoside (2)	The mixture of both 1 and 2 is 8 times more potent against DENV 2 (EC50=11.1 µg/mL) than isolated 1 (EC50 =86.4 µg/mL)	[40]
<i>Uncaria tomentosa</i>	Rubiaceae	Aqueous ethanolic extract and its oxindole alkaloid fraction	Showed invitro inhibitory activity by reducing DENV-Ag+ cell rates in treated monocytes. Alkaloid fraction was most effective in reducing monocyte infection rate and cytokine level.	[41]
<i>Quercus lusitanica</i>	Fagaceae	Methanol extract	Found to be completely inhibit DENV at TCID 50 of 1-1000 by absence of cytopathic effect at 180 µg/mL. Protease inhibition assay of crude fractionate methanolic extract show more than 90% at 0.2 mg/mL.	[42]
<i>Quercus lusitanica</i>	Fagaceae	Isolated compound methyl gallate	Showed 96% inhibition at TCID50 of 1000. DENV 2 protease inhibition assay showed more than 98% at 0.3 mg/mL	[42]
<i>Euphorbia hirta</i>	Euphorbiaceae	Ethyl acetate extract	Potent antiviral activity against DENV 1 and 2 by plaque reduction neutralization test	[43]
<i>Scutellaria baicalensis</i>	Lamiaceae	Isolated compound-Baicalein	Inhibited DENV 2 replication in vero cells with IC50 = 6.46 µg/mL.It exhibited direct virucidal effect against DENV 2 with IC50 = 1.55 µg/mL	[44]
<i>Sambucus nigra</i>	Adoxaceae	Methanolic extract	Exhibit anti DENV 2 activity at 400 µg/mL, when virus was pre incubated with extract for 1 h and then added to vero cells.	[45]
<i>Acorus calamus Cymbopogon citratus Myristica fatua</i>	Acoraceae Poaceae Myristicaceae	Methanolic extract	<i>Myristica fatua</i> Shown antiviral effects against DENV 2 with highest percentage inhibition -122.7 %. Also <i>Acorus calamus</i> and <i>Cymbopogon citratus</i> showed good percentage inhibition around 98 %.	[46]

<i>Syzygium aromaticum</i>	Myrtaceae	Isolated compound- Eugenin	Eugenin reported potent dengue protease inhibitory activity against DENV 2 and DENV 3 with IC50 94.7 nM and 7.5 μM	[47]
<i>Syzygium grandulae</i> <i>Syzygium campanulatum</i>	Myrtaceae Myrtaceae	Isolated compounds- Cyclododecane, n-hexadecanoic acid and caryophyllene	The findings revealed that cyclododecane and n-hexadecanoic acid found in the leaf extracts of <i>S. grande</i> and caryophyllene in extracts of <i>S. campanulatum</i> were likely the lead-compound that imparted the observed inhibitory effect on the DENV2 NS2B-NS3 protease.	[48]
<i>Azhadirachta indica</i>	Meliaceae	Lyophilized aqueous extract	Antiviral effect on DENV 2 virus in C6/36 cell line at a concentration of 500 mg/mL	[49]

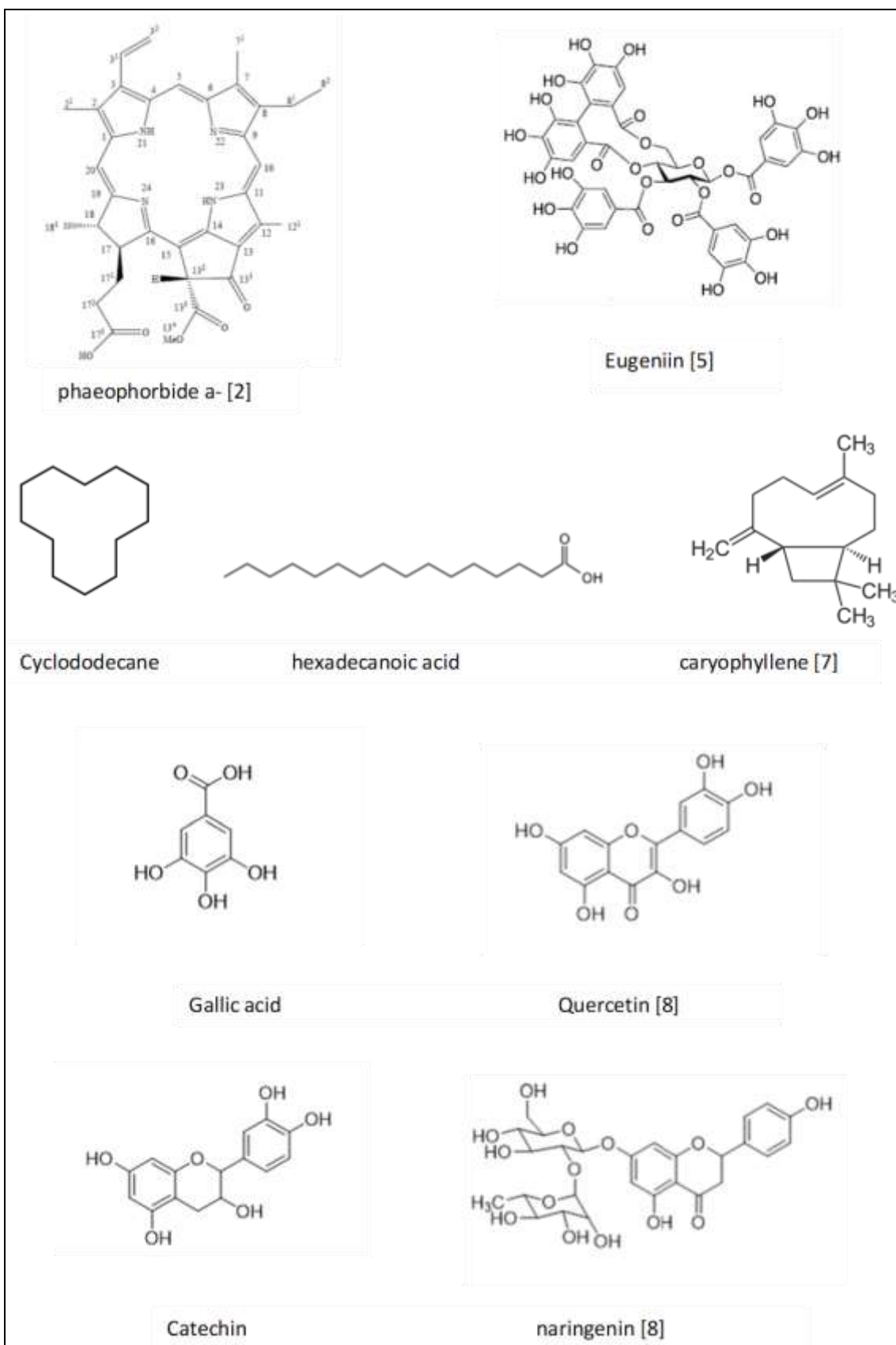


Fig 1: Structures of the isolated compounds from medicinal plants which having anti dengue properties

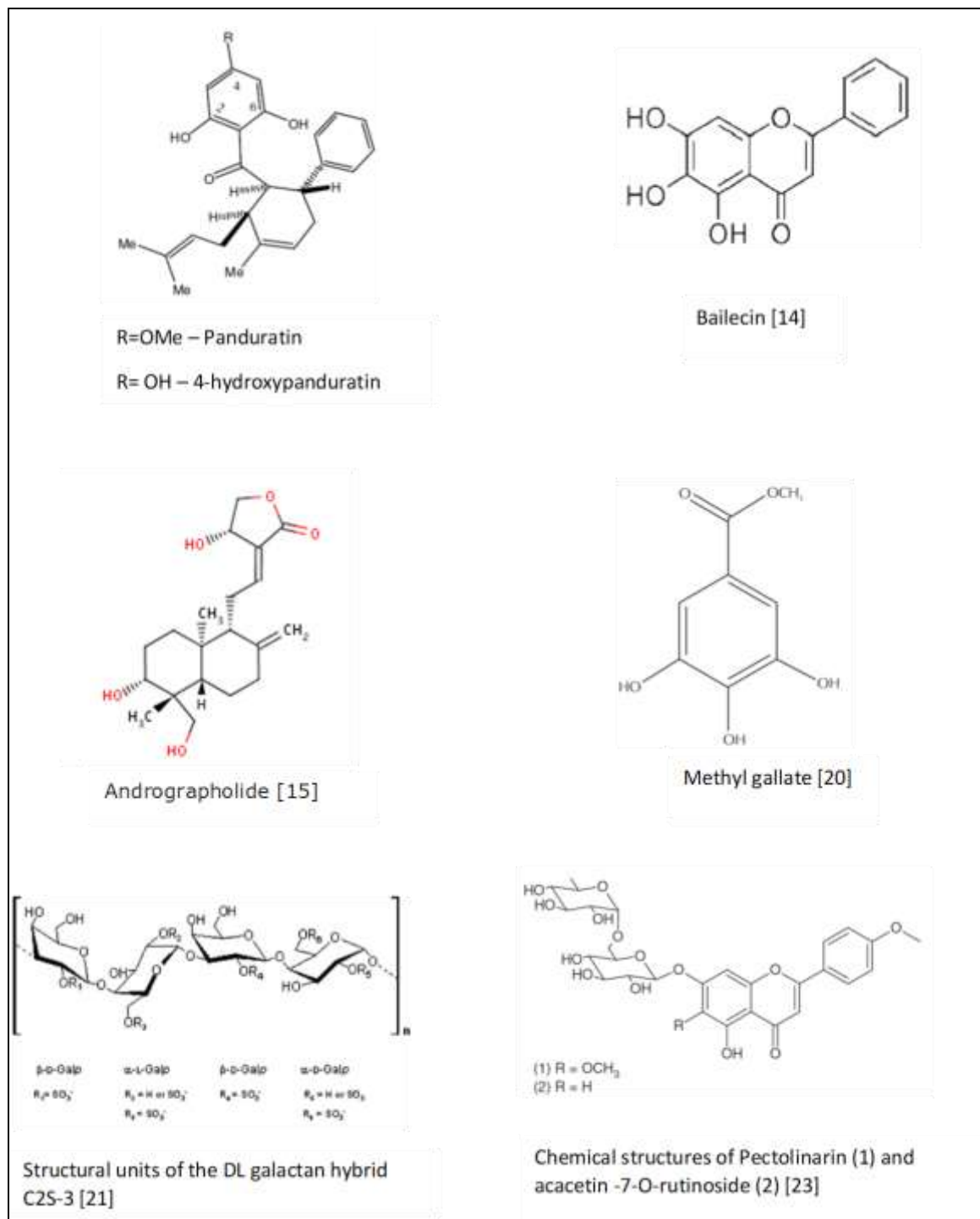


Fig 2: Structures of the isolated compounds from medicinal plants which having anti dengue properties

8. Conclusions and recommendations

This review summarizes the available reliable scientific evidence of medicinal plants which have anti dengue properties. As few studies illustrated, biologically active compounds should be isolated for further development of those medicinal plants as anti-dengue treatment.

Further research is a need to search anti-viral agents against DENV. It had been reported that the elevated sPLA2 enzyme level is observed in early phase of DHF patients. Based on that there is ongoing research in Sri Lanka that had been carried out to find potential sPLA2 inhibitors from herbal medicinal plants towards the treatment of dengue fever.

Potential herbal formulations which being used by community may provide a good piece of information to identify the drug

targets. Proper scientific validation of herbal formulations after screening is essential to validate and confirm their efficacy, understanding mechanistic action and safety.

9. List of abbreviations

DF: Dengue fever; DHF: Dengue hemorrhagic fever; DENV- Dengue virus; DSS- dengue shock syndrome, PAF: Platelet activating factor; PAFR: Platelet activating factor receptor; sPLA2: Secretory phospholipase A2; MNTD: Maximum nontoxic dose

10. Conflict of interest

There is no conflict of interests regarding the publication of this paper

11. References

1. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, *et al.* Dengue: A continuing global threat. *Nature Reviews Microbiology* 2010;8(12): S7-S16.
2. Martina BE. Clinical course, pathogenesis and treatment of dengue: An overview. *Culture* 2011;32(1):1-4.
3. World health organization. Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. WHO Regional Publication SEARO, 2011.
4. Withane N. Historical Account of Dengue Haemorrhagic Fever in Sri Lanka. *dengue bulletin* 1997;21:117-118.
5. Gibbons RV, Vaughn DW. Clinical Review, Dengue: an Escalating Problem. *BMJ Journal* 2002;324:1563-1566.
6. Ministry of Health N & I M. Dengue Epidemic 2017: Evidence and Lessons Learnt — Part 1, weekly epidemiological report, 2018.
7. World health organization. Dengue guidelines for diagnosis, treatment, prevention and control, 2009.
8. Sirisena PDNN, Noordeen F. Evolution of dengue in Sri Lanka — changes in the virus, vector, and climate. *International Journal of Infectious Diseases* 2014;19:6-12.
9. Jayarajah U, Faizer S, Zoysa IM, senevirathne S. A Large Dengue Epidemic Affects Sri Lanka In. *International Journal of Progressive Sciences and Technologies* 2017;6(1):84-86.
10. Malavige GN, Fernando N, Ogg G. Pathogenesis of Dengue viral infections. *Sri Lankan Journal of Infectious Diseases* 2011;1(1):2-8.
11. Surasombatpattana P, Hamel R, Patramool S, Luplertlop N, Thomas F, Desprès P, *et al.* Infection, Genetics and Evolution Dengue virus replication in infected human keratinocytes leads to activation of antiviral innate immune responses. *Infection, Genetics and Evolution.* Elsevier B.V 2011;11(7):1664-1673.
12. Souza GD, Fagundes, CT, Sousa LP, Amaral FA, Souza RS, Souza AL *et al.* Essential role of platelet-activating factor receptor in the pathogenesis of Dengue virus infection. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106(33):14138-14143.
13. Jeewandara C, Gomes L, Wickramasinghe N, Gutowska-Owsiak D, Waithe D, Paranavitane S. A *et al.* Platelet Activating Factor Contributes to Vascular Leak in Acute Dengue Infection. *PLoS Neglected Tropical Diseases* 2015;9(2):1-14.
14. Rosenson RS, Gelb MH. Secretory phospholipase A2: A multifaceted family of proatherogenic enzymes. *Current Cardiology Reports* 2009;11(6):445-451.
15. Jeewandara C, Gomes L, Udari S, Paranavitane SA, Shyamali NLA, Ogg GS, *et al.* Secretory phospholipase A2 in the pathogenesis of acute dengue infection. *Immunity, Inflammation and disease* 2017;5(1):7-15.
16. Malabadi RB. Role of Botanical Drugs in Controlling Dengue Virus Disease. *International Journal of Research and Scientific Innovation* 2018;V(Vii):134-159.
17. Fusco DN, Chung RT. Review of Current Dengue Treatment and Therapeutics in Development. *J Bioanal Biomed* 2014;S8:002.
18. Malavige GN, Wijewickrama A, Fernando S, Jeewandara C, Ginneliya A, Samarasekera S *et al.* A preliminary study on efficacy of rupertadine for the treatment of acute dengue infection. *Scientific reports* 2018;3(3857):1-14.
19. Waisundara VY, Watawana MI. The Classification of Sri Lankan Medicinal Herbs: An Extensive Comparison of the Antioxidant Activities. *Journal of Traditional and Complementary Medicine* 2014;4(3):196-202.
20. Fukuchi K, Sakagami H, Okuda T, Hatano T, Tanuma S, Kitajima K, *et al.* Inhibition of herpes simplex virus infection by tannins and related compounds. *Antiviral Research* 1989;11(5-6):285-297.
21. De Rodriguez DJ. Search for “*in vitro*” antiviral activity of a new isoflavonic glycoside from *Ulex europaeus*. *Planta medica* 1990;56 (1):59-62.
22. Chiang LC, Chiang W, Chang MY, Ng LT, Lin CC. Antiviral activity of *Plantago major* extracts and related compounds *in vitro*. *Antiviral research* 2002;55:53-62.
23. Subenthiran S, Choon TC Cheong KC, Thayan R, Teck MB, *et al.* *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* 2013, 1-7.
24. Ranasinghe P, Ranasinghe P, Abeyseker WP, Kaushalya M, Sirimal GA. *In vitro* erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts. *pharmacognacy research* 2012;4(4):196-202.
25. Sathasivam K. Thrombocyte counts in mice after the administration of papaya leaf Suspension. *The middle european journal of medicine* 2009;121(3):19-22.
26. Yunita F, Hanani E, Kristianto J. The effect of *Carica papaya* L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient. *International journal of medicinal aromatic plants* 2012;2(4):573-578.
27. Agrawal MJ, Chanda S, Rao M, Ganju L. Effect of *Hippophae Rhamnoides* Leaf Extract against Dengue Virus Infection in U937 Cells. *Virology & Mycology* 2016;5(2):1-8.
28. Talarico LB, Duarte MER, Zibetti RGM, Noseda MD, Damontae EB. An algal derived DL galactan hybrid is an efficient preventing agent for *in vitro* dengue virus infection. *Planta medica* 2007;73(14):1464-1468.
29. Sakdarat SS, Sittiso S, Ekalaksananan T, Pientong C, Charoensri N, Kongyingyoes B. Study on Effects of compounds from *Clinacanthus nutans* on dengue virus type 2 infection. *SSRN electronic Journal* 2010;25:272-275.
30. Haddad JG, Grauzdyt'e D, Koishi AC, Viranaicken W, Venskutonis PR, Santos CND, *et al.* The Geraniin-Rich Extract from Reunion Island Endemic Medicinal Plant *Phyllanthus phillyreifolius* Inhibits Zika and Dengue Virus Infection at Non-Toxic Effect doses in zebrafish. *Molecules* 2020;25(10):1-17.
31. Lee SH, Tang YQ, Rathkrishnan A, Wang SM, Ong KC, Manikam RM *et al.* Effects of cocktail of four local Malaysian medicinal plants (*Phyllanthus* spp.) against dengue virus 2. *BMC Complementary and Alternative Medicine* 2013;192:1-13.
32. Kiat TS, Phippen R, Yusof R, Ibrahim H, Khalid N, Rahman NA. Screening of selected Zingiberaceae extracts for dengue-2 virus protease inhibitory activities. *Sunway Academic Journal* 2006;3:1-7.
33. Kiat TS, Phippen R, Yusof R, Ibrahim H, Khalid N, Rahman NA. Inhibitory activity of cyclohexenyl chalcone derivatives and flavonoids of fingerroot, *Boesenbergia rotunda* (L.), towards dengue-2 virus NS3 protease. *Bioorganic & Medicinal Chemistry Letters* 2006;16(12):3337-3340.
34. Ling APK, Khoo BF, Seah CH, Foo KY, Cheah RK,

- Chye SM *et al.* Inhibitory activities of methanol extracts of *Andrographis paniculata* and *Ocimum sanctum* against Dengue-1 virus A.P.K, International Conference on Biological, Environment and Food Engineering 2014;4(5):47-52.
35. Ocazonez RE, Meneses R, Torres FA, Stashenko E. Virucidal activity of Colombian Lippia essential oils on dengue virus replication *in vitro*. Mem Inst Oswaldo Cruz 2010;105(3):304-309.
 36. Panraksa P, Ramphan S, Khongwichit S, Smith DR. Activity of andrographolide against dengue virus. Antiviral research 2016;139:1-33.
 37. Tang LC, Ling AP, Koh YK, Chye SM, Voon KG. Screening of anti-dengue activity in methanolic extracts of medicinal plants. BMC Complementary and Alternative Medicine 2012;12(3):1-10.
 38. Atik N, Tarawifa S, Avriyanti E, Rahmadi AR, Hilmanto D. *Psidium guajava* L. extract increases platelet count through enhancement of stem cell factor expression in thrombocytopenic mice model. International Journal of Pharmacy and Pharmaceutical Sciences 2018;10(1):23-26.
 39. Correa AIT, Quintero-Gil DC, Castillo FD, Quinones W, Robledo SM. Gutierrez. *In vitro* and *in silico* anti-dengue activity of compounds obtained from *Psidium guajava* through bioprospecting. BMC Complementary and Alternative Medicine 2019;19(1):1-16.
 40. Simoes LR, Maciel GM, Brandao GC, Kroon G, Castilho RO, Oliveira AB. Antiviral activity of *Distictella elongata* (Vahl) Urb. (Bignoniaceae), a potentially useful source of anti-dengue drugs from the state of Minas Gerais, Brazil. Letters in Applied Microbiology 2011;53(6):602-607.
 41. Sonia RIN, Reis A, Valentae MML, Sampio AL, Siani AC, Gandini M *et al.* Immunomodulating and antiviral activities of *Uncaria tomentosa* on human monocytes infected with Dengue Virus-2. International Immunopharmacology 2008;8(3):468-476.
 42. Rahman NA, Hadinur, Muliawan S, Rashid NN, Muhamad M, Yusof R. Studies on *Quercus lusitanica* Extracts on DENV-2 Replication. Dengue Bulletin 2006;30:260-269.
 43. Tayone WC, Tayone JC, Hashimoto M. Isolation and Structure Elucidation of Potential Anti-Dengue Metabolites from Tawa-tawa (*Euphorbia hirta* Linn.). Walailak Journal 2012;11(10):825-832.
 44. Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abubakar S. Novel antiviral activity of baicalein against dengue virus. BMC Complementary and Alternative Medicine 2012;12(214):1-9.
 45. Maldonado IC, Altamirano MMB, Galardo MBS. Anti-dengue serotype-2 activity effect of *Sambucus nigra* leaves-and flowers-derived compounds. Virology research and reviews 2017;1(3):1-5.
 46. Saptawati L, Febrinasari RP, Yudhani RD, Hudiono, Faza AG, Luthfiani S, *et al.* *In vitro* study of eight Indonesian plants extracts as anti Dengue virus. Health science journal of indonesia 2017;8(1):12-18.
 47. Saleem HN, Batool F, Mansoor HJ, Hussan SS, Saeed M. Inhibition of Dengue Virus Protease by Eugeniiin, Isobiflorin, and Biflorin Isolated from the Flower Buds of *Syzygium aromaticum* (Cloves). ACS omega 2019;4(1):1525-1533.
 48. Zakaria II, Salin NH, Amanah A, Othman S, Khairuddin F, Khawory MH *et al.* Potential anti-viral compounds from Malaysian Plant Natural Product Repository and Database (MyNature50000) for DENV2. Biotechnology & Biotechnological Equipment 2019;33(1):379-389.
 49. Shanthy G, Rajarajan S. A study on *in vitro* screening of antiviral activity of lyophilized extracts of three medicinal plants on dengue 2 & 4 serotypes. International Journal of Recent Scientific Research 2014;5(4):740-744.