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A Review on Unleashing the Potentials of Natural Products in Managing Dengue

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ABSTRACT

Background/Aims: Dengue virus (DENV) spreads widely in many tropical and sub-tropical countries by *Aedes sp*. In recent decades, dengue has been alarmingly on the rise and affects approximately half of the world population. The current dengue treatments are still mainly supportive without any approved vaccines or effective anti-dengue drugs. This leads to an urgency to seek alternative solutions in reducing dengue morbidity and mortality.

Methods: A total of 92 articles describing *in vitro* and *in vivo* studies were screened and selected through curated databases. The selected articles underpinned the potentials of natural products as alternative anti-dengue compounds.

Results: Those compounds have been employed as larvicide, mosquitocide, mosquito repellents, agents in sticky traps and non-specific interventions for dengue. In this review, their direct and indirect effects on dengue virus replication and dengue diseases were deliberated. Interestingly, the majority of them demonstrated remarkable anti-inflammatory effects on dengue diseases. Several phytochemical contents such as luteolin, coumarins and geraniin were shown to inhibit DENV replication *in vitro*.

Conclusion: Natural product-based anti-dengue agents are believed to be less costly, easy to derive, biologically effective and less toxic. This review, therefore, aims to provide current updates and insights on the benefits of natural products in preventing, managing and treating dengue.

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INTRODUCTION

Dengue virus (DENV) is the causative agent of dengue diseases in many tropical and subtropical countries since the beginning of 21st century. Female *Aedes* mosquitoes infected with DENV serotypes (DENV-1 to -4) are responsible for circulating the virus in human populations. A previous exposure to a DENV serotype induces immunity against the specific serotype, however, the cross-immunity to the other serotypes is short-term and becomes less effective over time.[1]

The number of confirmed dengue cases has been constantly on the rise, nonetheless, many cases are misclassified due to the unspecific clinical symptoms of dengue. One recent estimate indicates that 96 million of 400 million dengue infections recorded per annum are categorized as dengue with severe symptoms with 22,000 fatalities reported worldwide.[1,2] In terms of dengue prevalence, it was estimated that 3.9 billion people residing in 128 countries are at risk of dengue infections.[3] Dengue infections cause a wide spectrum of clinical manifestations, ranging from mild, acute febrile illnesses to severe dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).[3] According to World Health Organization (WHO) 2009, severe dengue, i.e. DHF was first identified in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue has been documented in the other Asian and Latin American countries,[4] and the number of outbreaks has escalated greatly. Human migration and international trade and travel are constantly introducing new vectors and pathogens into novel geographic areas. Of particular interest is the extent to which dengue virus (DENV) has spread in those regions through human activities. It has become a leading cause of hospitalization and death among children and adults in those regions. To ensure a more systematic management of dengue clinically, WHO classifies dengue illnesses as (i) dengue with or without warning signs, and (ii) severe dengue. The majority of dengue diseases are asymptomatic or associated with unspecific symptoms such as

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fever accompanied by headache, retro-orbital pain, myalgia and arthralgia, facial flushing, anorexia, abdominal pain and nausea, with or without warning signals for 4 to 10 days after the intrinsic incubation period.[4,5]

Persons experiencing multiple dengue infections especially by different DENV serotypes tend to undergo multiple clinical episodes. Among warning signs of severe dengue include abdominal pain or tenderness, constant vomiting, clinical fluid accumulation, mucosal bleeding, weak or fatigue, liver enlargement more than 2 cm or increase in haematocrit alongside rapid decreased platelet count. Eventually, the progression of the alarming signals to severe dengue is accompanied by severe plasma leakage that leads to septic shock or fluid accumulation with respiratory distress, severe bleeding, or in the worst-case scenario, severe organ failure.[6-9]

In DHF/DSS, capillary leakage and thrombocytopenia are seen alongside severe hemorrhage and septic shock. The accumulation of plasma in the chest and abdominal cavity causes fluid depletion in the circulation hence decreased blood supply to vital organs. Consequently, severe dengue patients might suffer from multi-organ failure, acute respiratory distress and death.[8]

The capillary leakage occurs due to increased capillary permeability. The increase is mainly concerted by a cascade of pro-inflammatory reactions in the infected individuals. During viremia, proliferation of leucocytes and release of pro-inflammatory cytokines induce uncommon conformation of endothelial glycocalyx that acts as a molecular filter of blood components.[3] The endothelial abnormality then promotes plasma leakage and adverse cellular damages in the liver, kidneys and brain.[1] The mortality rate associated with DHF is significant which accounts for 2.5% among severe dengue patients. The death rate is possible to increase up to 20% when proper treatments are delayed or not available.[3,10] In the worst-case scenario, the cross-reactivity might lead to severe dengue complications such as antibody-dependent enhancement (ADE) which in turn causes severe plasma leakage and haemorrhage. The severe disease conditions are usually seen in individuals suffering from secondary dengue infections.[1] Of note, dengue infections by all four dengue serotypes pose adverse health perils including death in high-risk and dengue endemic regions, such as Malaysia.

At present, dengue treatments are primarily supportive, such as intravenous fluid therapy, blood transfusion, and vasopressor (noradrenaline), and usually are prescribed based on the clinical symptoms.[11,12] In light of the circulation of four dominant dengue serotypes concurrently in human populations, development of universal dengue vaccines that are able to confer protection against all serotypes is highly demanded, however, the endeavour is rather challenging due to the remarkable antigenic variation among the serotypes. As a result, induction of adequate and equal protection against all serotypes in eligible vaccine recipients can be tricky.[13] Up to date, a few dengue vaccine candidates have been tested preclinically and clinically. They are formulated either as live, attenuated or purified inactivated vaccines. For instance, Dengavaxia®, TetraVax-DV-TV003/TV005, DENVax/TAK003/TDV, TDEN and TDEN PIV.[14] The first tetravalent vaccine approved for clinical trial is Dengvaxia®. The vaccine efficacy was validated in 20 Asian and Latin American countries. Unfortunately, the trial outcomes had raised multiple serious health concerns, which caused WHO to impose several restrictions on the use of Dengvaxia® after reviewing its adverse side effects in vaccinated children who were not previously infected by DENV.[15] In the absence of a safe, effective prophylactic dengue vaccine, traditional and alternative treatments are sought after in order to ameliorate dengue symptoms and improve dengue diseases in patients.

Traditional or alternative medicine has been used worldwide as the primary healthcare modality. It is usually applied based on the ancestral knowledge, experience, practices and belief that are passed down from a generation to another.[16] In traditional medicine, a variety of natural products, mainly plants, are used as the main remedies as they are abundant and cost-effective, easier to derive, effective and less toxic. Owing to its tremendous health benefits, alternative medicine has been envisioned as a potential therapy for dengue. Crude and purified plant-based compounds have been tested empirically for their anti-dengue effects, some of them are applied as repellents to control mosquito vectors in high-risk human residences .[15] In view of this, it is therefore an immediate need to seek effective, specific anti-dengue agents in preventing, managing and treating dengue diseases particularly in highly endemic regions.

METHODS

Ninety-two articles were identified and selected through PubMed, OVID, EBSCOhost, COCHRANE, Google scholar, Web of Science and SCOPUS after excluding duplicates, conference proceedings, abstracts and non-related articles. Those articles deciphered anti-dengue potentials and actions of natural products *in vitro* and *in vivo*. Keywords used in the search were dengue, dengue virus, dengue fever, natural product and anti-dengue.

RESULTS

Carica papaya

In the recent decades, various efforts have been endeavoured to explore the potentials of natural products as anti-dengue compounds[13] specifically in the Tropics and subtropic regions, which has been of major concern to governments and the World Health Organization (WHO). Among others, *Carica papaya*.[14,15,17,18] *Carica papaya* or papaya belongs to the family of *Caricaceae* and is generally found in Australia, Hawaii, Philippines, Sri Lanka, South Africa, India, Bangladesh, Malaysia and the tropical America.[19] Traditionally, papaya fruits, seeds, latex and extracts are adopted by many indigenous communities to treat various human diseases.[18] Empirically, papaya preparations and extracts including *C. papaya* leaf juice (CPLJ) were found to contain a large number of antioxidants and immunomodulators. Those compounds showed remarkable antioxidative and immunomodulatory properties *in vitro*,[20,21] *in vivo*.[15,22,23] and in clinical trials.[24,25] The papaya leaf extract helped regulate cytokine production in activated human peripheral blood mononuclear cells (PBMCs).[15,20,21] and reduced inflammation in rat oedema paws.[22] In addition, CPLJ was also found to reduce TNF-α production, increase phagocytic index and improve leucocyte count in cyclophosphamide-induced neutropenic rats without exerting detrimental effects in

healthy rats.[23] The beneficial properties of papaya extracts are speculated to be attributable to the flavonoid contents.[15,26] Flavonoids and hydroxycinammic acid derivatives have been isolated from the freeze-dried CPLJ (FCPLJ).[15,27] The dominant flavanoid contents encompass quinic acid, malic acid, manghaslin, clitorin, sinapsic acid, isoquercetin, ferulic acid, rutin, astragalin and nicotiflorin and carpaine. Those potential compounds exhibit excellent ADMET (adsorption, distribution, excretion, metabolism, and toxicity) properties that are needed for new drug development and antiviral effects.[26]

C. papaya leaf extracts also contain myricetin, caffeic acid, trans-ferulic acid, and kaempferol which help stabilize the cell membrane potential and reduce heat-induced hemolysis.[19] The improved cell membrane stability and hemolysis helps prevent the occurrence of DSS and DHF. Apart from that, the effects of FCPLJ on the expression of DENV NS1 and viremia were verified in the AG129 mouse model.[14,21] Although the administration of FCPLJ did not limit the expression of dengue NS1 in the mice, the level of dengue-associated viremia was reduced, which in turn improved the disease morbidity in DENV-infected AG129 mice.

In areas where papaya leaf juice has been consumed traditionally by dengue patients, the patients' thrombocyte counts were reported to improve gradually following the intake of papaya leaf juice.[28] The improvement was likely due to the synthesis of thrombopoietic cytokines, i.e. interleukin-6 (IL-6) and stem cell factors (SCF). The cytokines functioned synergistically with chemokines such as CCL2/MCP-1 in promoting the proliferation and extravasation of immune cells including thrombocytes during the peak of viremia[23] Those events clearly indicate the immunomodulatory effects of CPLF in preventing severe forms of dengue diseases, hence a potential source for anti-dengue compounds.

Viola yedoensis Makino

Traditional chinese medicine (TCM) has been widely accepted and applied by the ancient oriental communities to relieve disease symptoms such as fever, pain, bloating, rashes. These days, TCM continues to gain attention globally, and is well accepted by the Western consumers.[29]

One of the popular TCM herbs is *Viola yedoensis* that contains luteolin. Luteolin showed remarkable inhibition on the replication of Epstein-Barr virus (EBV), Japanese encephalitis virus (JEV), human immunodeficiency virus (HIV)-1, hepatitis B virus (HBV), hepatitis C virus (HCV), enterovirus (EV)-71, Coxsackievirus A (CA)-16 and Chikungunya virus (CHIKV).[29-38] More interestingly, luteolin was reported to alleviate dengue viremia in infected mice.[24] Due to limited empirical evidence to further support the direct anti-dengue function of luteolin, the study suggested that the anti-dengue potentials of luteolin could be enhanced through combination with the other antiviral inhibitors.

Mammea americana and *Tabernaemontana cymosa*

Mammea americana (*M. Americana*) (family *Clusiaceae*) is an indigenous plant to the Caribbean and Central America.[39] *Tabernaemontana cymosa* (*T. cymose*) (family *Apocynaceae*) is, on the other hand, indigenous to Colombia, Venezuela, Trinidad and many tropical and subtropical regions.[40]. Their extracts exhibited antibacterial, antiparasitic, antitumoral, antifebrile, analgesic, and antiviral effects.[41,42] Their antiviral activities are mostly attributable to the presence of active phytocompounds, among others, coumarins that was reported to actively inhibit DENV and CHIKV infections in Vero cells.[43] Coumarins was able to inhibit DENV and CHIKV infections greater than 50% and therefore is recommended as a potential lead compound for anti-DENV and anti-CHIKV drugs.

The other phytocompounds such as lupeol acetate and voacangine isolated from *T. cymosa* also inhibited DENV infection *in vitro*, however, to a lesser extent.[25] The precise inhibitory pathway is yet to be discovered, as a result, more rigorous investigations are warranted to prove their values as prominent anti-dengue agents.

Honeysuckle (*Lonicera japonica* Thunb.)

Honeysuckle or *Lonicera japonica* Thunb. (*Caprifoliaceae* family) is a perennial evergreen plant that is widely cultivated in China, Japan, Korea and India.[44] Traditionally, it is believed to have neuroprotective,[45,46] anti-oxidative,[47,48] anti-inflammatory,[49-51] anti-carcinogenic,[51-53] as well as anti-bacterial and antiviral properties[54,55] properties. However, the underlying mechanism is not fully understood.

Interestingly, honeysuckle extract was reported to attenuate DENV replication *in vivo* and the expression of let-7a miRNA was believed to be responsible for the attenuation.[55] Following the expression of let-7a miRNA, the expression of DENV-2 NS1 gene and viral replication in ICR-suckling mice were inhibited. As a result, the mice experienced less severe disease symptoms and better prolonged survival. The antiviral effects were comparable to that observed in control mice injected intracranially with the control let-7a miRNA. In view of the strong correlation between honeysuckle extract and the expression of let-7a miRNA, it is crucial to better understand the pathway involved so that honeysuckle extract can be a more convincing source for anti-dengue agents.[56]

Cissampelos pariera Linn

In an attempt to screen indigenous Indian herbs and plants possessing anti-dengue properties, *Cissampelos pareira* Linn (also known as Cipa) extract was found to inhibit DENV replication and therefore protected the challenged mice from lethality.[57] Besides its anti-dengue functions, its antipyretic and anti-inflammatory properties also helped reduce the disease symptoms. Importantly, the plant extract did not exert damaging effects in the mice particularly on the platelet and red blood cell counts.[57]

In Wistar rats, the administration of Cipa extract was reported to downregulate the synthesis of inflammatory cytokine, i.e. TNF-α that has been associated with increased plasma permeability and leakage that eventually leads to severe forms of dengue.[58] Altogether, Cipa extract is perceived as a promising source for anti-dengue compounds especially in endemic countries where people are living on limited access to medical resources.[59]

Vernonia cinerea, *Tridax procumbers* and *Senna angustifolia*

In a study by Rothan et al.,[60] medical plants such as *Vernonia cinerea* (*V. cinereal*), *Tridax procumbers* (*T. procumbers*)

and *Senna angustifolia* (*S. angustifolia*) showed promising anti-dengue activities. The ethanolic extracts of *S. angustifolia* leaf and *T. procumbens* stem, and methanolic extract of *V. cinerea* leaf were able to inhibit the proteolytic activities of DENV NS2B-NS3 protease. The plant extracts reduced dengue-induced cytopathic effects (CPE) in Vero cells. Although the presented data are promising, they are mostly preliminary data; therefore, more detailed investigations are entailed in order to unveil their mechanisms of actions against DENV. This ensures precise application of those medicinal plant extracts as a source for effective anti-DENV compounds.

Food ingredients - garlic organosulfur compounds, rambutan, avocado, wine and tea

Garlic has been used for centuries in treating ailments and diseases and its biological actions are attributable to the active organosulfur contents in crushed garlic, such as alliin, diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) [61–65]. DADS, DAS and alliin were reported to reduce DENV-induced inflammation via antioxidative reactions. Therefore, those garlic compounds were proposed to be used in combination with the other antivirals in fighting DENV [65].

A famous tropical fruit, *Nephelium lappaceum* or locally known as rambutan was explored for its anti-dengue properties.[66] A specific phytocompound namely geraniin extracted from the rambutan rind was tested in male BALB/C mice and Vero cell line infected with DENV-2.[66] Upon the geraniin administration, the level of viral RNA was found to reduce markedly at 72-h post-infection. In this light, it is hypothesized that early administration of geraniin is able to help avoid severe dengue diseases in dengue patients.

Phytochemical (2R,4R)-1, 2, 4-trihydroxyheptadec-16-yne (THHY) isolated from avocado (*Persea americana*) was reported to inhibit DENV replication via the upregulation of NF-κB-dependent interferon responses.[67,68] The roles of interferons in limiting virus infections and activating innate and cellular antiviral immunity have been extensively deliberated.[67] For examples, interferon-α and -ß activate the cellular RNase to degrade viral mRNA, and subsequently shut down the expression of viral proteins.[69] Interferon-γ, on the other hand, promotes the activation of macrophages for viral clearance, and enhances the expression of MHC class I on infected cells which in turn increases the recognition of cytotoxic T cells.[69] In short, interferon responses help reduce the virus load and heighten the host's immunity to prevent the systemic spread of DENV that usually results in severe dengue. Noteworthy, food ingredients with remarkable health benefits such as garlic, avocado and fruits are potential sources for anti-dengue drugs, thereby, their biological properties should be further described in order to ensure precise use of the food ingredients for treating dengue diseases.

Polyphenols are key plant metabolites found in various types of wine and tea.[70] They have excellent anti-oxidative properties that are proven to be effective in preventing and treating various diseases, such as cancers, diabetes, osteoporosis, cardiovascular and neurological disorders, and infections.[71,72] Among the reported polyphenols, epigallocatechin gallate (EGCG) isolated from green tea has been extensively studied and reported to inhibit a number of virus infections such as HCV, CHIKV, HBV, HHV-1, influenza A virus (AIV), and, most recently, ZIKV infections.[73-76] Honokiol, baicalein, naringin, and quercetin, on the hand, are found in wine. They also demonstrated significant antiviral actions in several studies.[77-80] In a nutshell, plant- and natural product-derived polyphenols are economical, simple and safe to use, and environmental friendly, it is therefore worth exploring their values in fighting DENV infections in dengue patients.[81]

Melia azedarach

Melia azedarach, often known as chinaberry, has a variety of biological properties. It contains a variety of phytochemicals such as flavonoids, chromones, coumarins, benzofurans, mono-, sesqui-, di-, tri- and tetranortriterpenoids. Among the identified compounds, limonoids were reported to show inhibitory effects on ssRNA, dsRNA, and dsDNA viruses.[81,82] The other compounds such as 3-tigloyl-melianol and melianone, on the other hand, exhibited significant antiviral activities against WNV, DENV and yellow fever virus (YFV).[81] Despite their antiviral activities, those studies are preliminary, and therefore it requires more empirical evidence to support their roles as anti-dengue drugs.

Syzygium campanulatum (Kelat Paya) and Syzygium grande (Keriang Batu)

Extracts of *Syzygium campanulatum* (Kelat Paya) and *Syzygium grande* (Keriang Batu) displayed prominent inhibition on the DENV2 NS2B-NS3 protease.[82,83] Through a detailed phytochemical analysis, the phytochemicals were identified as cyclododecane, n-hexadecanoic acid, and caryophyllene. They were found to interfere with the proteolytic activities of DENV2 NS2B-NS3.[83,84] Besides the promising anti-dengue activity, the plant extracts were non-toxic to mammalian cells; collectively, it implies their potential as anti-dengue medications.[85]

Makino (*Lindera erythrocarpa*)

One of bioactive compounds extracted from Makino (*Lindera erythrocarpa*) is luteolin. Luteolin is a naturally occurring flavonoid with a wide range of activities including anti-tumour, anti-inflammation, anti-oxidative and antiviral.[86] Peng et al.[32] deduced that the anti-dengue effects of luteolin was mainly on the cellular proprotein convertase (furin), albeit weakly. The similar inhibitory effects were also observed on EBV, JEV, HIV-1, HBV, HCV, EV-71, CA-16 and CHIKV.[44,45,47,86] Although proven effective, the level of protection conferred by luteolin is dubious due to the relatively low bioavailability, limited potency and other technical hindrance.[87] In view of the challenges, further structure-based analyses could be explored in order to improve the bioavailability and biological properties of luteolin prior to developing it into an anti-dengue agent.[88]

Kelulut honey

Honey is a popular natural food with antioxidative, anti-inflammatory, anti-diabetic, anti-hypertensive and antibacterial properties.[89,90] Its biological properties are mostly due to its high phenolic and flavonoid contents that are well known for controlling over-reactive immune responses.[89-91] Intake of high-quality honey was reported to upregulate the expression of NF-kß which is then translocated into the cell nucleus

to induce the expression of antiviral cytokines.[91] Once the cytokine response is initiated, replication of DENV is halted and thus improves the systemic inflammation caused by the virus replication.[92]

Nan et al.[92] studied the effect of Kelulut honey on clinical, hemodynamic and biochemical markers in dengue patients. In the study, Kelulut honey intake did not negatively impact on the patients' conditions. Nonetheless, the effect of Kelulut honey on the improvement of dengue was inconclusive. The study, therefore, suggested to involve a larger subject population and resort to cross-institutional collaboration in future research in order to better delineate the impact of Kelulut honey on dengue especially in improving dengue symptoms.

CONCLUSION

Dengue diseases still represent a major public health issue locally and internationally as dengue morbidity and mortality are continuously on the rise. Until now, dengue treatments still rely predominantly on supportive therapies without the presence of effective vaccines and drugs. Several lines of empirical evidence imply the potential of natural products as a source for anti-dengue compounds, moreover, development of biologically active natural products into anti-dengue agents is considered more cost effective, easier to derive and less toxic. However, the available data are mostly preliminary and inconclusive. Further studies are, therefore, needed to better utilize phytochemicals in preventing and managing dengue diseases more effectively in endemic regions like Malaysia.

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