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Review Article

An overview of traditional medicinal plants as dengue virus inhibitors

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ABSTRACT

Dengue fever has caused serious health problems around the world. Continents affected include Asia, Europe, North America, and Africa. Dengue fever, dengue hemorrhagic fever, and dengue shock syndrome are diseases caused by DENV. Promising antiviral activity of medicinal plants against DENV has been reported in several experimental studies. These plants are rich in bioactive constituents that have antiviral activity. This review extensively discussed the antiviral activity of these plants against DENV and the phytoconstituents responsible for the observed effects. The review discussed possible targets of these plant extracts or phytochemicals on the biological process of the virus as a potential mechanism for the observed inhibitory effects. Harnessing plants' chemical constituents can lead to the development of an antiviral against DENV.

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1. Introduction

The DENV virus belongs to the Flaviviridae family. It is found in most tropical and sub-tropical nations worldwide (Brady et al., 2012). Two mosquito species, *Aedes aegypti* (L.) and *Aedes albopictus* (Skuse), are responsible for transmitting DENV to humans. About half of the world's population is at risk of DENV infection, and nearly one hundred million cases of the disease are recorded annually (Messina et al., 2014). DENV is an enveloped (11 kb) positive single-stranded RNA virus having a singular open reading frame bordered by 5' and 3'-untranslated regions (UTR) (Cleaves and Dubin, 1979; Normile, 2013). As presented in Fig. 1, DENV has three structural proteins: capsid (C), precursor-membrane (prM) and envelop (E) protein, followed by seven non-structural proteins arranged in the order of NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Rice et al., 1985; Henchal and Putnak, 1990; Murray et al., 2008). The structural and non-structural proteins are constituents of mature DENV particles and components involved in DENV genomic replication, expressed in infected host cells but absent in the virion (Mackenzie et al., 1996; Tan et al., 1996; Welsch et al., 2009; Ranji and Boris-Lawrie, 2010; Gebhard et al., 2012). DENV has four different serotypes (DENV 1-4) that are genetically related but antigenically distinct (Chen and Vasilakis, 2011). The clinical manifestations of dengue infection can range from mild fever to severe plasma leakage with hemorrhagic appearances. In severe dengue (SD), a variety of factors are implicated, including secondary infections, age, viral load, and infection serotypes and genotypes (Burke et al., 1988; Rico-Hesse et al., 1997; Guzman and Kouri, 2003). There has been evidence that secondary DENV-2 infection is more likely to result in severe disease in children than any other serotype (Nisalak et al., 2003; Balmaseda et al., 2006). Contrary to this, primary DENV-1 cases tend to be overt, whereas

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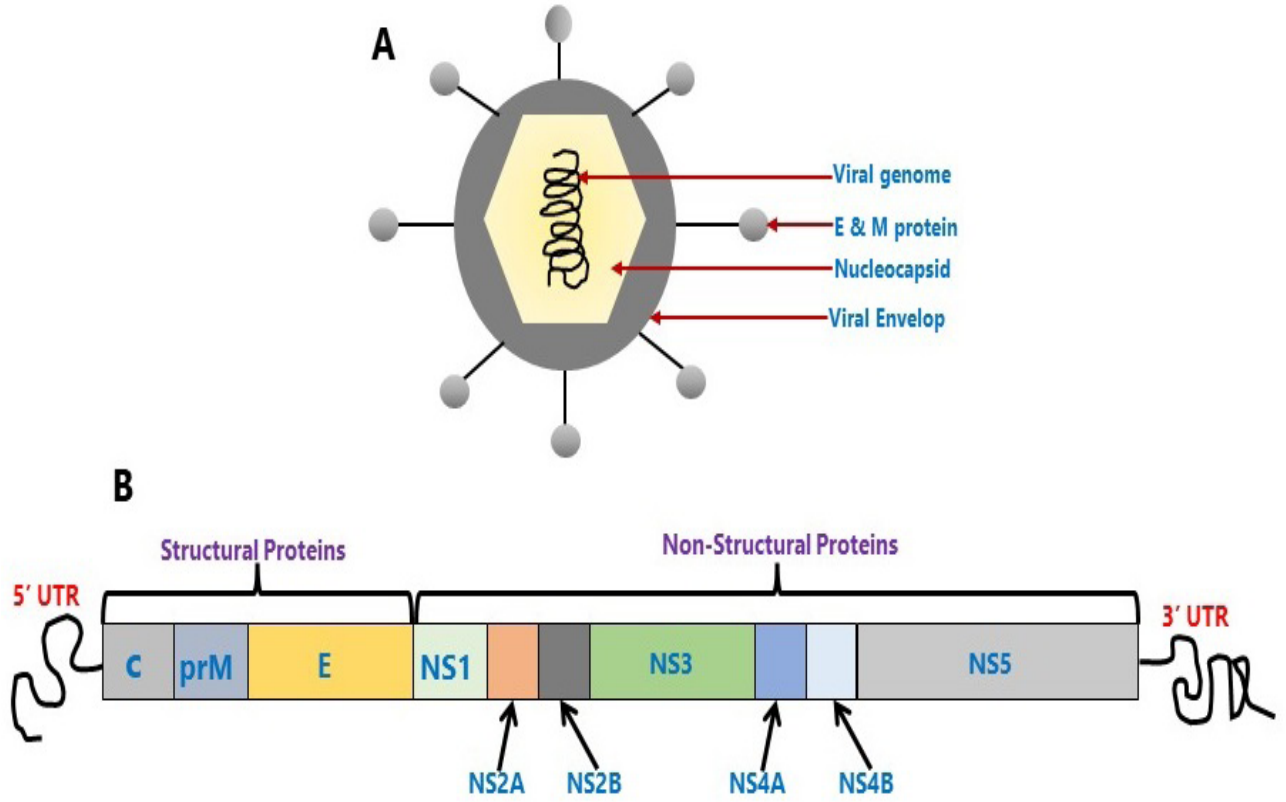

Fig. 1. DENV structure and genome specifying structural and non-structural poly-proteins encoded in the DENV genome.

DENV-2 and DENV-3 cases are typically silent (Guzman et al., 2000, Guzman et al., 2012). The capsid (C) protein is found on the virus speck, forming the viral genomic RNA tagged as nucleocapsid (Ma et al., 2004). The prM is located on the immature viral particle surface. It forms mature viral particles by cleavage to furin during maturation in the *trans*-Golgi apparatus (Kuhn et al., 2002). The E-protein controls viral entry and attachment to the host cells. It is found on the surface of the viral particle (Crill and Roehring, 2001; Rey, 2003; Modis et al., 2005; Huang et al., 2010). NS1 has an important role in viral replication and forms part of the viral replication complex (RC). NS2A is significant in viral assembly, maturation, and evasion of the host immune response. It is also involved in the viral replication complex (RC) (Xie et al., 2013). NS3 is significant during proteolytic cleavage of polyproteins and viral replication. NS3 is a serine protease dependent on cofactor NS2B, considered as a helicase/ATPase (Falgout et al., 1991; Cahour et al., 1992). NS4A and NS4B are components of the viral replication complex. While NS4A is connected to vimentin localization and promotes viral replication (Teo and Chu, 2014), NS4B is an RNA interference (RNAi) suppressor, controlling the host RNAi pathway and supporting viral replication (Kakumani et al., 2013). NS5 is an RNA-dependent RNA polymerase (RdRp) and methyltransferase. It is significant during viral replication (Yap et al., 2007; Zhou et al., 2007). The 5′ UTR is essential for polymerase-promoter recognition and viral replication (Yu et al., 2008; Lodeiro et al., 2009a), while the 3′ UTR is a well-ordered RNA element that is essential for RNA synthesis, viral translation, and replication (Lodeiro et al., 2009b).

Nature has provided man with medicinal plants for thousands of years, dating back to about 2600 B.C. (Cragg and Newman, 2001). Based on their use in traditional medicine (Cragg and Newman, 2001), a number of modern drugs have been isolated from natural sources. In recent times, there has been a shift from the use of orthodox drugs to herbal medicines, which can be said to be "going back to nature." They are widely used as therapeutic agents for the treatment and prevention of diseases (Sharma et al., 2008). Herbal medicinal practise has been well documented and established in Asian countries (Krishnaraju et al., 2005). The majority of the medicinal plants of global importance come from India and China. Pharmaceutical companies are now using medicinal plants for drug research and development due to their extensive knowledge of medicinal plants and their use in the health care system (Krishnaraju et al., 2005). People in Europe and North America also use medicinal plants for the treatment of diseases and for the daily maintenance of good health. This has greatly increased the use of medicinal plants (Krishnaraju et al., 2005). The use of natural products has become an important test material in the development of antiviral agents in traditional medicinal practise (Meneses et al., 2009). Herbal pharmaceuticals are traditional medicines that predominantly use medicinal plant preparations for therapy, as specified by regulatory criteria. Traditional medicine (including herbal medications) has lately been classified by the WHO as therapeutic approaches that

have existed for hundreds of years before the invention and spread of modern medicine. In recent years, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have shown a significant interest in botanical medication development and have examined the regulatory frameworks that regulate their usage. This burgeoning interest has given the natural products industry a major boost, lowering the barriers to entry for botanicals and allied items. These new standards also safeguard botanical market exclusivity and the adoption of synergistic combinations of plant-derived bioactive products. India and China, for example, have a distinct inherent edge over other developing country (Chauhan et al., 2010). Medicinal plants have been used for the treatment of viral infections in humans and animals (Betancur-Galvis et al., 1999; Kudi and Myint, 1999; WHO, 2008). They have been reported to inhibit RNA and DNA replication in viruses (Mahmoudi et al., 2014). During the COVID-19 pandemic, Bhuiyan and his group reported 219 plants belonging to 83 families having potent antiviral activity. From the list, 149 plants belonging to 71 families were evaluated for major secondary metabolites for use against covid-19 (Bhuiyan et al., 2020). Studies have shown that plant used for research often has higher antiviral effect compared to the synthesised analogues (Tang et al., 2012). Development of plant-based antiviral drug could be alternative in fighting viral diseases (Gupta et al., 2005; Atanasov et al., 2015; Newman and Cragg, 2016). The World Health Organization (WHO) encouraged exploiting traditional medicine in order to identify effective and safer antiviral agents from plant sources (Muliawan et al., 2006; Tang et al., 2012; Carvalho et al., 2016). In view of the search for antiviral agents from plants sources, the review discussed the anti-DENV inhibitory effects of some plants and their phytoconstituents.

2. Current gap and regulatory developments

Presently, there is no antiviral drug used for the treatment of DENV disease. Several candidates have been reported for antiviral activity against the virus, but none has turned out to be an anti-DENV drug. DENV patients are normally treated supportively using intravenous hydration therapy with careful observation, especially for those with substantial vascular leakage (Wilder-Smith et al., 2019). Repurposed drugs such as balapiravir, chloroquine, celgosivir, lovastatin, and prednisolone used in clinical trials were not very effective in decreasing viral load or antigenemia of DENV patients (Whitehorn et al., 2014; Low et al., 2017). Clinical studies evaluating balapiravir, a nucleoside analogue prodrug, have shown that it could be used as a potential antiviral medication against dengue. However, in 69 adult dengue patients, there was no strong antiviral effect that resulted in terminating the trial (Nguyen et al., 2013a). Further studies have revealed that balapiravir is not metabolized to its active form in immune-activated cells, suggesting that this may have played a role in the clinical trial results (Chen et al., 2013). The efficacy of chloroquine to combat viral infections as well as to modulate immune responses to infection was investigated. The trial (n = 307 adult patients) failed to demonstrate clear clinical or antiviral benefits (Tricou et al., 2010). A third antiviral candidate is celgosivir, which works by inhibiting cellular glucosidase. Celgosivir had antiviral activity against all four serotypes of DENV isolated *in vitro*, and *in vivo*, celgosivir was found to inhibit DENV-2 in a lethal mouse model (Watanabe et al., 2012). Celgosivir was shown to be safe and well tolerated in a clinical trial of 50 dengue cases, but it was not shown to have antiviral activity at the doses used (Durantel, 2009; Low et al., 2014). Immunomodulatory properties of prednisolone were investigated in the hope that early initiation of treatment would prevent or attenuate severe manifestations of illness. Although 225 paediatric patients were included in the study, no evidence of therapeutic benefit (on the basis of safety) was found (Tam et al., 2012) and there was limited evidence of attenuation of the immune response (on the basis of attenuation of the host response) (Nguyen et al., 2013b). A Randomized, double-blinded placebo-controlled clinical trial was conducted among 300 adult dengue patients. The result showed that lovastatin was safe and well tolerated in adult infected with dengue. However, there was no beneficial effect on the clinical manifestation or on dengue viremia. There is evidence that dengue's severe manifestations are partly caused by inflammation of the vascular endothelium. In addition to lowering lipid levels, statins have pleiotropic effects that improve endothelial function. Furthermore, studies indicate that patients already taking statin therapy fare well from a range of acute inflammatory conditions (Whitehorn et al., 2016). Studies have shown that the level of viremia matches the severity of the disease as observed in severe DENV. The use of antivirals that can decrease the level of viremia and severity of the disease is therefore necessary. Medicinal plant products in this study have proven effective and could be an option for the development of anti-DENV medicine. This review provides an insightful and comprehensive literature discussion on medicinal plants having potent anti-DENV effects.

3. Methodology

This review discussed medicinal plants reported to have potent antiviral effects against DENV. The review shed light on the phytoconstituents of these plants and their possible target on the biology of the virus. The literature search was conducted independently using PubMed, Google and a detailed search in the library database for relevant articles in journals not indexed in PubMed in order to provide a complete science-based survey of the topic. The keywords used for the search included "medicinal plants," "dengue virus," and "antiviral effect."

4. Results and Discussion

4.1. Anti-DENV inhibitory activities of medicinal plants

Since many modern drugs are derived from natural precursors, ethno-pharmacology and traditional medicine offer an attractive option for identifying pharmaceutical starting materials (Newman and Cragg, 2016). Plants contain a wide variety of natural

compounds belonging to different molecular families that have various medicinal properties. The isolation of various bioactive compounds from a variety of plants has established them as sources of novel antiviral compounds (Severson et al., 2008; Li et al., 2009). The antiviral properties of plant-based extracts tend to be higher than synthetic analogues in several studies (Tang et al., 2012). Therefore, the development of plant-derived antivirals may offer a promising alternative to combating viral diseases. Following this, several extracts and some phytoconstituents of medicinal plants were discussed in detail for their anti-DENV inhibitory activities. These plants were firstly verified by a Botanist from Botany Department, Adamawa State University Mubi, Nigeria.

4.2. *Vernonia cinerea* L., *Tridax procumbens* L., *Hemigraphis reptans* (G.Forst.) T. Anderson ex Hemsl., *Hedyotis auricularia* L., *Laurentia longiflora* (L.) Peterm., *Tridax procumbers* L. and *Senna angustifolia* (Vahl) extract

Five traditional medicinal plants, including *V. cinerea, H. reptans, H. auricularia, L. longiflora, T. procumbers,* and *S. angustifolia* extract, were employed in a study to determine their inhibitory activity against DENV-2 NS2B/NS3 protease (Rothan et al., 2013). The highest inhibitory activities (IC_{50}) against DENV NS2B-NS3pro were observed in *S. angustifolia* ethanolic leaf extract with IC_{50} values of 30.1 ± 3.4 µg/mL, *V. cinerea* methanolic leaf extract with IC_{50} values of 23.7 ± 4.1 µg/mL and *T. procumbens* ethanol stem bark extract with IC_{50} values of 25.6 ± 3.8 µg/mL. The methanolic leaf extracts of *V. cinerea*, *T. procumbens*, and *S. angustifolia* preserved the normal morphology of DENV-2 infected Vero cells without causing much cytotoxic effects (Fig. 2). *V. cinerea* methanolic leaf extract showed 80.6% ± 6.1 and *T. procumbens* ethanol stem bark extract showed 64.0% ± 9.4 significant percentage inhibition compared with *S. angustifolia* ethanolic leaf extract with 26.3% ± 3.8 ($p < 0.0001$) measured by plaque formation assay. The observed inhibitory effect was confirmed by quantifying the viral RNA using real-time PCR. A percentage of viral inhibition was observed after treating the infected cells with 50 µg/mL of each extract. The result corresponds to the significant effect observed for the plaque formation assay. *T. procumbens* ethanol stem bark extract and *V. cinerea* methanolic leaves extract showed the highest percentage inhibition with 86.3% ± 2.7 and 79.5% ± 4.3, compared with *S. angustifolia* ethanolic leaves extract which showed 67.2% ± 6.3. *V. cinerea* and *T. procumbens* belong to the family *Asteraceae*. The plants have been documented in the medicinal and aromatic plants database for their medicinal purposes (DOMAP, 2020). *T. procumbens* has antioxidant, antiviral, antifungal, anti-inflammatory, anti-diabetic, and wound healing activity (THDC, 2020). *V. cinerea* is traditionally used for the treatment of diarrhoea, cough, colic pain, roundworms, threadworms, intestinal colic, coughs, dysuria, flatulence, leucoderma, psoriasis, and other chronic skin diseases (DOMAP, 2020). *Cassia angustifolia* Vahl., commonly known as *Senna angustifolia* or *Senna,* is a small, erect, perennial growing shrub with a height of 100-120 cm. *Senna* belongs to the family *Leguminosae* and sub-family *Caesalphine* (Trease and Evans, 1983). *Senna's* medicinal uses were first explored by the Arabians, who have been using the plant since 900 AD (Abulafatih, 1987). In addition to its importance in the Unani system of medicine, the plant has been accepted by several traditional medicine systems in the world, such as Ayurvedic, Homeopathic, and Allopathic medicine, and is also included in the Indian, British, US, and other pharmacopoeias of the world (Shahine, 1994). The leaves are used for the treatment of constipation, loss of appetite, indigestion, malaria, anaemia, jaundice, splenomegaly, and hepatomegaly (Anon, 1966). The leaves and fruits are also used in the form of decoctions, powders, confections, and many other herbal and household preparations. Unani and Ayurvedic systems prescribe the administration of an infusion of the leaves or fruit of the plant (Anon, 1966 and Gupta, 1971). The antiviral activity of *V. cinerea* and *S. angustifolia* extracts could be attributed to the fact that they have over twenty-seven phytochemicals with gallic acid (Fig. 3) and being the most predominant phenolic compound (Rajamurugan et al., 2011). These compounds were reported to have high antiviral activity against rhinovirus (Choi et al., 2010). The extract also has a vast amount of sesquiterpene lactone that exhibited antiviral activity against Herpes simplex type-1 parainfluenza and HCV (Hwang et al., 2006; Zhu et al., 2008). Additionally, *S. angustifolia's* higher inhibitory effect against DENV-protease could be due to the high content of phenolic glycoside in the ethanolic extracts (Van Hoof et al., 1989). Antiviral activities of phenolic glycosides have been documented against respiratory syncytial viruses, parainfluenza type 3 virus (Ma et al., 2001), HSV-1, and poliovirus virus (De Rodriguez et al., 1990). The antiviral activity of *T. procumbens* could be attributed to different flavonoids in the extract, including quercetin, apigenin, kaempferol (Jindal and Kumar 2012), limonene, selinene, falcarinol, zerumbone (Joshi and Badakar, 2012) and pentahydroxyflavone 7-β-D-glucopyranoside (Ali et al., 2001) that have been reported to have antimicrobial activity. These flavonoids have been documented to exhibit inhibitory activities against DENV-2 NS2B/NS3 protease (Tan et al., 2006a).

4.3. *Andrographis paniculate* (Burm. f.) and *Ocimum sanctum* L. methanol extract

A. paniculata and *O. sanctum* belong to the families *Acanthaceae* and *Lamiaceae,* respectively. Both plants are documented in Ayurvedic medicine due to their healing properties (Akbar, 2011). *A. paniculata* has anti-HIV (Nanduri et al., 2004), antihepatitis (Tang and Eisenbrand, 1992), antidiarrheal and anti-inflammatory activity (Shen et al., 2002), and antimicrobial and antimalarial activity (Wiart et al., 2005). *O. sanctum,* also known as Tulsi, mostly consumed as tea, is used for the treatment of malaria, common colds, inflammation, stomach disorders, headaches, heart disease, and poisoning (Warrier, 1995; Biswas and Biswas, 2005). *A. paniculata* and *O. sanctum* methanol extracts were investigated for their inhibitory effects against DENV-1 on HepG2 cells. The antiviral activity was based on the

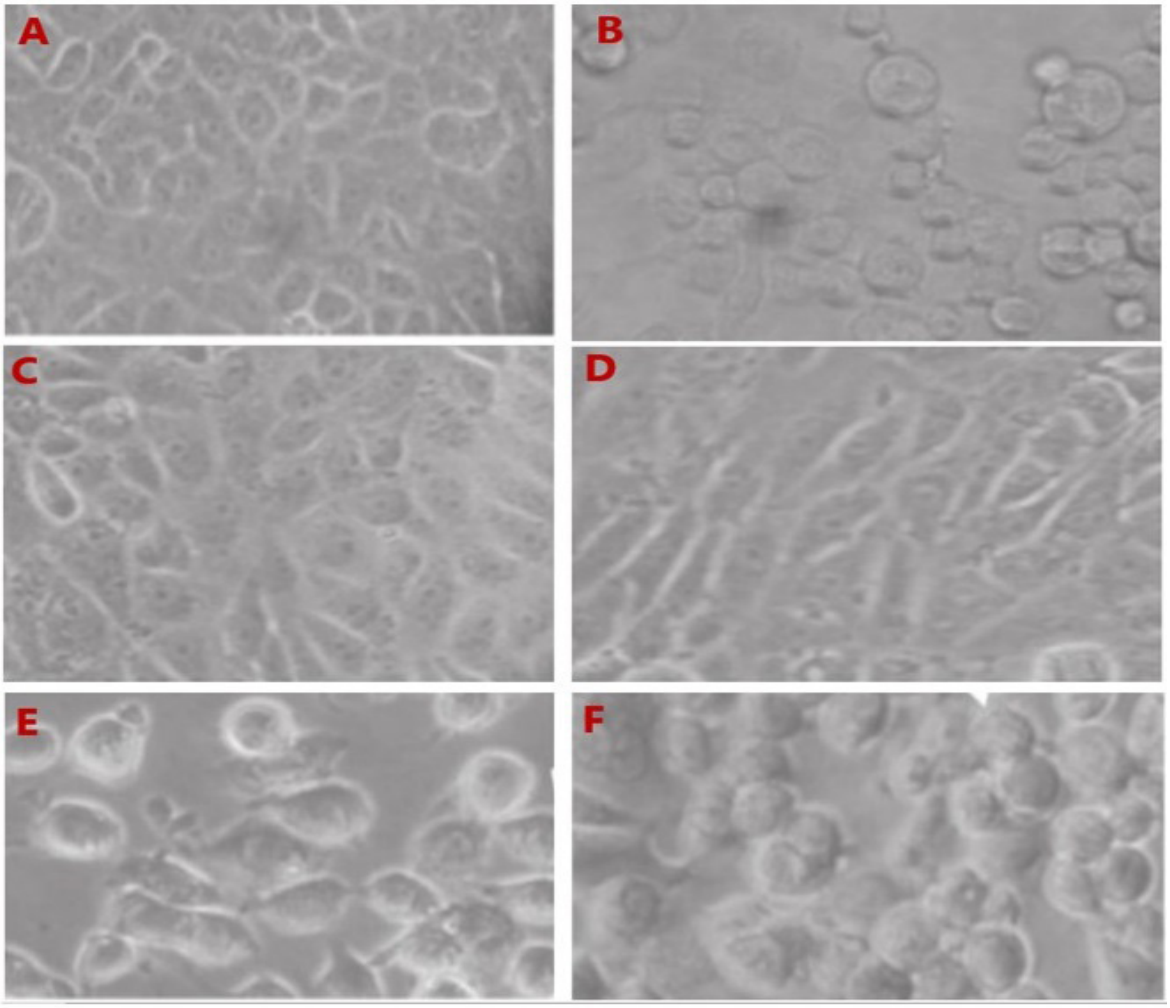

Fig. 2. Morphological changes observed in DENV-2 infected Vero cells upon 72 hours post treatment with *V. cinerea* methanol leaf extract, *T. procumbens* ethanol leaf extract and *S. angustifolia* methanol leaf extract. **(A)** Normal Vero cells morphology prior to DENV-2 infection. **(B)** Cells Morphology post-DENV-2 infection with cytopathic effects (CPE). **(C)** Infected Cells showing almost normal monolayer sheet without CPE after treatment with *V. cinerea* methanol leaf extract. **(D)** Infected Cells showing almost normal monolayer sheet and less CPE upon treatment with *T. procumbens* ethanol leaf extract. **(E and F)** Infected cells showing reduced CPE with round and spindle shape upon treatment *S. angustifolia* methanol leaf extract (Rothan et al., 2013).

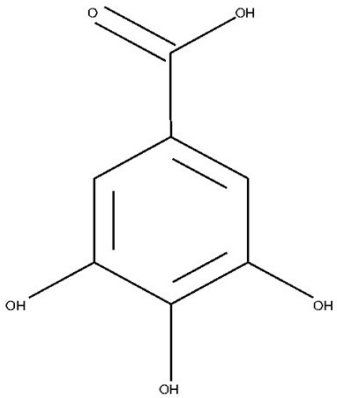

Fig. 3. Chemical structure of gallic acid identified from *V. cinerea* L. and *T. procumbens* L. as an antiviral (Sravan et al., 2015).

CPE, MTT assay, and plague inhibition assay. MNTD was conducted to determine the maximum concentration of methanolic extract that could be non-toxic to the cells. *A. paniculata* and *O. sanctum* methanol extracts had 20.00 and 23.44 µg/mL. This indicates that the extracts below the MNTD value showed no cytotoxicity. CPE was defined based on the degree of inhibition. The inhibition of DENV-1-infected HEPG-2 cells by *A. paniculate* methanol extract showed that the degree of inhibition for both MNTD + virus and ½MNTD + virus was 50% and less than 50%, respectively. The negative control had 100% inhibition (++++) without showing any sign of CPE, and the positive control cells showed 50% inhibition (+). *O. sanctum* methanol extract at MNTD + virus and ½MNTD + virus had 75% CPE inhibition (+++) compared to the positive control,

which had 50% inhibition (+) and the negative control, which had 100% inhibition (++++). Negative control is untreated cells, while positive control is cells infected with DENV-1. The above findings were verified by the percentage of cell viability using the MTT assay. *A. paniculate* methanol extract at MNTD + virus and ½MNTD + virus recorded a 77.1% and 71.9% increase compared to the positive control, which had 61.35% cell viability. Negative controls had a total of 100% cell viability. Similarly, *O. sanctum* methanol extract at MNTD + virus (64.29%) and ½MNTD + virus (68.67%) increases the percentage cell viability compared to the positive control (49.59%). Negative controls had a total of 100% cell viability. The anti-DENV properties of the extracts were further evaluated using a plague inhibition assay. The results showed that *A. paniculate* methanol extract at ½MNTD + virus showed a total of 48.3 ± 2.9 PFU/mL lower than the positive control (78.3 ± 2.9 PFU/mL), while the ½MNTD control (13.3 ± 10.4 PFU/mL) was lower than the negative control (23.3 ± 27.5 PFU/mL). Similarly, *O. sanctum* methanol extract at ½MNTD significantly inhibited plague formation compared to the positive control. The extract at ½MNTD showed a total of 157.5 ± 67.6 PFU/mL lower compared to the 1020.0 ± 271.0 PFU/mL recorded in the positive control. However, it was higher in the ½MNTD control (58.8 ± 45.2 PFU/mL) than in the negative control (6.3 ± 7.5 PFU/mL). These findings revealed that *A. paniculate* and *O. sanctum* methanol extract had an anti-DENV inhibitory effect (Anna et al., 2014). Similarly, Ramalingam et al. (2018) determined the antiviral activity of *A. paniculata* ethanolic and aqueous extracts. The antiviral activity was evaluated using the MTT assay and quantitative real-time polymerase chain reaction (RT-qPCR) against DENV 1, 2, 3, and 4 infected Vero cells. *A. paniculata* extracts exhibited DENV virus serotype 1-4 inhibitory activity. The results showed 55% - 97% cell viability for DENV 1-4 infected cells at different durations, while viral load estimated using RT-qPCR between DENV and healthy controls revealed that DENV-1 had 5.6×10^2 copies/mL, DENV-2 had 4.8×10^2 copies/mL, DENV-3 had 5.5×10^2 copies/mL, and DENV-4 had 5.3×10^2 copies/mL. The findings showed significant changes reflected in the RT-qPCR assay (Ramalingam et al., 2018). *A. paniculate* extract contains a class of compounds called diterpenoids. It contains the major diterpenoids called andrographolide (Cheung et al., 2001; Pholphana et al., 2004). Andrographolide from the *A. paniculate* aqueous extract was reported to have anti-HIV activity (Chang and Yeung, 1988). Additionally, neo-andrographolide and 14-deoxy-11,12-didehydroandrographolide was isolated from *A. paniculate* (Fig. 4a, Fig. 4b, and Fig. 4c), it inhibits herpes simplex virus 1 (HSV-1) (Wiart et al., 2005). *A. paniculate* ethanol extract and andrographolide inhibited the expression of Epstein-Barr virus (EBV) lytic proteins during the viral lytic cycle in P3HR1 cells. These constituents also inhibited HIV by interfering with HIV-induced cell fusion and HIV binding to the cell (Chao and Lin, 2010). The inhibitory effect of the methanol extract reported in this study could exhibit a similar mechanism to DENV-1. Andrographide could block or bind the envelope protein of DENV-1, preventing membrane adhesion since the envelope is important during cell membrane adhesion (Modis et al., 2004). The inhibitory effect of *O. sanctum* methanol extract could be due to the plant's flavonoid content, orientin and vicenin-2 (Fig. 4d and Fig. 4e) (Anna et al., 2014). Orientin isolated from *Trollius chinensis* Bunge showed antiviral activity against para-influenza virus type 3 (Yao-Lan et al., 2002), while vicenin-2 isolated from *Urtica circularis* showed anti-inflammatory activity (Carla et al., 2011). Orientin and vicenin-2 have also been reported to have antioxidant properties (Uma et al., 1999). The inhibitory effect could be due to the blockade capability of the extracts on the envelope protein, preventing the viral inflow into the cells. For the envelope glycoprotein of flavivirus, fusion of the virus is a necessary step during fusion process and cell membrane binding to cells (Más and Melero, 2013). Another reason for the antiviral activity could be that the reverse transcriptase of the virus was affected. A flavonoid was found to have an inhibitory effect on viral reverse transcriptase (Ono et al., 1990). Flavonoid from *O. sanctum* methanol extract can hinder the reverse transcriptase of DENV.

4.4. *Cissampelos pareira* Linn. ethanol extract

C. pareira belongs to the family *Manispermaceae*. It is a perennial climbing herb having small greenish-yellow flowers. Its traditional uses include treatment of inflammation, gastro-toxicity, diarrhoea, haemorrhage, diabetes, pain, cancer, sores, cardiotoxicity, and hepatoprotective activity (Singh and Pandey, 1998). Pharmacological studies revealed that it has antioxidant activity, anti-nociceptive and anti-arthritic activities (Amresh et al., 2007a), anti-inflammatory activity (Amresh et al., 2007b), anti-ulcer activity and anti-asthmatic activity (Amresh et al., 2007c), anti-diabetic activity (Yadav et al., 2013), anti-anxiety activity (Thakur and Rana, 2013), anti-anxiety activity (Thakur and Rana, 2013), and anti-fertility activity (Ganguly et al., 2007). Considering the usefulness of the plant in treating several diseases, Sood et al. (2015) evaluated *C. pareira* ethanol extract for its antiviral activity against DENV serotypes. This was done using cell-based assays, assessment of DENV NS1 antigen secretion and a plague formation assay. *C. pareira* ethanol extract was tested in a type-1 assay against all DENV serotypes. The extract was effective in inhibiting DENV with an IC_{50} value of 11.11 µg/mL on DENV-1, 1.97 µg/mL on DENV-2, 3.17 µg/mL on DENV-3 and 1.23 µg/mL on DENV-4. The extract further inhibited all DENV serotypes even after their entry into cells with an IC_{50} value of 100 µg/mL on DENV-1, 125 µg/mL on DENV-2, 78 µg/mL on DENV-3, and 100 µg/mL on DENV-4 on the type-2 assay. The kinetics of virus inhibition by *C. pareira* ethanol extract was analysed in a type-3 assay for the presence of viral NS1 antigen. In control experiments where infected cells were not exposed to *C. pareira* ethanol extract, NS1 antigen was detected after day 2 onwards and raised throughout the course of the experiment. In the experiments, exposure of cells with *C. pareira* ethanol extract at concentrations of 22 µg/mL, 66 µg/mL and 200 µg/mL had a dose-dependent inhibitory effect on NS1 antigen secretion. While the

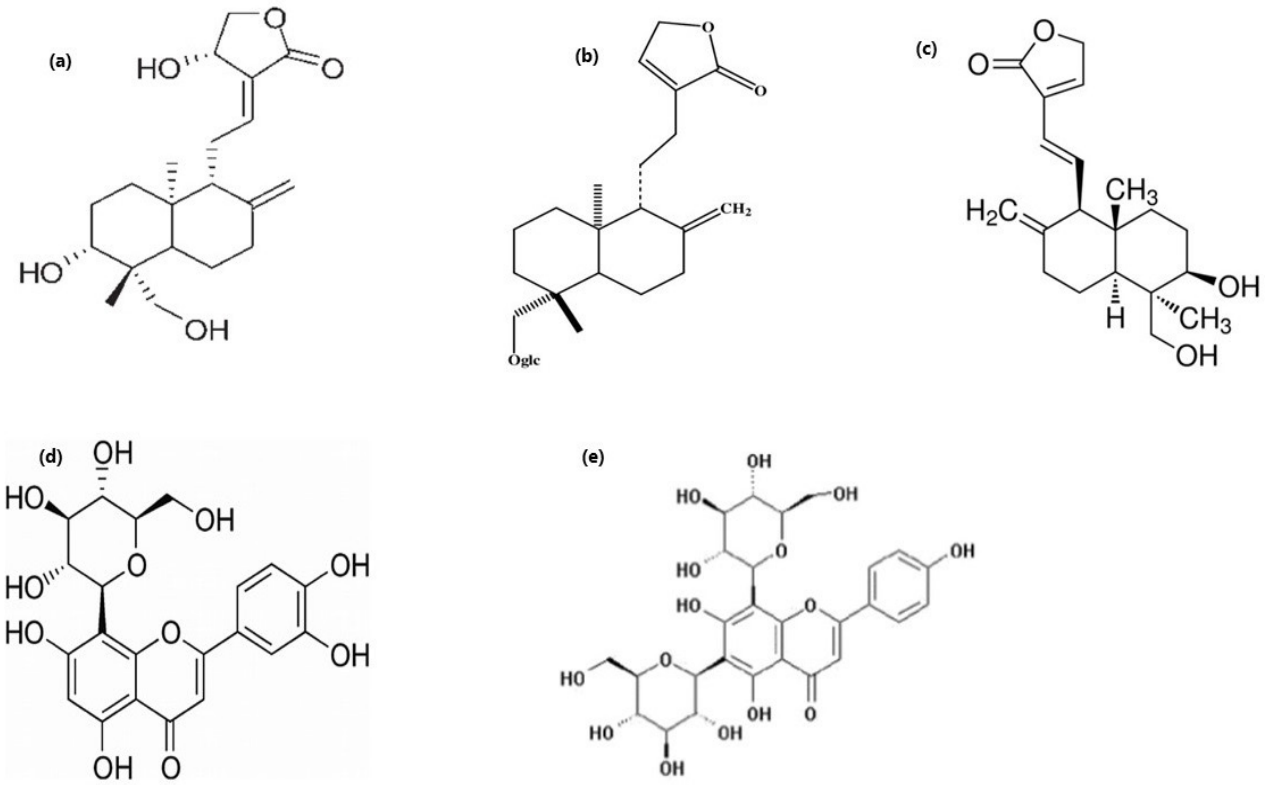

Fig. 4. Chemical structure of **(a)** Andrographolide; **(b)** Neo-andrographolide and **(c)** 14-deoxy-11,12-didehydroandrographolide (Pfisterer et al., 2010) and **(d)** Orientin (Thangaraj et al., 2018) and **(e)** Vicenin-2 (Islam et al., 2014) isolated from *A. paniculate* (Burm. f.) and *O. sanctum* L. having antiviral activity.

inhibition resulting from exposure to a low dose of *C. pareira* ethanol extract was manifested after day 4 post-infection, inhibition at higher doses was evident earlier and at relatively higher magnitudes. Further, DENV-3 was pre-incubated with increasing concentrations of *C. pareira* ethanol extract at different time points before infection (type-1 assay) and overlay. Plaque counts revealed a dose and time-dependent virucidal effect of *C. pareira* ethanol extract on DENV-3.

The IC_{50} values corresponding to DENV-3 dosages of 50, 500, and 5000 PFUs were 9.92, 12.5, and 44.45 µg/mL respectively. This means the antiviral potency of *C. pareira* ethanol extract extends over a wide range of viral loads. Next, *C. pareira* ethanol extract was tested for its efficacy *in vivo* using an AG129 mouse. Recently, the AG129 mouse has emerged as a promising DENV model for testing potential DENV inhibitors (Shresta et al., 2006; Schul et al., 2007). A mouse brain-passaged DENV-2 (New Guinea C)-derived challenge strain was developed (Mani et al., 2013). A dose of 10^6 PFU (given intravenously) was lethal to AG129 mice, causing them to die 25 days after infection. They developed ruffled fur, lethargy, hunched backs, and hind limb paralysis prior to death. A dose-dependent increase in the median survival time (MST) of challenged mice treated orally with *C. pareira* ethanol extract twice a day for 5 days post-challenge was observed. Under the experimental conditions, the MST of challenged mice was 19 days. At 125 mg twice a day for five days, survival was 50%, and the median survival time was 28 days ($p = 0.1$). The survival rate rose to 67% when the dosage was doubled. In comparison with the placebo-treated group (0.25% methyl cellulose), the 250 mg/kg dose provided significant protection ($p = 0.021$) (Sood et al., 2015). *C. pareira* aerial parts and roots have been reported to contain alkaloids including hayatidin, hayatin, hayatinin, cissampareine, cissampeline, tetradrine, warifterine, sepeerine, pareirubrines A and B, bebeerine, and cissampelo-flavone, sterol, quercitol, essential oil, and saponins (Dwuma-Badu et al., 1975). Recently *C. pareira* was reported for anti-SARS-CoV-2. The extract showed 98% percentage inhibition on SARS-CoV-2 replication in infected Vero cell. Pure compounds isolated from *C. pareira* including of pareirarine, cissamine, magnoflorine exhibited 40-80% inhibition (Haider et al., 2022).

4.5. *Carica papaya* L. and *Psidium guajava* L. extract

C. papaya is a medicinal plant belonging to the family *Caricaceae*. It is produced in many parts of the world, with India being one of the largest producers globally (FAOSTAT, 2012). *C. papaya* leaves has been reportedly used for centuries in folk medicine (Singhai et al., 2016). It is rich in phytochemicals like alkaloids, flavonoids, saponins, tannins, and glycosides (Ikeyi et al., 2013). *C. papaya* has antioxidant activity (Imaga et al., 2010), anti-inflammatory activity (Owoyele et al., 2008), anti-tumour effects (Otsuki et al., 2010), and wound healing

properties (Gurung et al., 2009). *Psidium guajava* belongs to the family *Myrtaceae*. *P. guajava* is richly grown for its fruit (Dakappa et al., 2013). The fruits and leaves are highly enriched in antioxidants. The fruits and leaves contain alkaloids, flavonoids, triterpenoid, glycosides, steroids, tannins, and saponins. The fruits and leaves also contains essential oils, minerals, iron, phosphorus, polysaccharides, and vitamins (Rueda et al., 2005). *P. guajava* fruits and leaves also contains oleanolic acid, lyxopyranoside, arabopyranoside, guaijavarin, and quercetin (Arima and Danno, 2002; Das et al., 2011). The fruits and leaves have anti-mutagenic activity (Grover and Bala, 1993), antioxidant activity (Thaipong et al., 2005; Manikandan and Vijaya, 2015), antimicrobial activity (Limsong et al., 2004; Joseph and Priya, 2011), and anti-inflammatory activity (Jeong et al., 2014). Due to the abundant phytochemical constituents and pharmacological activities reported, Leli et al. screened eight Indonesian indigenous plant extracts against DENV-2 *in vitro* using the Huh7it-1 cell line. *C. papaya* and *P. guajava* extracts showed the most potent antiviral activity compared to other plant extracts (Leli et al., 2017). *C. papaya* and *P. guajava* extracts had low cytotoxicity of 2.5% and 11.3%, respectively, and inhibited viral replication by 89.5% and 92.6%, respectively. In a dose-dependent test, *P. guajava* extract had a CC_{50} of 153.18 µg/mL, an IC_{50} of 7.2 µg/mL, and an SI of 21.28, whereas *C. papaya* had a CC_{50} of 244.76 µg/mL, an IC_{50} of 6.57 µg/mL, and an SI of 37.25. *In vitro, C. papaya and P. guajava* extracts exhibited anti-dengue activity *in vitro* (Leli et al., 2017). Similarly, Fadzilah et al. studied the interactive effect of *C. papaya* leaf extract on DENV-2 infected Vero cells. The extract inhibited DENV-2 infected cells. *C. papaya* leaf extract had a CC_{50} of 104.37 µg/mL, an IC_{50} value of 137.6 µg/mL and an SI of 75.85 (Fadzilah et al., 2018). Another study revealed that *C. papaya* leaf juice was administered to DENV patients having high fever, headache, severe muscle pain, joint pain, body rashes, itching, and low platelet count in the blood. The leaf juice was effective in reducing DENV fever and increased the patient's platelet count within 24 hours of administration. Patients' platelet rise was between 8000 to 11000 since the increase varied among patients. The patients also confirmed significant improvement in their health status within 24 hours of the leaf juice administration (Kala, 2012). To date, people are still taking the leaf juice or decoction to prevent DENV infection locally. The observed effects from these plant extracts can be due to the high amounts of phenolic compounds, mainly flavonoids such as quercetin (Fig. 5), which was identified to have anti-dengue activities. Quercetin consistently exhibited antiviral activity against DENV-2 and hampered DENV replication with an IC_{50} of 35.7 µg/mL (Zandi et al., 2011). Quercetin inhibited DENV non-structural proteins NS2B/NS3 by the formation of six hydrogen bonds and amino acid residues at the binding site of the receptor, including Ala 164, Asn 152, Lys 74, Asn 167, Leu 149, and Gly 87 (Senthilvel et al., 2013). Quercetin and its derivatives (quercitrin and myricetin 3-*O*-β-D-galactopyranoside) inhibited HIV-1 reverse transcriptase, all with an IC_{50} value of 60 µm (Yu et al., 2007).

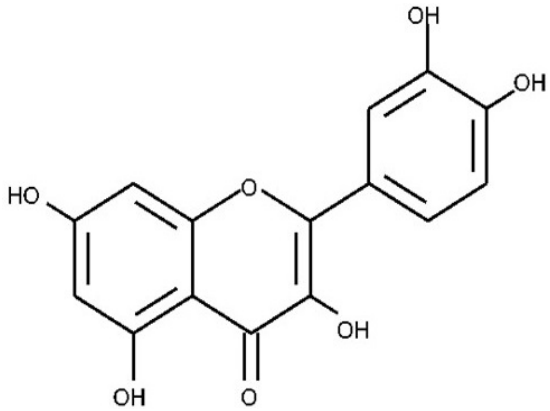

Fig. 5. Chemical structure of quercetin identified as antiviral from *C. papaya* L. (Sanda et al., 2012).

4.6. *Sambucus nigra* L. methanol extract

S. nigra L. belongs to the family *Adoxaceae*. It contains flavonols, glycosides, organic acids, and anthocyanins (Nakajima et al., 2004; Wu et al., 2004). It is rich in antioxidants (Zakay et al., 2004; Zafra et al., 2007; Jing et al., 2008), vitamins, minerals, carbohydrates (Veberic et al., 2009), and has high amounts of anthocyanins (Fossum et al., 2008). *S. nigra* leaves, bark, flowers, and fruit berries have been utilized for many traditional uses. In addition to boosting the immune system, berries can also be used to treat obesity and diabetes. It also has antitumor activity, antibacterial activity, antifungal activity, diuretic, and laxative activity (Gray et al., 2000; Chrubasik et al., 2008; Picon et al., 2010; Chen et al., 2012; Bhattacharya et al., 2013; and Folmer et al., 2014). The fruit berries have been reported to have antiviral activity against influenza A and B (Zakay et al., 2004), Herpes simplex-1 viruses (Morag et al., 1997), HIV (Sahpira-Nahor et al., 1995), and pathogenic chicken coronavirus (Chen et al., 2012). In the above manner, Castillo-Maldonado et al. (2017) evaluated *S. nigra* methanol leaf and flower extract for anti-DENV-2 activity. The antiviral activity was estimated under three conditions (i) methanol extract was added 1 hour before DENV-2 was added, (ii) pre-incubation of cells with DENV-2 before extract addition, and (iii) one-hour pre-incubation of DENV-2 and extract followed by addition of the mixture to the cells (BHK-21 and Vero). Toxicity bioassay revealed LD_{50} for *S. nigra* leaf and flower extracts was higher than 1000 µg/mL which indicates low toxicity. *S. nigra* methanol extracts treated at 400 µg/mL revealed between 60% and 80% cell viability. *S. nigra* leaf and flower methanolic extracts showed protection against DENV-2 induced cytopathic effect on BHK-21 cells at 400 µg/mL. The finding corresponds to a report by Roschek et al. (2009) which showed that *S. nigra* elder berry fruit-derived compounds exhibited anti-human influenza A (H1N1) activity at 252 ± 34 µg/mL. Pre-incubation of cells with *S. nigra* methanolic extracts to time difference revealed that the maximum effect was achieved when DENV-2 was pre-incubated with the extracts for 1 h and then added to the cells, although these images were

not provided in the article. The inhibitory activity was attributed to *S. nigra* flavonoids. Two flavonoids were isolated from the elder berry extract which inhibited H1N1 infection *in vitro* through binding to H1N1 virions and obstructing host cell entry. These compounds are 5,7,3′,4′-tetra-O-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl) chroman-3-yl-3,4,5 trihydroxycyclohexanecarboxylate Fig. 6a and Fig. 6b (Roschek et al., 2009). Flavonoids are not the only plant-derived compounds that are antiviral. Plant-derived proteins, such as lectins, have also been found to inhibit virus interactions with their envelope proteins or with their receptors (François and Balzarini, 2012; Hidari et al., 2013). *S. nigra* berry has been reported to have three lectins agglutinin-I (SNA-I), agglutinin-II (SNA-II), and agglutinin-III (SNA-III) (Mach et al., 1991a and Mach et al., 1996b) which it uses in blocking host cell receptor in IBV. *S. nigra* lectins can bind directly to virus proteins and stop infection (Chen et al., 2012). *S. nigra* effect on viral tropism is essential. Further studies are necessary to provide an adequate understanding of the observed activity and how S. *nigra* exerts its effect.

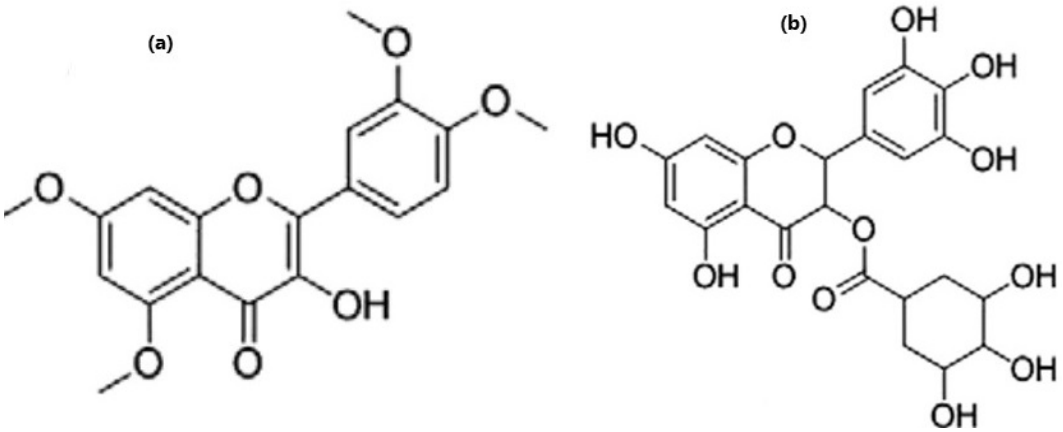

Fig. 6. Chemical structures of **(a)** 5,7,3′,4′-tetra-*O*-methylquercetin and **(b)** 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl) chroman-3-yl-3,4,5 trihydroxycyclohexanecarboxylate isolated from *S. nigra* L. having antiviral activity (Roschek et al., 2009).

4.7. *Curcuma longa* L. extract

C. longa, called turmeric in English, belongs to the family *Zingiberaceae* (Thomas-Eapen, 2009). It is used as a food product and in herbal medicines. The pharmacological properties include antioxidant, anti-inflammatory, antimicrobial, anti-angiogenic, anti-clotting, anticancer, skin regeneration, antiplatelet aggregation, and antiviral activities (Aggarwal and Harikumar, 2009; Akbik et al., 2014; Kocaadam et al., 2017; Widowati et al., 2018); anti-diabetic (Kuroda et al., 2005), and Alzheimer's effects (Kim et al., 2001) were also reported. Due to the medicinal uses of turmeric, the extract was harnessed for its anti-DENV inhibitory activity. Ichsyani et al. (2017) studied the effects of *C. longa* extract *in vitro* and *in vivo* against DENV-2 along with a toxicity study of the mouse liver and kidney. After mice were orally administered with 0.147 mg/mL 2 hours after being injected with DENV-2 infected Huh7it-1 cells, anti-DENV activity was evaluated. The serum was collected at 6 hours and 24 hours after infection, which was used for a focus assay to evaluate viral load. There was a remarkable decrease in viral load after 24 hours of treatment with *C. longa* extract, with IC_{50} and CC_{50} values of 17.91 µg/mL and 85.4 µg/mL respectively. A toxicity study of *C. longa* extract showed an LD_{50} of 10 g/kgBW in the mice. The dose showed neither toxic symptoms nor the death of mice after 72 hours of administration. Histopathology examination revealed no abnormalities in the liver and kidneys of mice that were orally administered 500 mg/kgBW and 1000 mg/kgBW of *C. longa* extract for 14 days. SGPT, SGOT, urea, and creatinine showed no significant increase (Ichsyani et al., 2017). An acute toxicity study of *C. longa* extract having an LD_{50} of 5 g/kgBW showed no toxic effect on the liver, heart, and kidney histology studied in mice and monkeys (Bhavani et al., 1980). *C. longa* was also reported to be a potent inhibitor of DENV by targeting the NS2B/NS3 protein of DENV (Tan et al., 2006b). The observed effect was believed to be due to curcumin (Fig. 7). Curcumin has been shown to inhibit IMDPH, an enzyme that catalyses purine oxidations and thus plays a significant role in DNA and RNA synthesis as well as signal transduction (Moghadamtousi et al., 2014). Curcumin is one of the essential constituents of *C. longa* that has antiviral properties. Padilla et al. (2014) disclosed that curcumin from *C. longa* interfered with DENV infection processes. The interference can be due to curcumin's effects on various cellular systems, including the cytoskeleton, the ubiquitin-proteasome system, and the apoptosis process. The selective index of curcumin was 2.56 while the selective index of *C. longa* extract in the present study was 4.8. This could be due to several differences in the experimental methods and cultured cells. Curcumin's antiviral activity should be evaluated to determine the actual mechanism of action against DENV.

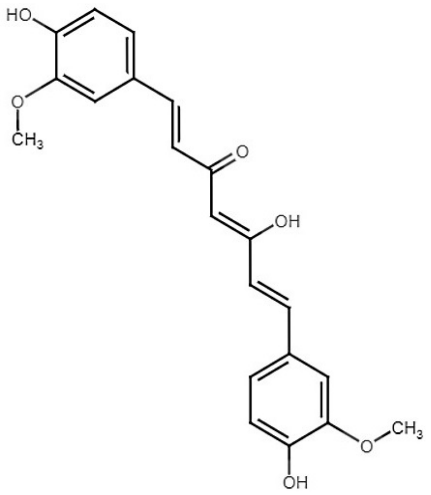

Fig. 7. Chemical structure curcumin isolated from *C. longa* L. having antiviral activity (Owais et al., 2014).

4.8. *Pterocarpus indicus* (narra.) extract

P. indicus leaf extract was evaluated *in vitro* against DENV replication on Huh-7 it-1 cells using the Focus assay and MTT assay (Dewi et al., 2017). *P. indicus* crude leaf extract, hexane, and ethyl acetate fraction showed very strong inhibition of DENV replication at < 0.125 µg/mL. On the other hand, butanol and the aqueous fraction of *P. indicus leaves* showed low inhibition of DENV replication with an IC_{50} of 15.68 µg/mL and 20.76 µg/mL. The crude extract, hexane, and ethyl acetate fractions were found to be low-cytotoxic, with CC_{50} values of 174.31 µg/mL, 35.67 µg/mL, and 21.07 µg/mL, respectively, while butanol and aqueous fractions had CC_{50} values of 11.75 µg/mL and 21.37 µg/mL, respectively. The crude extract, hexane, and ethyl acetate fractions demonstrated strong inhibition with SI values of 1.392, 285.36, and 168.56, respectively, whereas butanol and aqueous fractions demonstrated low SI values of 0.75 and 1.03, respectively. Further evaluation of the sub-fraction tagged Pi2.12.1 on DENV replication using a focus assay revealed IC_{50}, CC_{50}, and SI values of 1.174 µg/mL, 48.6 µg/mL, and 24.16, respectively. Evaluation of a sub-fraction tagged Pi 2.12 on DENV replication to determine the mechanism of inhibition revealed that the addition of Pi.2.12 to block DENV receptor at the entry stage showed the lowest inhibition at 24.23%. Pre-inhibition of the Pi.2.12 sub-fraction revealed 63.65 % inhibition, whereas the addition of Pi.2.12 after DENV infected Huh7 it-1 cell revealed 90.19% inhibition. Pre- and post-inhibition, however, showed 100% inhibition, indicating the pre-and post-inhibition mechanism to be the strongest. The findings showed that sub-fractions have antiviral activity against DENV-infected cells (Dewi et al., 2017). The inhibitory effect could be due to procyanidin. Procyanidin has a protease inhibitory effect and antiviral activity (Appanah and Weinland, 1993). Procyanidin inhibited herpes simplex virus type 1 (HSV-1) through an extracellular mechanism (Shahat et al., 2002).

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4.9. *Lawsonia inermis* L., *Dryobalanops aromatica* C.F. Gaertn, *Punica granatum* L., *Zizyphus jujuba* Lam. and *Zingiber zerumbet* L. extract

In an attempt to determine DENV protease inhibitory activity, Salleh et al. (2019) evaluated five Malaysian medicinal plant extracts, *e.g.*, *L. inermis, D. aromatica, P. granatum, Z. jujuba* Lam., and *Z. zerumbet* against DENV2 NS2B/NS3B for their potent inhibitory activity (Salleh et al., 2019). Their findings revealed that *D. aromatic* methanol bark extract exhibited the most potent antiviral effect with 99.70% inhibition and an IC_{50} value of 0.30 ± 0.16 µg/mL and ethyl acetate leaf extract with an inhibitory effect of 95.10% and an IC_{50} value of 3.49 ± 0.65 µg/mL at a concentration of 200 µg/mL. This was followed by *Z. jujuba* methanol bark extract with 94.58% inhibition, while the ethyl acetate showed an extract of 93.10% and an IC_{50} value of 2.47 ± 0.72 µg/mL. *Z. jujuba* methanol showed 57.67% while the ethyl acetate leaf extract showed 94.44% and an IC_{50} value of 7.83 ± 0.99 µg/mL. *P. granatum* methanol bark extract showed 91.84% and an IC_{50} value of 1.72 ± 0.29 µg/mL

while the ethyl acetate bark extract exhibited 85.36% and an IC_{50} value of 17.55 ± 0.54 µg/mL. *P. granatum* methanol leaf extract had a 91.02% inhibitory effect and an IC_{50} value of 3.10 ± 0.14 µg/mL while the ethyl acetate leaf extract had a 92.23% inhibitory effect and an IC_{50} value of 9.03 ± 3.21 µg/mL. *Z. zerumbet* rhizomes ethyl acetate extract showed the most significant inhibitory effect with 90.32% and an IC_{50} value of 2.39 ± 0.86 µg/mL compared to the hexane extract, which had 63.25% and the ethanol extract, which had 32.29%. *L. inermis* methanol bark extract with 87.99% and an IC_{50} value of 0.33 ± 0.14 µg/mL and ethyl acetate bark extract with 86.43% and an IC_{50} value of 0.77 ± 0.37 µg/mL exhibited the most significant inhibitory effect compared to the methanol leaf extract with 56.52% and ethyl acetate leaf extract with 17.62%. *D. aromatica* belongs to the family *Dipterocarpaceae* (Wibowo et al., 2012). It has been reported to have anti-HIV-1 activity and cytotoxic activity (Dai et al., 1998; Pacher et al., 2002), antifungal activity (Pacher et al., 2002), and antioxidant activity (Ryu et al., 2002), like other Dipterocarpaceae. The stem bark extract contains phytochemicals including tannins, coumarin, flavonoids, saponins, and cardiac glycosides (Yakubu et al., 2019). Additionally, Wibowo et al. (2011) isolated resveratrol oligomers (ε-viniferin, diptoindonesin A, laevifonol, α-viniferin, ampelopsin E, malaysianol A, flexuasol A, vaticanol B, vaticanol C and bergenin) from the extract of *D. aromatica* (Wibowo et al., 2011). The potent antiviral effect of the plant extract was attributed to the resveratrol and its oligomers (Fig. 8). Resveratrol was reported to have antiviral activity against Epstein-Barr virus (EBV) (Yiu et al., 2010 and De Leo et al., 2012), enterovirus 71 (EV71) (Zhang et al., 2015), and herpes simplex virus (HSV) (Faith et al., 2006 and Chen et al., 2012), influenza virus (Lin et al., 2015), respiratory syncytial virus (RSV) (Zang et al., 2011 and Liu et al., 2014) and rhinovirus (Mastromarino et al., 2015). Different inhibitory mechanisms of resveratrol have been reported in viruses, including that resveratrol's mechanism of action is linked to protein synthesis inhibition, a decrease in the production of reactive oxygen species, and obstruction of transcription factors AP1 and NF-$\kappa\beta$ in the Epstein-Barr virus (De Leo et al., 2012). The inhibition of viral protein 1 (VP1) synthesis and proinflammatory cytokine phosphorylation by resveratrol was associated with the inhibition of EV 71 (Zhang et al., 2015). Resveratrol inhibited HSVs by inhibiting DNA synthesis, early and late HSV protein expression, NF-$\kappa\beta$ and extracellular signal-regulated kinases/mitogen-activated protein kinases (ERK/MAPK) (Faith et al., 2006 and Chen et al., 2012). Resveratrol was reported to block nuclear-cytoplasmic translocation of viral ribonucleoproteins in influenza viral infectivity and reduce the expression of late viral proteins, which is connected with the inhibition of protein kinase C pathways (Palamara et al., 2005).

4.10. Effect of *Rumex dentatus* L., *Commelina benghalensis* Linn, *Ajuga bracteosa* Wall. ex Benth and *Ziziphus mauritiana* Lam. extracts

Batool et al. (2018) studied the effects of five different fractions extracted from *R. dentatus, C. benghalensis, A. bracteosa,* and *Z. mauritiana* and their constituents (gallic acid, emodin, and isovanillic acid). The fractions and three pure compounds were tested against the DENV-2 serotype. All of the fractions were tested for anti-DENV2 activity by the plaque reduction neutralisation test assay at a concentration of 200 µg/mL and two-fold serially diluted to 0.09 µg/mL. The samples were pre-incubated with the virus (prophylactic) and 6h post-infection effects (chemotherapeutic), that is the fractional ability to inhibit virus replication at trial doses of 45 and 90 PFU. Their findings showed that *R. dentatus* fractions at 45 PFU virus dose revealed the highest inhibitory activity compared to the other fractions, with an IC_{50} of 0.154 µg/mL, CC_{50} of 211.300 µg/mL, and a selectivity index of 1.372.080; while at 90 PFU virus dose, the fraction exhibited an IC_{50} of 0.234 µg/mL, CC_{50} of 211.300 µg/mL, and a selectivity index of 902.990. The fraction had an IC_{50} of 0.516 g/mL, a CC_{50} of 298.100 µg/mL, and a selectivity index of 577.490 at 45 PFU. Similarly, *A. bracteosa* fraction exhibited the highest inhibitory activity with an IC_{50} of 0.340 µg/mL, CC_{50} of 290.000 µg/mL, and a selectivity index of 852.940 at 45 PFU; but at 90 PFU, the values were IC_{50} of 0.831 µg/mL, a selectivity index of 348.980. *Z. mauritiana* fraction at 45 PFU also revealed the highest IC_{50} of 0.182 µg/mL, with CC_{50} of 324.100 µg/mL and selectivity index of 780.770; while at 90 PFU, the values were IC_{50} of 0.640 µg/mL, CC_{50} of 324.100 µg/mL, and selectivity index of 506.410. Following the same experimental strategy, Batool et al. (2018) also tested three pure compounds (gallic acid, emodin, and isovanillic acid) for their inhibitory activity against DENV-2 at the highest concentration of 200 µg/mL down to 0.195 µg/mL. Gallic acid at 45 PFU revealed the highest inhibitory activity with an IC_{50} of 0.19 µg/mL, CC_{50} of 89.765 µg/mL, and a selectivity index of 469.408, while at 90 PFU, gallic acid had an IC_{50} of 0.522 µg/mL, CC_{50} of 89.765 µg/mL, and a selectivity index of 171.963. This was followed by emodin, which showed antiviral activity with IC_{50} values of 2.368 µg/mL and 5.515 µg/mL at 45 and 90 PFU, respectively. In this study, Isovanillic acid did not show significant inhibition on DENV-2 with IC_{50} of 22.067 µg/mL, and 40.186 µg/mL, CC_{50} of 83.254 µg/mL, and 83.254 µg/mL and selective index of 3.772 and 2.071 at 45 PFU and 90 PFU respectively. The antiviral activity exhibited by *R. dentatus* fraction corresponds with that reported by Cos et al. (2002) for *R. bequaertii,* another Rumex specie belonging to the same family of "*Polygonaceae*" as *R. dentatus*. They showed that *R. bequaertii* exhibited anti-HIV-1 activity. *R. dentatus* is traditionally used as a tonic, diuretic, laxative agent, and cholagogue (Demirezer, 1993). It has astringent, anti-tumor and anti-dermatitis activity (Litvinenko and MuzychKina, 2003), anti-malarial and anti-inflammatory activity (Getie et al., 2000), anti-diarrheal activity (Rouf et al., 2002), antifungal activity (Nusrat et al., 2017) and bactericidal activity (Mothana et al., 2010). The observed activities could be attributed to the presence of secondary metabolites like anthraquinones, flavonoids, glycosides, proanthocyanidins, phenolic compounds, and steroids (Hasan et al., 1995). The findings have paved the way for

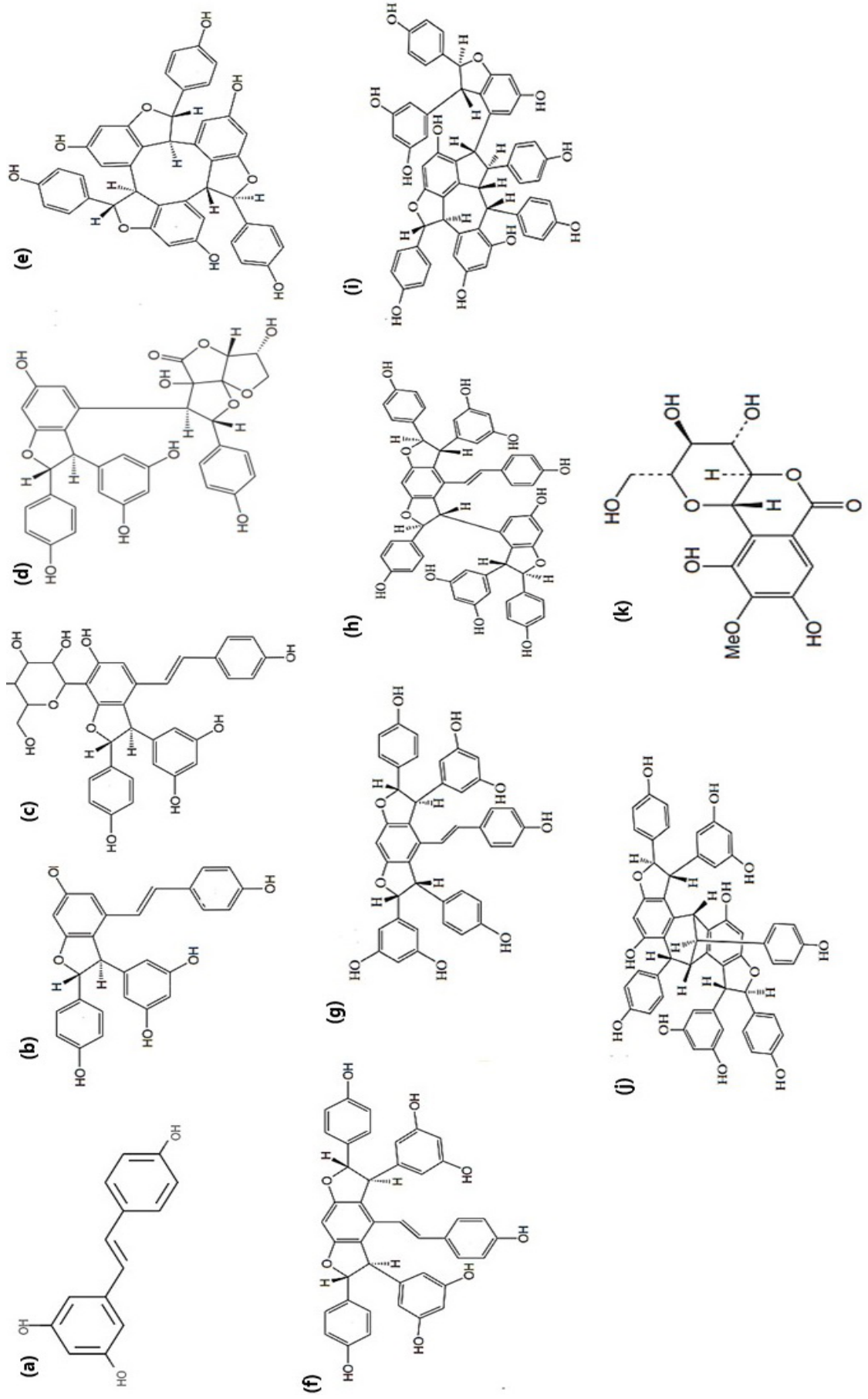

Fig. 8. Chemical structure of resveratrol and resveratrol oligomers (**a**) resveratrol (**b**) ε-viniferin, (**c**) diptoindonesin A, (**d**) laevifonol, (**e**) α-viniferin, (**f**) ampelopsin E, (**g**) malaysianol A, (**h**) flexuasol A, (**i**) vaticanol B, (**j**) vaticanol C and (**k**) bergenin identified as antiviral compounds isolated from *Dryobalanops aromatica* C.F. (Wibowo et al., 2012).

further research to identify novel anti-dengue agents from the *R. dentatus* extracts.

4.11. *Myristica fatua* Houtt. var, *Cymbopogon citratus* Stapf. and *Acorus calamus* L. methanol extract

M. fatua, C. citratus, and *A. calamus* methanol extract were evaluated for their anti-DENV inhibitory activity and safety using *in vitro* and *in silico* approaches on Huh7it-1 cell lines against the DENV-2 strain (Rosmalena et al., 2019). The extracts were non-toxic to the cells with CC_{50} of 424.93 µg/mL, 183.74 µg/mL, and 474.42 µg/mL for *A. calamus, C. citratus*, and *M. fatua,* respectively, and cell viability of 96.5%, 98.9%, and 122.7% after cells were treated with *A. calamus, C. citratus*, and *M. fatua* extracts, respectively, at 20 µg/mL dose. The extracts showed an inhibitory effect at an EC_{50} of 29.37 µg/mL and 25.33 µg/mL for *C. citratus*, and *M. fatua* respectively, while *A. calamus* was not detected. Molecular docking analysis showed that artesunic acid from *M. fatua* extract has the best free energy binding of − 7.2 kcal/mol followed by homoegonol, which has 7.1 kcal/mol compared to geraniol (− 5.2 kcal/mol), geranial (− 5.3 kcal/mol), and geranyl acetate (− 5.5 kcal/mol) from *C. citratus*. *β*-asarone, ascorbic acid, and Calamusin D from *A. calamus* had binding energies of − 4.7 kcal/mol, − 5.5 kcal/mol, and − 6.1 kcal/mol, respectively. Although the other extracts showed promising effects, *M. fatua* extract and bioactive compounds were found to be the best, showing the highest anti-dengue activity evaluated *in vitro* and *in silico*. The antiviral activity of *M. fatua* could be linked to its bioactive compounds including artesunic acid, homoegonol, and myristica, which showed strong binding energies with DENV NS5 protease, known for their function during viral RNA replication and thwarting host antiviral responses. Additionally, two neolignan compounds (malabaricone C and malabaricone B) isolated from the ethyl acetate fraction of *M. fatua* stem bark extract exhibited antiviral activity (Fig. 9) (Megawat, 2017).

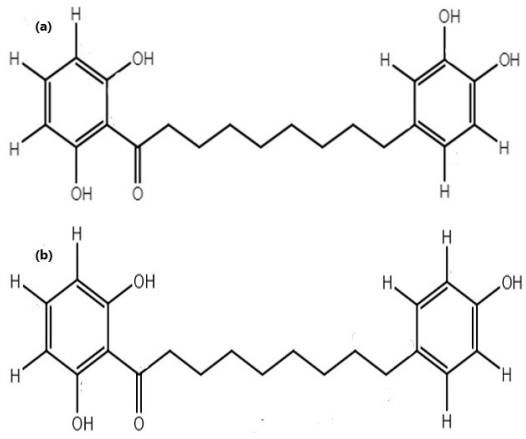

Fig. 9. Chemical structure of **(a)** Malabaricone C, and **(b)** Malabaricone B isolated from ethyl acetate fraction of *M. fatua* Houtt. Var stem bark extract having antiviral activity (Megawati, 2017).

M. fatua has been reported for anti-mycobacterial activities (Billo et al., 2005), antioxidant activities, antibacterial activities (Viveka and Chandrashekar, 2016), and anti-parasitic activities (Desrivot et al., 2007; Pandey et al., 2016). The plant belongs to the *Myristicaceae* family (Ramachandra et al., 2012).

5. Concluding remarks

According to several studies, medicinal plants possess potent inhibitory properties against DENV. Diverse bioactive compounds found in these plant extracts are responsible for their antiviral properties either individually or synergistically. There is a need for further investigation to isolate, purify, and characterize these bioactive principles for possible drug development, as well as to elucidate the specific mechanism of action that inhibits DENV infection.

Abbreviations

H1N1: Anti-human influenza A; **LD_{50}**: **SNA-I:** Lectin's agglutinin-I; **SNA-II:** Agglutinin-II; **SNA-III:** agglutinin-III; **DENV:** Dengue virus; **IC_{50}:** Half-maximal inhibitory concentration**; CC_{50}:** Half-maximal cytotoxic concentration; **SGPT:** Serum Glutamic Pyruvic Transaminase; **SGOT:** Serum Glutamic-Oxaloacetic Transaminase; **IMDPH:** Inosine Monophosphate Dehydrogenase; **EBV:** Epstein-Barr virus; **EV71:** Enterovirus 71; **HSV:** Herpes simplex virus; **VP1:** viral protein 1; **ERK/MAPK:** Extracellular signal-regulated kinases/mitogen-activated protein kinases; **RSV:** Respiratory syncytial virus; **IBV:** Infectious bronchitis virus.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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