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Review Article

Quercetin and its derivatives are potent inhibitors of the dengue virus

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ABSTRACT

Dengue virus belongs to the *Flaviviridae* family. It causes dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Still, no licensed antiviral or vaccine is available. Quercetin is a plant-derived flavonoid found in fruits and vegetables. Several *in silico* and experimental studies revealed quercetin and its derivatives as potent inhibitors of DENV. This review extensively discussed the outcomes of these studies. This review employed PRISMA guidelines for systematic review. Literature was retrieved from PubMed and other databases using the keywords "Dengue virus", "Quercetin", "Quercetin derivatives", "Flavonoids", "Antiviral Activity", "*In vitro*", "*In vivo*" and "*In silico*". Twenty-nine articles were screened; twenty-five met the eligibility criteria and were reviewed. This review is the first insightful and comprehensive document that reveals quercetin and quercetin derivatives are inhibitors of DENV. Quercetin could lead the way in developing antiviral drugs against dengue diseases.

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1. Introduction

Dengue virus (DENV) is a member of the Flaviviridae family. DENV is an important human pathogen. It causes a widespread of clinical diseases ranging from mild febrile infection, self-limited dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The virus has four distinct serotypes, DENV-1, DENV-2, DENV-3, and DENV-4. Reports have shown that infection with secondary DENV-2 results in severe disease compared with other serotypes (Vaughn et al., 2000; Balmaseda et al., 2006; Fried et al., 2010). On the contrary, primary DENV-1 cases were overt while primary DENV-2 and DENV-3 cases were regularly silent (Guzman et al., 2012). The virus is transmitted by two species of mosquitoes, *Aedes aegypti* and *Aedes albopictus* (Che et al., 2009). DENV is a single-stranded positive-sense RNA genome. It is approximately 11KB in size and encodes three structural proteins which form the viral particle Capsid (C), pre-membrane (prM) and envelope (E) protein, and seven non-structural proteins essential for viral replication (NS1, NS2A/NS2B, NS3, NS4A/NS4B, and NS5) (Qi, 2008). The C-terminal domain of NS5B encodes RNA-dependent RNA polymerase (RdRp) and is hence important for dengue viral replication (Bollati et al., 2010). NS5 is a conserved protein of all dengue virus serotypes (Yap et al., 2007). The host cells are lacking in RdRp activity and this presents an emerging target for the development of antiviral medication (Malet et al., 2008). Dengue has been reported to be endemic in more than one hundred countries with Western Pacific, South-Eastern Asia, and America is largely affected regions. These regions continuedly to record higher cases of dengue diseases (WHO, 2017). For instance, America recorded about 1.2 million dengue cases in 2014 while Brazil recorded around 600,000. Analysis of the reported cases was found to increase by approximately two-fold and three-fold for

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America and Brazil in 2016, respectively (PAHO, 2018). In recent years, there has been increased attention on the use of natural products for their medicinal benefits (Baharfar et al., 2015). Medicinal plants and their derivative compounds are an important source for the discovery and development of novel antiviral agents owing to their availability, accessibility, and little or no side effects (Zandi et al., 2009; Kwon et al., 2010; Yasuhara-Bell et al., 2010). Several studies have reported on the antiviral activity of phytochemicals including flavonoids against dengue virus (Laille et al., 1998, Parida et al., 2002, Talarico et al., 2005, Talarico and Damonte, 2007). Flavonoids such as quercetin are low molecular weight phenolic compounds (Petersen et al., 2016; Garzón et al., 2017) found in different parts of medicinal plants like roots, stem bark, leaves, flowers, fruits, and seeds (Ferreres et al., 2010; Zhang et al., 2010). Some biological activity of quercetin includes antioxidant, anti-inflammatory activity, and antitumor properties (Mamani-Matsuda et al., 2006). Flavonoids have been reported to have antiviral activity against human adenoviruses, HSV-1, HSV-2, and human cytomegalovirus (HCMV) (Chiang et al., 2003; Evers et al., 2005; Lyu et al., 2005), Porcine Epidemic Diarrhoea Virus (Song et al., 2011), Japanese Encephalitis Virus (Johari et al., 2012), Influenza virus (Wu et al., 2015), Murine Coronavirus (Chiow et al., 2016), Dengue Virus (Lu et al., 2016), Hepatitis C Virus (Lyu et al., 2005), Herpes Simplex Virus (Gomes et al., 2016), Respiratory Syncytial Virus and Parainfluenza Virus (Ozçelik et al., 2011). Medicinal plants have been widely used in folk medicine (Mohammadhosseini et al., 2021). The *Siparuna* Aublet genus is found in the southern hemisphere's tropical and subtropical regions (Leito et al., 2000). Species found in the state of Bahia are traditionally taken as tea for the treatment of fevers, infections, inflammation, wounds, and pain (Gomez et al., 2016). Another specie known as "Negramina" in the state of Mato Grosso is used to treat bodyaches, weakness, sinusitis, and nose bleeds (Valentini et al., 2010a). In French Guyana, the leaves are used for the treatment of fevers and as intimate and postpartum washes by "Quilombola" women (Tareau et al., 2017). In the Amazon, Schultes and Raffauf (1990) found that the leaves of S. guianensis are used to relieve rheumatic pains. *S. aspera* (Ruiz & Pav) *A. DC. leaves, also* known as "Mejentsuna," and S. radiata (Poepp. & Endl.) A. DC. leaves, both native to Peru, are used to treat fever and asthenia (Valadeau et al., 2009). S. macrotepala Perkins leaves, a native of Ecuador, are used for the treatment of malaria and influenza (Noriega et al., 2019). *S. andina* (Tul.) A. DC. (Poepp. & Endl.) A. DC. leaves are used to treat fever and malaria (Frei et al., 1998). *S. gilgiana* Perkins (Poepp. & Endl.) A. DC.) leaves are used for the treatment of stomachaches and female sterility (Chiu et al., 1982), whereas S. thecaphora (Poepp. & Endl.) A. DC. is used in Guatemala for the treatment of swelling, muscle cramps, anemia, headaches, coughs, and eye infections (Hitziger et al., 2016). Quercetin and its derivatives are among the flavonoids isolated from the Siparuna genus. Quercetin-3-*O*-rutinoside-7-*O*-rhamnoside, quercetin-3-*O*-pentosyl-pentoside-*O*-rhamnoside quercetin-3,7-di-*O*-rhamnoside and quercetin-3-*O*-pentosyl-rhamnoside-7-*O*-rhamnoside were isolated from *S. gigantotepala* S.S. Renner & Hausner, *S. glycycarpa* (Ducke) S.S. Renner & Hausner and *S. guianensis* Aublet, respectively (Negri et al., 2012). Their pharmacological activities include antioxidant activity, antimicrobial activity, antiplasmodial activity, larvicidal activity, and cytotoxic (Silva et al., 2021). Similarly, the Ekebergia (Meliaceae) genus represents four species: *E. capensis* Sparrm, *E. benguelensis* Welw. ex C.DC, *E. pterophylla* (C.DC.) *Hofmeyr*, and *E. pumila* I. M. Johnst. was reported to have pharmacological activities including antioxidant activity, anti-inflammatory activity, antiplasmodial activity, antimicrobial activity, antihypertensive activity, acetylcholinesterase inhibitory properties, antiproliferative or uterotonic activities (Mouthe Kemayou et al., 2021). Among these species, *E. capensis* Sparrm is recognised and documented to be used traditionally for the treatment of fever and malaria (Opio et al., 2017, Suleman et al., 2018), breast, skin, and throat cancer (Williams et al., 2013; Ochwang'I et al., 2014), respiratory problems like colds, coughs, chest pains, and runny noses (Zerabruk and Yirga, 2012; Meragiaw et al., 2016), dysentery, diarrhea, gastritis, and stomach aches (Opio et al., 2017; Tuasha et al., 2018), and skin diseases and skin rash (Getaneh and Girma, 2014). *E. benguelensis,* the second species of Ekebergia, is used for the treatment and management of malaria, abdominal pain, painful menstruation, and pneumonia (Chavez et al., 2001). Irungu et al. (2014) documented that dichloromethane/methanol (1:1) leaf and root extracts from *E. capensis*, and proceranolide, oleanonic acid, oleanolic acid, and quercetin-3-*O*-*β*-D-glucopyranoside a derivative of quercetin, exhibited moderate antiplasmodial activity against the chloroquine-sensitive *P. falciparum* D6 and the chloroquine-resistant *P. falciparum* W2 with IC_{50} values ranging from 18.2 μM to 84.7 μM (Irungu et al., 2014). Another medicinal plant of folk medicine importance is the *Ruta* L. specie. *Ruta* comprises three species: *Ruta chalepensis* L., *Ruta graveolens* L., and *Ruta montana* L. *Ruta* species have been documented in traditional medicine as an aborticide and emmenagogue, for treating lung diseases, microbial infections, and for the treatment of neuromuscular diseases, anxiety, and dysmenorrhea. They have been widely studied for the composition of their essential oils and their numerous bioactivities. This indicates they have medicinal and agrochemical applications (Nahar et al., 2021). *Ruta* essential oil has been used to prepare various traditional medicines, and a significant amount of literature has been able to establish its bioactivity and medicinal potential (Coimbra et al., 2020). *Ruta* essential oils possess a variety of bioactive properties, including anti-inflammatory, antimicrobial, antioxidant, antiprotozoal, cytotoxic, insecticidal, larvicidal, nematocidal, and phytotoxic properties. This review explores the anti-dengue properties of quercetin and its derivatives. The study is the first to provide a detailed record of the antiviral potency of quercetin and quercetin derivatives as reported in several studies. The study also highlighted the possible mechanism of quercetin and its derivatives against the dengue virus. Quercetin is a promising compound that has been

documented to have numerous medicinal properties, some of the pharmacological relevance of quercetin includes but is not limited to the following: (i) anti-inflammatory activity: quercetin was reported to impede inflammatory enzymes cyclooxygenase (COX) and lipoxygenase while decreasing inflammatory mediators such as prostaglandins and leukotrienes (Warren et al., 2009, Xiao et al., 2011); quercetin also significantly reduced the levels inflammatory mediators (COX-2, NO synthase, and CRP) in a human hepatocyte cell line in an *in vitro* preclinical study (García-Mediavilla et al., 2007). (ii) Antibacterial activity: quercetin, quercetagetin-7-arabinosyl-galactoside, quercetin, 3-*O*-methylquercetin, and various quercetin glycosides has shown inhibitory activity against bacteria infecting the skin, respiratory system, gastrointestinal tract, and urinary system (Rauha et al. 2000; Arima and Danno, 2002; Cushnie and Lamb, 2005; Ramos et al., 2006). (iii) Anti-allergic activity: quercetin acts as a natural antihistamine thus inhibiting the release of histamine from mast cells and allergic substances (Coles et al., 2016). (iv) Anti-ulcer and anti-gastritis: quercetin have anti-ulcer activity owing to its antioxidant properties and its capability of increasing gastric mucus production (Alarcón de la Lastra et al., 1994; Suzuki et al., 1998). Quercetin has inhibitory activity against *Helicobacter pylori* and gastroprotective properties by inhibiting gastric acid secretion and lipid peroxidation of gastric cells (Lakhanpal and Rai, 2007). (v) Anticancer properties: quercetin was reported for its potent anticancer effects owing to its antioxidant activity, antiproliferative effect, and growth factor suppression (Lamson and Brignall, 2005). Quercetin was reported to have an apoptosis inductor which enables it decreases tumor growth in the brain, colon, liver, other tissues. It also inhibits the spread of malignant cells (Vásquez-Garzón et al., 2009; Akan and Garip, 2013). (vi) Prevention of cardiovascular diseases: flavonoids such as quercetin hold a wide range of biological activities which have a positive impact on cardiovascular diseases. A study revealed that consumption of red grape polyphenol-rich in quercetin by a patient with coronary heart disease (CHD) increases flow-mediated dilation of major arteries which indicates improvement in endothelial health (Lekakis et al., 2005). Quercetin provides protection against CHD, decreases the risk of mortality caused by low-density lipoprotein (LDL), and showed to have vasorelaxant effects on isolated arteries which assist to lower blood pressure and blocks cardiac hypertrophy development (Edwards et al., 2007). A study revealed that consumption of quercetin alongside an alcohol-free red wine extract (containing quercetin) impedes LDL oxidation thereby preventing LDL cholesterol damage (Chopra et al., 2000). Additionally, a clinical trial conducted for 6-week on overweight subjects who were at risk of heart disease revealed that quercetin decreases systolic blood pressure and plasma oxidized LDL levels (Egert et al., 2009). (vii) Prevention of neurodegenerative diseases: quercetin when combined with ascorbic acid decreases the rate of oxidative damage to the human lymphocytes, neurovascular structures and inhibits impairment to the neuron damage. Quercetin protects the brain cells against oxidative stress that lead to Alzheimer's and certain neurological disorders (Lakhanpal and Rai, 2007).

2. Current gaps in the dengue virus treatment

Up to now, there has been no actual vaccine or antiviral drug for the treatment of DENV disease despite the increasing cases. Although numerous candidates have been reported for antiviral activity against the dengue virus, none of these candidates has turned out to be anti-DENV agents. Dengue symptomatic 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 like chloroquine, balapiravir, prednisolone, lovastatin, and celgosivir used in clinical trials were not effective on DENV patients either in decreasing viral load or antigenemia (Whitehorn et al., 2014; Low et al., 2017). Several findings have shown that the level of viremia corresponds with the severity of the disease as observed in severe dengue. Consequently, the use of antivirals can reduce the level of viremia and hence the severity of the disease. This warrants the hasty need for anti-DENV medicine. The use of computational approaches predicts the conformation of the ligand within the receptor and quantifies the binding affinity as docking score (kcal/mol), which might allow for rapid and moderately inexpensive evaluation of numerous compounds (Dwivedi et al., 2018; Alfani et al., 2021). Given the potent antiviral effect of quercetin and quercetin derivatives, this review is the first to document insightful and comprehensive literature discussion on quercetin or its derivatives against DENV following PRISMA guidelines for systematic review.

3. Literature review

3.1. Literature search strategy and selection criteria

A literature search was conducted in December 2021-January 2022. Related literature was searched, screened, and included in the study following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literature was searched from several databases including PubMed, Scopus, ScienceDirect, BioMed Central, and Google scholar using different or combined keywords like "Dengue virus", "Quercetin", "Quercetin derivatives", "Flavonoids", "Medicinal Plants", "Antiviral Activity", "*In vitro*", "*In vivo*", and "*In silico*". All databases were restricted to original articles published in English.

3.2. Inclusion and exclusion criteria

In addition to the outlined searching strategy, inclusion criteria were *in vitro, in vivo,* and *in silico* findings on anti-DENV effects of quercetin. Exclusion criteria include newspapers, letters, and lectures conveying independent opinions on the anti-DENV effects of quercetin and quercetin derivatives. Articles were searched based on titles, abstracts, and keywords. Each study was recognized for its value and contribution and hence did not exclude articles based on quality and reproducibility.

4. Results and Discussion

The data in Table 1 shows the number of published articles searched from the databases using keywords. Data presented showed a strong interest in the study that involved "quercetin or its derivatives," a flavonoid from medicinal plants.

Table 1
Summary of publications on dengue virus and quercetin.

Keywords	Number of publications
Dengue virus	16,842
Medicinal Plants	79,777
Dengue AND "Medicinal Plants"	75
Dengue virus AND "Flavonoids"	67
Dengue virus AND "Quercetin"	29
Total	96,790

Based on the search strategy, twenty-nine articles were screened, out of which twenty-five met the inclusion criteria and were selected for the final review process as presented in Fig. 1. Data in Table 2 summarizes studies that were carried out experimentally (*in vitro),* while Table 3 summarises studies carried out *in silico*. Most studies were conducted on DENV-2, while selective studies were conducted on DENV-1, DENV-3, and DENV-4. This may be because DENV-2 seems to be marginally associated with more severe dengue diseases, as evident by the significant relationship with dengue hemorrhagic fever grade 1 compared to other dengue serotypes (Fried et al., 2010). Furthermore, most of the studies targeted dengue replication in different cell lines, while other studies targeted DENV envelope protein, NS2B-NS3 protease, NS5-RdRp, TNF, CCL-2, and CXCL8. Fig. 2 presents the chemical structures of quercetin and its derivatives that were identified from different plant sources that met the inclusion criteria in this study. Dengue studies are gaining relevance since the virus has spread to more than 100 countries. It is estimated that over 40% of the global population is at risk of DENV (WHO, 2017). The antiviral effect of quercetin and quercetin derivatives against the dengue virus is also getting more attention. This is because many researchers are optimistic about developing antiviral medication from quercetin. Historically, natural products have been used in folk medicine and are important in treating several viral diseases (Musarra-Pizzo et al., 2019). There is evidence of developing antiviral compounds from natural product sources since they have fewer side effects, low resistance, and potent antiviral activities (Goh et al., 2020). In this study, quercetin and its derivatives were majorly identified from different plant sources. Twenty-nine studies were screened; twenty-five reached the inclusion criteria, while four were excluded from the study. Ten reports were experimental studies (*in vitro* or "*in vitro and in silico*") while eleven were *in silico,* as presented in Table 2 and Table 3, respectively. In the studies conducted, quercetin and quercetin derivatives had a potent antiviral effect against the dengue virus. The outcomes of these studies are discussed in subsequent paragraphs. Reports on the antiviral effect of quercetin and its derivatives against the dengue virus assessed using molecular docking studies were verified experimentally in this study. Quercetin or its derivatives were found safe and had no or lower toxicity. There is an urgent need to further investigate and consider quercetin and its derivatives as promising antivirals against the dengue virus. This can be achieved by conducting clinical trial studies as dengue disease is spreading fast and continually. The antiviral activity of quercetin and its derivatives can be attributed to its various inhibitory activities on viral proteases, cell platelet signaling and thrombus formation, plague formation, down-regulating the production of proinflammatory cytokines and inhibition of viral entry receptors, internalization, assembly, and attachment (Fig. 3). Quercetin and its derivatives interact with structural and non-structural proteins of DENV, precisely the envelope protein, NS2A/NS2BB, NS3, and NS5 (Fig. 4). Quercetin's effects could also be attributed to the hydroxyl group at the R2 position compared to other flavonoids (Dubber and Kanfer, 2004). This proposition was supported by Wleklik et al. (1998), stressing structurally distinct differences in antiviral activities of flavonoids. The characteristic suggests substitution or addition of free hydroxyl groups at certain positions might lead to a decrease or complete abolishment of the antiviral effect. These structural-activity relationships may lead to the design and development of more active, less or non-toxic flavonoids with proper pharmacokinetic properties that can match or even surpass the effectiveness of the prevailing antiviral medications (Choi et al., 2009a, 2009b; De Sousa et al., 2015).

4.1. *In silico* evidence of antiviral activity of quercetin and quercetin derivatives

Senthilvel et al. (2013) isolated quercetin from *C. papaya* L. leaf extract. The leaf extract was previously prescribed as a tonic for fever and DENV patients. Previously reported GC/MS analysis of *C. papaya* L. leaf extract revealed the presence of quercetin, *p*-coumaric acid, caffeic acid, protocatechuic acid, kaempferol, chlorogenic acid, and 5,7-dimethoxycoumarin (Canini et al., 2007). Quercetin, compared with other flavonoids, significantly inhibited DENV NS2B-NS3 protease and prevented DENV-2 viral assembly.Quercetin formed a total of six hydrogen bonds and key residues, including Ala 164, Asn 152, Lys 74, Asn 167, Leu 149, and Gly 87 (Senthilvel et al., 2013). Anusuya and Gromiha (2016) investigated the DENV polymerase inhibitory activity of a quercetin derivative, quercetin 3-(6''-(*E*)-*p*-coumaroylsophoroside)-7-rhamnoside targeting of RNA-dependent RNA polymerase (RdRp) was essential for the inhibition of DENV replication. Water bridges and hydrogen bonds were identified as key contributors to polymerase-lead complex stability in molecular dynamics simulation studies. Interactions of hydrogen bonding and water bridges with Trp795, Arg792, and

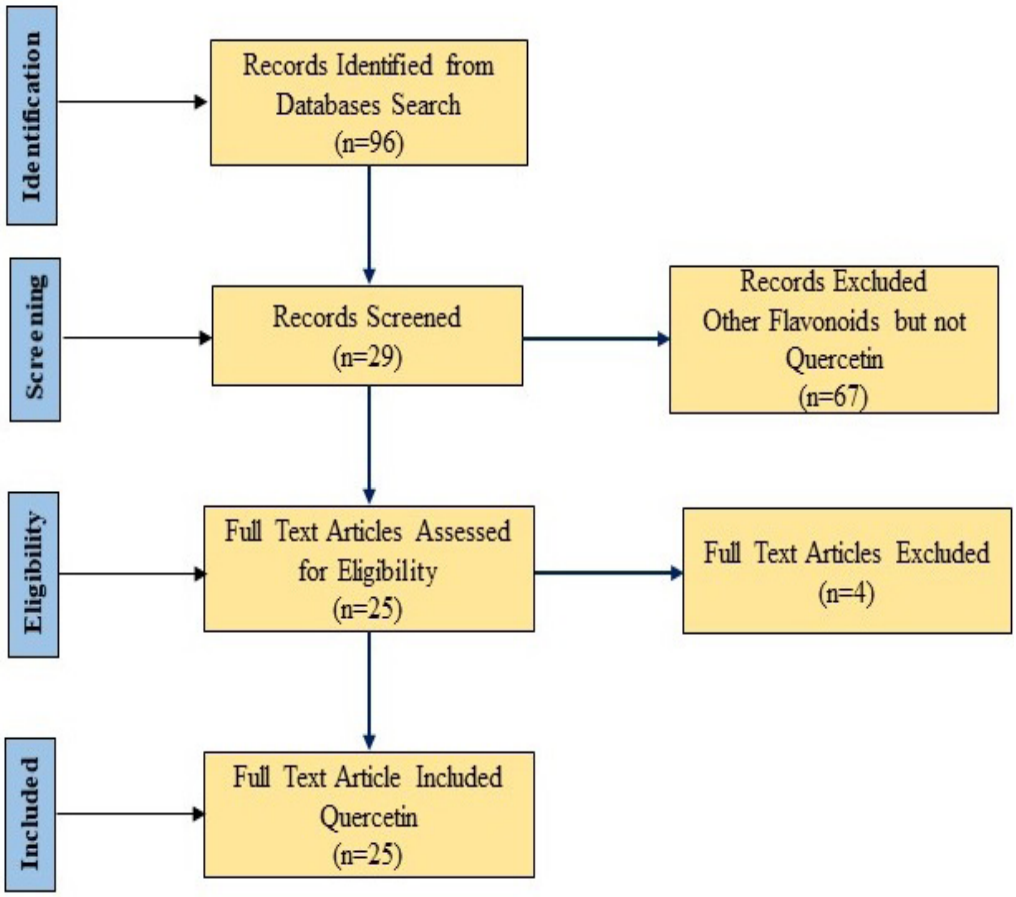

Fig. 1. Fluxogram of searching strategy for inclusion of full text published articles based on PRISMA.

Glu351 residues are found to be essential for the stability of the polymerase-lead complex. These findings demonstrated quercetin as a potent non-nucleoside inhibitor of DENV polymerase. Ismail and Jusoh (2016) studied eight flavonoids including baicalin, baicalein, EGCG, fisetin, glabranine, hyperoside, ladanein, quercetin, and flavone that docked in the same binding pocket located between the domain I and domain II of different subunits of DENV2-Thai and DENV2-Malaysian envelope proteins and the envelope protein structures of tick-borne encephalitis virus and Japanese encephalitis virus. Molecular dynamics simulations analysis revealed Ile4, Gly5, Asp98, Gly100, and Val151 residues of the DENV2-Malaysian envelope protein aligned to the same residues in the DENV2-Thai envelope protein, forming consistent hydrogen bond interactions with quercetin, baicalein, and EGCG. Conclusively, quercetin and other flavonoids interact with the envelope protein of DENV-2. In an attempt to potently discover inhibitors against DENV envelope protein, Aarthy and Singh (2018) identified fifty-five molecules as potential binders to the envelope protein. Five top compounds, including DB00179, quercetin, silymarin, dapagliflozlin, and fisetin, were regarded as potent inhibitors of DENV envelope protein. The findings revealed strong interactions and very good binding energies. Additionally, their interaction was mostly in the electropositive region. Molecular dynamics simulation studies confirmed no loss of interactions and very high stability between the complexes. Sarwar et al. (2018) studied over 100 flavonoids using molecular docking analysis for potential inhibitors of DENV-2 NS2B-NS3. Ten flavonoids were studied, including quercetin 3-*O*-(2″,3″-digalloyl)-β-D-galactopyranoside (−26.101 Kcal/mol), quercetin 3-*O*-α-(6‴-caffeoylglucosyl-β-1,2-rhamnoside) (−24.987 Kcal/mol), schaftoside (−23.399 Kcal/mol), myricetin (−21.987 Kcal/mol), quercetin-3-sulfate (−20.989 Kcal/mol), eriocitrin (−20.693 Kcal/mol), catiguanin B (−20.414 Kcal/mol), 4′,5,7-trihydroxy-3-methoxyflavone-7-*O*-α-L-arabinofuranosyl(1 → 6)-β-D-glucopyranoside (−20.378 kcal/mol), wogonin 7-*O*-β-D-glucuronide (−20.102 kcal/mol) and silychristin (−20.085 kcal/mol) were considered top inhibitors of NS2B-NS3 protein. Their interactions were strong between the ligand and receptor atoms. Structure-activity relationship (SAR) and quantitative structure-

Table 2
Summary of included experimental study.

Title	Type of study	Dengue serotype	Target	References
Antiviral activity of four types of bioflavonoid against dengue virus type-2	*In vitro*	DENV-2	DENV replication	(Zandi et al., 2011)
Taraxacum officinale L. and *Urtica dioica* L. extracts inhibit dengue virus serotype 2 replication *in vitro*	*In vitro*	DENV-2	DENV replication	(Flores-Ocelotl et al., 2018)
Effectivity of quercetin as antiviral to dengue virus-2 strain New Guinea C in Huh 7-it 1 cell line synthetic	*In vitro*	DENV-2	DENV replication	(Dewi et al., 2020)
Nanosuspension of quercetin: preparation, characterization, and effects against *Aedes aegypti* larvae synthetic	*In vitro*	*Aedes aegypti* larvae	Not applicable	(Pessoa et al., 2018)
Antiviral and immunomodulatory effects of polyphenols on macrophages infected with dengue virus serotype 2 and 3 enhanced or not with antibodies	*In vitro*	DENV-2 & 3	DENV replication	(Jasso-Miranda et al., 2019)
New inhibitors of the DENV-NS5 RdRp from *Carpolepis laurifolia* (Brongn. and Gris) as potential antiviral drugs for dengue treatment	*In vitro*	DENV	DENV NS5-RdRp	(Coulerie et al., 2014)
Structural features of NS3 of dengue virus serotypes 2 and 4 in solution and insight into RNA binding and the inhibitory role of quercetin	*In vitro*	DENV-2 & 4	DENV-2 & 4 NS3 protein	(Pan et al., 2017)
Evaluation of antiviral activities of *Houttuynia cordata* Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection	*In vitro*	DENV-2	DENV-2 replication	(Chiow et al., 2016)
In vitro antiviral action of Eupatorium perfoliatum L. against dengue virus infection: Modulation of mTOR signaling and autophagy	*In vitro*	DENV-2	DENV-2 replication	(Sinha et al., 2022)
Flavonoids as non-competitive inhibitors of dengue virus NS2B-NS3 protease: Inhibition kinetics and docking studies	*In vitro* & *In silico*	DENV-2 & 3	NS2B-NS3 protease	(De Sousa et al., 2015)
In vitro and *in silico* anti-dengue activity of compounds obtained from *Psidium guajava* L. through bioprospecting	*In vitro* & *In silico*	DENV-2	DENV-2 replication	(Trujillo-Correa et al., 2019)

Table 2 Continued

Title	Type of study	Dengue serotype	Target	References
In vitro and *in silico* study to evaluate the effectiveness of quercitrin as an antiviral drug to dengue virus	*In vitro* & *In silico*	DENV-2	DENV replication	(Dewi et al., 2019)
Physico-chemicals characterization of quercetin from the *Carica papaya* L. leaves by different extraction techniques	Not applicable	Not applicable	Not applicable	(Khawory et al., 2021)
Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans	Not applicable	Not applicable	Not applicable	(Hubbard et al., 2004)

Table 3
Summary of included *in silico* study.

Title	Dengue serotype	Target	References
Quercetin for COVID-19 and dengue co-infection: a potential therapeutic strategy of targeting critical host signal pathways triggered by SARS-CoV-2 and DENV	DENV-Patient	TNFα, CCL-2, and CXCL8	(Zheng et al., 2021)
Quercetin derivatives as non-nucleoside inhibitors for dengue polymerase: molecular docking, molecular dynamics simulation, and binding free energy calculation	DENV-3	DENV RNA-dependent RNA polymerase (RdRp)	(Anusuya and Gromiha, 2016)
In silico docking of quercetin-3-*O*-β-D-glucoside from *Azadirachta indica* A. Juss. with NS2B-NS3 protease in dengue virus	DENV-2	DENV-2 NS2B-NS3	(Dwivedi et al., 2018)
Quercetin from Miana leaf (*Coleus scutellarioides* (L.) Benth.) extract as an inhibitor of dengue virus NS5 protein	Non-Specific	DENV NS5	(Alfani et al., 2021)
Investigation of plant flavonoids as potential dengue protease inhibitors	DENV-1 & 4	DENV-1 & 4 NS2/NS3 protease	(Jayadevappa et al., 2020)
Flavonoid from *C. papaya* L. inhibits NS2B-NS3 protease and prevents dengue 2 viral assembly	DENV-2	DENV-2 NS2B-NS3	(Senthilvel et al., 2013)
In vitro and *in silico* study to evaluate the effectiveness of quercitrin as an antiviral drug to dengue virus	DENV-2	DENV replication	(Dewi et al., 2019)
In silico prediction of the phosphorylation of NS3 as an essential mechanism for dengue virus replication and the antiviral activity of quercetin	DENV-2	DENV NS3 protease	(Alomair et al., 2021)
Structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) studies showed plant flavonoids as potential inhibitors of dengue NS2B-NS3 protease	DENV-2	DENV-2 NS2B-NS3	(Sarwar et al., 2018)
Discovery of potent inhibitors for the inhibition of dengue envelope protein: An *in-silico* approach	DENV-2	DENV Envelope protein	(Aarthy and Singh, 2018)
Molecular docking and molecular dynamics simulation studies to predict flavonoid binding on the surface of DENV2 E protein. Interdisciplinary sciences	DENV-2	DENV Envelope protein	(Ismail and Jusoh, 2016)

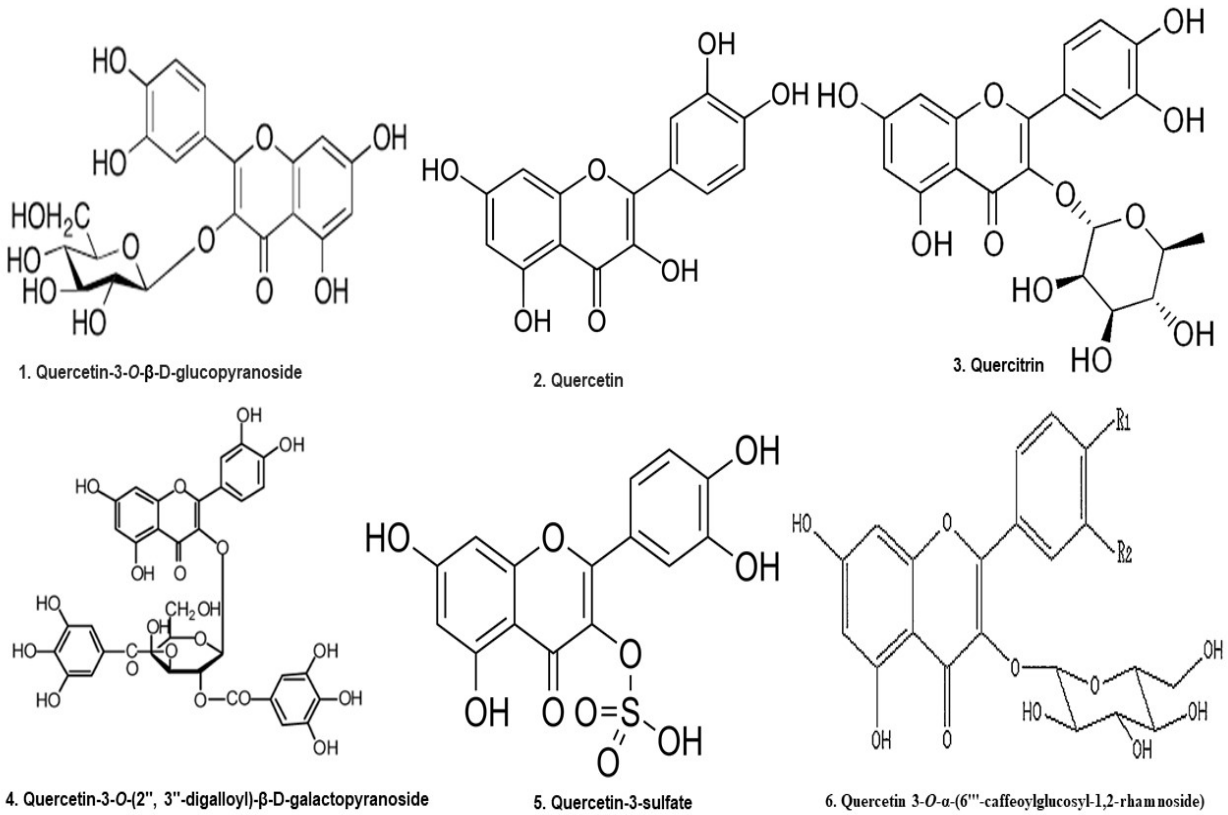

Fig. 2. Chemical structures of quercetin and quercetin derivatives. **1.** Quercetin-3-*O*-β-D-glucopyranoside (Jayadevappa et al., 2020). 2. Quercetin (Hubbard et al., 2004; Zandi et al., 2011; Senthilvel et al., 2013; De Sousa et al., 2015; Anusuya and Gromiha, 2016; Chiow et al., 2016; Ismail and Jusoh, 2016; Pan et al., 2017; Pessoa et al., 2018; Jasso-Miranda et al., 2019; Trujillo-Correa et al., 2019; Dewi et al., 2020; Alomair et al., 2021; Khawory et al., 2021; Sinha et al., 2022; Zheng et al., 2021). **3.** Quercitrin (Coulerie et al., 2014; Chiow et al., 2016; Dewi et al., 2019). **4.** Quercetin-3-*O*-(2'', 3''-digalloyl)-β-D-galactopyranoside (Sarwar et al., 2018). **5.** Quercetin-3-sulfate (Sarwar et al., 2018); **6.** Quercetin-3-*O*-α-(6'''-caffeoylglucosyl-1,2-rhamnoside) (Sarwar et al., 2018).

activity relationship (QSAR) further revealed a good correlation between the top flavonoids and DENV-2 NS2B-NS3 protease. The findings collectively revealed that these flavonoids may serve as anti-DENV drugs with little structural modification. Dewi et al. (2019) studied the effectiveness of quercitrin *in vitro* and *in silico* methodologies as an antiviral drug against DENV. *In silico* findings revealed quercitrin as a good candidate for the development of antiviral medication owing to its good binding energy (-7,54 kcal/mol) on NS5 protein. This finding was backed by the effectiveness of quercitrin in inhibiting DENV replication *in vitro* with an IC_{50} of 1.1 µg/mL, CC_{50} of 38.8 µg/mL, and a selective Index (SI) of 38. Jayadevappa et al. (2020) tested six flavonoids for antiviral activity against DENV-1 and 4 NS2/NS3 protease, including quercetin-3-*O*-β-D-glucopyranoside, amentoflavone, reynoutrin, avicularin, silymarin, and scutallarein.These flavonoids exhibited antiviral activity and inhibited viral replication. Amentoflavone was found to be a lead compound with binding energies -15.8 kcal/mol and -16.8 kcal/mol followed by quercetin-3-*O*-β-D-glucopyranoside with -15.1 kcal/mol and -15.7 kcal/mol against DENV-1 and DENV-2 protease respectively. Alfani et al. (2021) indicated quercetin from *Coleus scutellarioides* (L.) Benth. extract inhibited DENV NS5 Protein. The findings revealed that quercetin satisfied Lipinski's rule for drugs; quercetin was non-toxic and non-carcinogenic when evaluated using Swissadme and AdmetSAR. Quercetin had a binding affinity of -7.6 kcal/mol for NS5 protein, whereas Ribavirin, a control ligand, had a binding affinity of -5.8 kcal/mol. Alomair et al. (2021) evaluated quercetin for its antiviral activity against DENV NS3 proteases. Using simulation analysis, the phosphorylation of NS3 revealed a remarkable structural change at serine 137 when phosphorylated at threonine 189 using simulation analysis. This was confirmed by docking analysis, which revealed phosphorylation at serine 137 increased the binding affinity between NS3 and NS5, while phosphorylation at threonine 189 decreased it. NS3 and NS5 protease interactions are essential for viral replication. These studies revealed a site-specific mechanism of DENV inhibition. Zheng et al. (2021) were the first to report

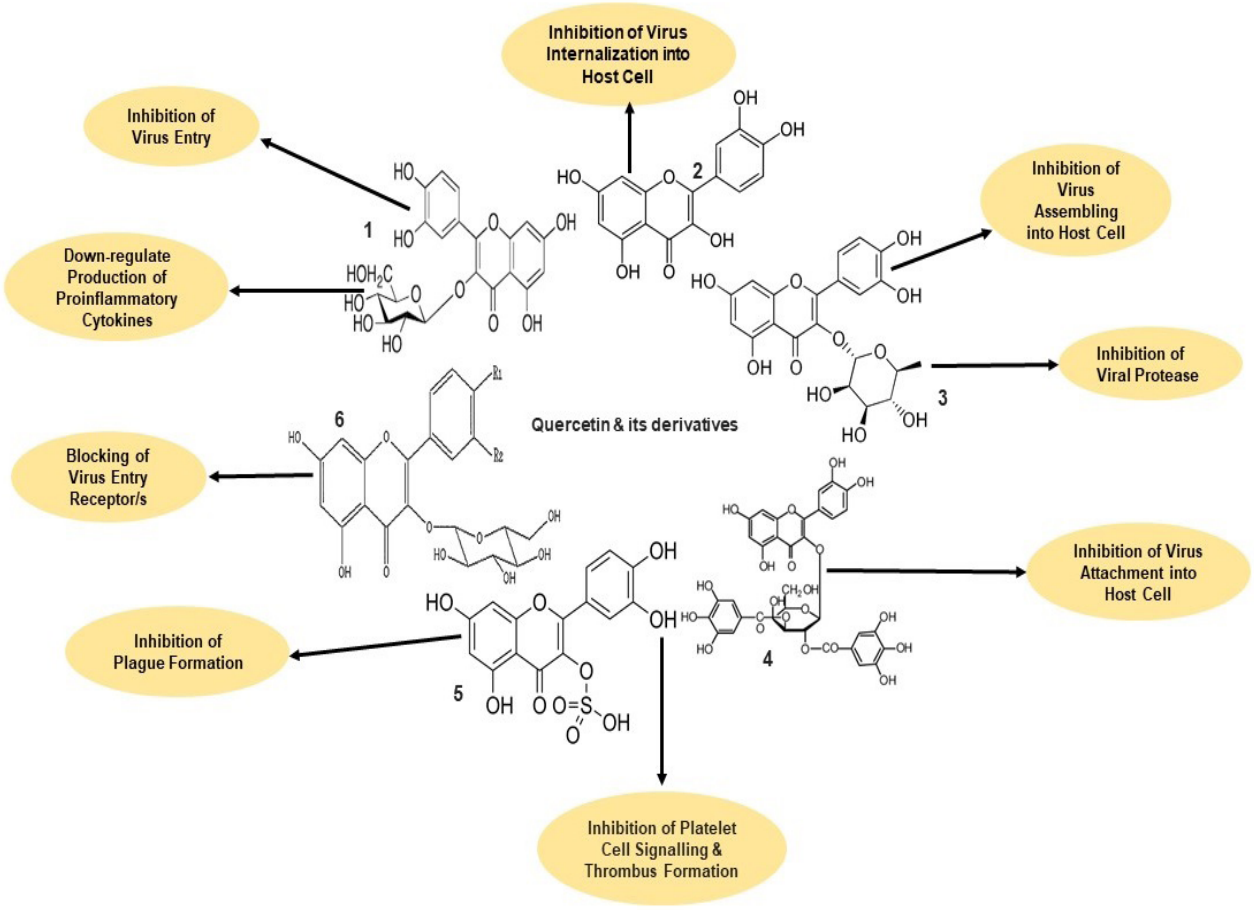

Fig. 3. Multi-target antiviral effects of quercetin and its derivatives for dengue virus inhibition.

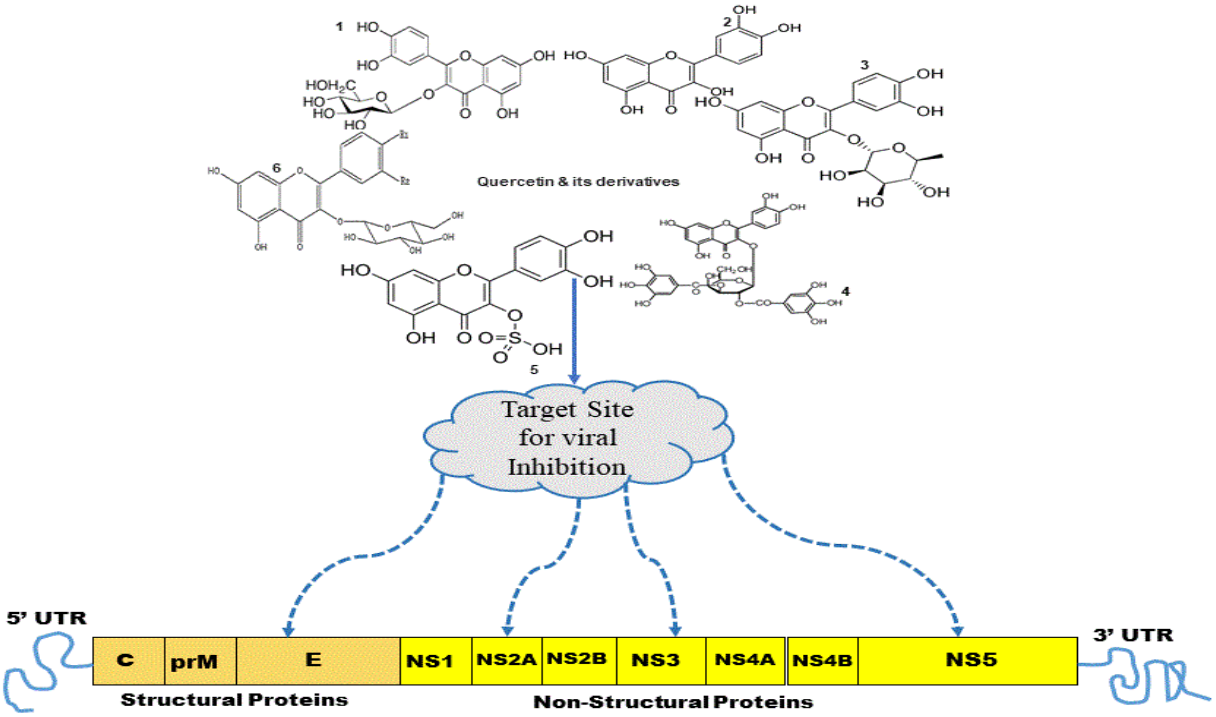

Fig. 4. The potential target of quercetin and its derivatives on dengue virus structural and non-structural proteins (NS2/NS3 & NS5).

quercetin as a pharmacological drug for the inhibition of COVID-19 and DENV co-infections, although this has not been verified in clinical trials. Biological functions, signaling pathways, and upstream pathway activity revealed that quercetin inhibited cytokine release, inflammation, and excessive immune responses through NF-κB, IL-17, and Toll-like receptor signaling pathways. They demonstrated that TNFα, CCL-2, and CXCL8 might be potential drug targets.

4.2. Experimental evidence of antiviral activity of quercetin and quercetin derivatives

Zandi et al. (2011), revealed quercetin had significant anti-DENV-2 inhibitory activities compared to daidzein, naringin, and hesperetin flavonoids. Quercetin's half-maximal inhibitory concentration (IC_{50}) was 35.7 μg mL^{-1} against DENV-2 after virus adsorption to the cell. Quercetin further decreased with an IC_{50} of 28.9 μg mL^{-1} after continuous cell treatment for 5 hours before virus infection and for up to four days post-infection. Quercetin exhibited the highest SI and IC_{50} values, with 7.07 and 8.74 μg mL^{-1} respectively, compared to Naringin (IC_{50} = 168.2 μg mL^{-1} and SI: 1.3), which showed anti-adsorption effects, and Daidzein (IC_{50} = 142.6 μg mL^{-1}) when cells were treated after virus adsorption. The observed activity could be due to the intracellular replication stage of the virus rather than the early stages of its replication cycle, such as entry and attachment, even though the anti-attachment effect of quercetin was not reported. The antiviral effect of quercetin against human cytomegalovirus was reported with an IC_{50} of 3.2 μM (Evers et al., 2005). Other studies have reported the effect of flavonoids on cellular RNA polymerases and complex formation with RNA, implying that quercetin may act similarly by affecting enzyme replication (Shinozuka et al., 1998; Nafisi et al., 2009). Flores-Ocelotl et al. (2018), isolated quercetin from *T. officinale* L. and *U. dioica* L. The extracts showed an anti-dengue effect, which could be attributed to quercetin since it was earlier isolated from these plants' extracts. Quercetin's interaction with NS2B-NS3 protease (Senthilvel et al., 2013; Ramana et al., 2015), envelope (E) protein (Manikandan et al., 2014; Mir et al., 2016), and NS5 polymerase (Anusuya and Gromiha, 2016) was speculated using *in silico* analysis as presented in Fig. 4. Coulerie et al. (2014) isolated quercetin, quercitrin, and other phytochemicals from *C. laurifolia* (Brongn. and Gris). Quercitrin and the other phytochemicals were active against dengue DENV-NS5 RdRp compared to commercially available flavonoids. Quercitrin and other phytochemicals had an IC_{50} ranging from 1.7 to 2.1 μM. Quercitrin serves as a new inhibitor for DENV-NS5 RdRp. Similarly, Chiow and his group evaluated the antiviral activity of *H. cordata* Thunb. ethyl acetate (EA) fraction, quercetin, and cinanserin on murine coronavirus and DENV-2 infection. Interestingly, quercetin inhibited MHV with an IC_{50} of 125.00 μg/mL, cytotoxicity CC_{50} value of 116.50 μg/mL, and a selectivity index of 0.93, and DENV-2 with an IC_{50} of 176.76 μg/mL, CC_{50} value of 155.38 μg/mL, and a selectivity index of 0.88. Quercitrin inhibited DENV-2 with an IC_{50} of 467.27 μg/mL but not MHV. The synergistic activity of quercetin and quercitrin (at a 1:1 ratio) significantly increased anti-DENV-2 activity and decreased cytotoxicity with IC_{50} values of 158.21 μg/mL, CC_{50} values of 270.00 μg/mL, and selectivity index values of 1.71 (Chiow et al., 2016). Quercetin and other flavonoids isolated from *P. guajava* L. also showed antiviral activity against DENV-2 as reported by Trujillo-Correa et al. (2018). In addition, three of these compounds, including gallic acid, quercetin, and catechin, had antiviral activity and inhibited the production of infectious viral particles in pre-treatment and post-treatment experiments. In the pre-treatment strategy, gallic acid, quercetin, and catechin decreased infection in a significant manner, with percentage viral inhibition of 52.6, 50.0, and 100%, respectively. In the post-treatment strategy, all the compounds inhibited infection except hesperidin. Quercetin percentage inhibition was 100.0%, followed by catechin 91.8%, gallic acid 67.3%, and naringin 64.5% in the culture treated. Additionally, four of these compounds were effective at concentrations lower than 100 μg/mL with quercetin being the most effective (EC_{50} = 19.2 μg/mL), followed by gallic acid (EC_{50} = 25.8 μg/mL), catechin (EC_{50} = 33.7 μg/mL), Naringin (EC_{50} = 47.9 μg/mL) while Hesperidin was effective at a higher concentration (EC_{50} = 225.8 μg/mL) (Trujillo-Correa et al., 2019). Another study conducted by Sinha et al. (2022) isolated quercetin from *E. perfoliatum* L. plants. Quercetin exhibited the most significant and preventive effect against DENV-2 infection. Quercetin showed the maximum reduction in viral copy number yield by 2.47-fold ($p < 0.0001$) during pre-treatment compared to the other bioactive compounds determined by RT-qPCR. Other bioactive components were also effective in reducing DENV-2 infection in HepG2 cells ($p < 0.0001$). Molecular docking and protein-ligand interaction showed that quercetin, caffeic acid, and eupafolin interact with the residues of the TIM-1 receptor protein. Quercetin had the best docking score (−23.59 kJ/mol) compared to caffeic acid (−17.7 kJ/mol) and eupafolin (−20.7 kJ/mol). The protective action of quercetin against DENV-2 infection corresponds with the *in vitro* study on the antiviral activity of quercetin. Recently, TIM-1, or T-cell/transmembrane immunoglobulin and mucin domain protein-1, is considered as a putative DENV-2 entry receptor in liver cells (Dejarnac et al., 2018; Brunton et al., 2019). Inhibiting the TIM-1 receptor could be a target for the development of novel antiviral therapeutics (Chu et al., 2019). Quercitrin, a pure, commercially available compound, showed antiviral activity against DENV-2 *in vitro* and *in silico*. Antiviral activity of quercitrin was determined based on Focus assay and MTT assay with IC_{50}, CC_{50}, and Selectivity Index (SI) of 1.1 mg/mL, 38.8 mg/mL, and 38 respectively while *in silico* study revealed -7.54 kcal/mol binding energy between quercitrin and DENV-2 NS5 protein revealing it as an inhibitor of DENV (Dewi et al., 2019). It can be concluded that quercitrin inhibited dengue virus replication. Although the antiviral mechanism is unknown, flavonoids have been reported to affect RNA polymerase and the formation of complexes with RNA, suggesting quercitrin may utilize a similar mechanism for disrupting viral replication complexes. In an attempt to study the effectiveness of quercetin on DENV-2 in Huh 7-it 1 cell line, Dewi et al. (2020) reported quercetin has low toxicity on Huh 7it-1 cells, exhibiting a half-toxicity value of 217.113 μg/mL and an IC_{50} of 18.41 μg/mL and an SI value of 11.8. This indicates that quercetin has a high effect against DENV-2. Antiviral activity and immunomodulatory properties of quercetin and other

polyphenols were tested against DENV-2 and DENV-3 infected human U937-DC-SIGN macrophages in the presence or not of enhancing antibody 4G2. Viral titers, secretion of tumor necrosis factor-alpha, IL-6, IL-10, and interferon-alpha were investigated. Only quercetin and fisetin (flavonoid) completely inhibited both DENV serotype infection in the presence and absence of enhancing antibody (> 90%, $p < 0.001$) and inhibited TNF-α, and IL-6 secretion. Quercetin inhibited DENV-2 infection alone or in the presence of 4G2 antibody ($0.7 \pm 0.1 \times 10^3$ and $3.5 \pm 1.5 \times 10^3$ PFU/mL, $p < 0.001$ upon treatment with 100 µM quercetin while treatment with fisetin 40 µM also inhibited DENV-2 infection alone or in the presence of 4G2 antibody ($2.5 \pm 1.1 \times 10^3$ and $1.5 \pm 0.5 \times 10^3$ PFU/mL, respectively, $p < 0.01$). Quercetin and fisetin half inhibitory concentrations (IC_{50}) on DENV-2 infection were 24.5 µM and 7.3 µM while SI values were 13.9 and 21.78, respectively. Similarly, quercetin and fisetin also inhibited DENV-3 infection alone ($0.5 \pm 0.1 \times 10^3$ and $0.8 \pm 0.4 \times 10^3$ PFU/mL, respectively, $p < 0.001$) or in the presence of 4G2 antibody ($15 \pm 8.8 \times 10^3$ and $9.3 \pm 4.5 \times 10^3$ PFU/mL, respectively, $p < 0.001$). Quercetin also down-regulates proinflammatory cytokine production upon induction by DENV infection. IL-6 was down-regulated by quercetin (19 ± 3 pg/mL, $p < 0.001$) and fisetin (168.1 ± 31.9 pg/mL, $p < 0.001$,) compared to DENV-2-infected cells. TNF-α was down-regulated by quercetin (84.6 ± 29.6 pg/mL at 24 hpi, $p < 0.001$) and partially by fisetin (93.5 ± 6.5 pg/mL at 24 hpi, $p < 0.001$) compared to untreated DENV-2-infected cells. Half effective concentrations (EC_{50}) of these compounds were calculated. Fisetin EC_{50} values were 11.4 µM for IL-6, 3.1 µM for TNF-α, 3.3 µM for IFN-γ and 3.1 µM for IL-10, while Quercetin EC_{50} values were 16.9 µM for IL-6, 20.5 µM for TNF-α, < 2.5 µM for IFN-γ and 11.9 µM for IL-10 in DENV-2-infected cells. Quercetin and fisetin showed good immunomodulatory activity. In DENV-3 infected cells, quercetin down-regulated TNF-α production in the absence (91 ± 16 pg/mL) or the presence of 4G2 antibody (260 ± 60 pg/mL). Fisetin temporally reduced TNF-α but inhibited 90% of TNF-α induced in the presence of 4G2 antibody (149 ± 54 pg/mL). IL-6 was reduced by quercetin and fisetin (21.5 ± 9.2 and 31.7 ± 9.2 pg/mL) respectively, while only quercetin reduced IL-6 secretion (30.2 ± 5.4 pg/mL) in the presence of 4G2 antibody (Jasso-Miranda et al., 2019). Quercetin and fisetin were reported to interact with different DENV proteins; envelope (Ismail and Jusoh, 2016), NS1 (Qamar et al., 2014), NS3 (De Sousa et al., 2015), and NS5 (Senthilvel et al., 2013; De Sousa et al., 2015), thereby inhibiting different processes involved in the replication cycle. Quercetin and fisetin have a positive effect on cells and alter the signaling pathways involved in the innate response. Another study found that quercetin reactivates the type 1 IFN-mediated JAK-STAT pathway, activating transcription of antiviral response genes (Igbe et al., 2017). Pan and colleagues provide insights into the allosteric effect of quercetin inhibitors against DENV-2 and DENV-4 NS3 (Pan et al., 2017).

5. Concluding remarks

This study reviewed quercetin and quercetin derivatives as potent anti-DENV. Twenty-five articles met the inclusion criteria and were reviewed. *In silico* and experimental investigations reportedly showed a strong inhibitory effect of quercetin and its derivatives against DENV. The findings revealed quercetin and quercetin derivatives as potential drugs for treating DENV diseases. Clinical studies should be conducted to confirm the observed effect in these studies, as this will pave the way for the development of quercetin and quercetin derivative medications against DENV disease in the future.

Abbreviations

SAR: Structure activity relationship, **QSAR**: Quantitative structure activity relationship, **NS**: Non-structural protein, **DENV**: Dengue virus, **RdRp**: RNA-dependent RNA polymerase, **DENV:** Dengue virus, **DF**: Dengue fever, **DHF:** Dengue hemorrhagic fever, **DSS:** Dengue shock syndrome, **C:** Capsid, **prM:** pre-membrane, **E:** Envelope, **HCMV:** human cytomegalovirus, **HSV-1/2:** Herpes simplex virus, **COX:** Cyclooxygenase, **CHD:** Coronary heart disease, **LDL:** low-density lipoprotein, **PRISMA:** Preferred Reporting Items for Systematic reviews and Meta-Analyses, **NO synthase:** Nitric Oxide synthase, **CRP:** C-reactive protein, **GC/MS:** Gas Chromatography Mass Spectrometry, **Trp795**: Tryptophan, **Arg792**: Arginine, **Glu351**: Glutamic acid, **Ile4:** Isoleucine, **Gly5:** Glycine, **Asp98:** Aspartic acid, Val151: Valine, TNFα: Tumor necrosis factor-α, CCL-2: C-**C motif chemokine ligand 2**, **CXCL8:** C-X-C motif chemokine ligand 8, **NF-κB:** nuclear factor kappa-light-chain-enhancer of activated B cells, **IL-17:** Interleukin-17, **IFN-γ:** Interferon gamma, **IC_{50}:** Half inhibitory concentrations, **EC50:** Half effective concentrations, SI: Selective Index.

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Conflict of Interest

The author declares that there is no conflict of interest.

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