REVIEW ARTICLE

A Narrative Review on Current Development and Future Prospects for the Treatment of Dengue Virus Infection

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Abstract

Incidences of dengue-virus infection are increasing globally. Around 3.90 billion population is at high risk of infection. There is no cure/ prevention available. Hence aim of the current review was the evaluation of current development and prospects for the production of safe anti-dengue drugs. The data of review was synthesized by PRISMA. Grading of Recommendation Assessment, Development, and Evaluation criteria were employed to establish the quality of the literature. Many drugs/compounds have shown promising prospects. Target site of these drugs on dengue virus were inhibition of replication (N-sulfonyl peptide-hybrids, milk-exosomes, sunitinib, schisandrin-A, cavinafungin, minocycline, 4-hydroxyphenyl retinamide, Goniothalamus umbrosus, Dryopteris crassirhizoma, Morus alba, statins), protease-enzyme (Thiazolidinone-peptide, nelfinavir, carnosine, 1,2-benzisothiazol-3(2H)- one and 1,3,4-oxadiazole), capsid-protein (Juglanin and silymarin), NS4B-gene (Desatinib), entry-in-host-cell (Duramycin, glycodendrimers, curdlan sulfate), RNA-capping (Lanatoside-C), fusion (Chloroquine) and NS3-helicase (Suramina). Many compounds/drugs are found effective by targeting the structural proteins of the dengue virus to use as a therapy in the future.

Keywords: *Dengue infection, virus replication, fusion, capsid, NS3 helicase, protease, treatment.*

INTRODUCTION

Burden of Infection: It is a bleak reality that in the last few decades; cases of dengue infection have increased frequently and up to 30% of incidences are reported worldwide [1]. Globally deaths of the majority of individuals occurred due to dengue infection in urban areas; therefore, it is found that most dengue fever cases have a linkage with urbanization [2]. It is also noted that the antibody-dependent enhancement (ADE) effect raises the risk of mortality in second exposure to dengue viral infections; it is perhaps due to the complex formation between dengue virus and non-neutralizing antibodies and prevents phagocytosis of the virus by immune cells [3]. ADE is the first time reported in clinical trials of dengue virus vaccine [4]. Pakistan is located in a subtropical region geographically; faced abrupt cases of dengue infection across the major cities in 2005, with about 257 deaths reported in the city of Lahore due to dengue fever in 2021 [5]. Historically, the first dengue fever observed in Madras, India in 1780; while first reported endemic dengue fever situation was existed in India during 1963-1964, in Calcutta and coastal areas of India towards the Eastern side [6].

Dengue Virus: Dengue infection is one the vector born infection; mostly found in humid and sub-humid zones including Pakistan [7]. The dengue virus belongs to the flavivirus family; having four serotypes DEN-1, DEN-2, DEN-3, and DEN-4 [8]. It is a single-stranded RNA (Robinucleic acid) virus and contains 10,700 bases [9]. Transmission of dengue virus infection is mainly due to female mosquito species (*Aedes aegypti* and *Aedes albopictus*) [10]. Unfortunately, the dengue viral infection is responsible for a high mortality rate in individuals across the globe [11]. The incubation period experienced by most infected persons is about 2-7 days [12]. The disease is sometimes asymptomatic as well as symptomatic, clinical symptoms include; pyrexia, dizziness due to loss of blood in case of hemorrhagic fever (HF), extreme fatigue, skin rashes, muscular tightness, pain in the whole body, throat infection and decreased level of hemoglobin [13]. Study shows that dengue infection is responsible for multiple organ failure with different clinical manifestations; ultimately resulting in the death of individuals if not managed properly [14]. The guideline (1997) of the World Health Organization shows the categorization of infected people due to dengue infection as; simple dengue infection, complicated infection due to internal bleeding, and anaphylactic shock disorder [15]. Clinical diagnosis of dengue is possible by numerous modern techniques; using genetic modeling of the dengue virus, detection of antibodies of anti-dengue virus, and by using non-structural (NS1) antigen [16].

Classical Dengue Fever: Dengue hemorrhagic fever is a classical dengue fever. It has four clinical manifestations; high grade fever, hemorrhages, sometimes hepatomegaly, and circulatory failure [4]. Some individuals with dengue hemorrhagic fever may develop hypovolemic shock [17]. This fever is reported in many countries in Asia and the Pacific Island; the mechanism is still not well understood yet, however, some

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hypothesis suggests risk factors for the development of dengue hemorrhagic fever *e.g.* virulence of the virus, a storm of cytokines, autoimmune response and genetic factor of host cells [4]. Another classical fever is dengue shock syndrome. Dengue shock syndrome is more severe than dengue hemorrhagic fever; in this clinical situation, patients may have bleeding, pleural effusion, leakage of plasma, pain in the abdomen, thrombocytopenia, hypotension, impairments of vital organs, cardiac arrest and/or cardiopulmonary failure [4]. Due to the severity of dengue hemorrhagic fever and dengue shock syndrome, early detection of infection is required for optimum treatment and to get desirable clinical outcomes [4].

Treatment of Infection: The point of concern is that there is no proper treatment against dengue virus infection either suitable antiviral or immune-therapeutics [18]. Since there is no systematic treatment for dengue; some antibiotics and anti-inflammatory drugs are commonly used to moderate the symptoms caused by secondary microbial infections, such as tetracycline derivatives and non-steroidal anti-inflammatory drugs (NSAIDs) [19]. Normally infection recovery is possible within 4 to 9 days [20]. The use of natural sources was found scientifically beneficial against dengue infection-induced thrombocytopenia. Recently extract or juice from *Carica papaya* gained attraction for the potential use in dengue infection control by increasing platelet counts [21]. Another study revealed that the derivatives of phenolthiazine and trifluoperazine (TFP) are found successful in restricting the growth of flavivirus by showing antiviral mechanisms against all four serotypes of dengue viruses [22]. Literature reported several compounds as direct-acting anti-viral and host-directed anti-viral drugs for the treatment; however, none is established yet as a promising drug [23]. World Health Organization reports show that environmental management effectively contributes to the control of dengue viral infection; climate change, abrupt modifications in the environment, lifestyle changes, proper treatment of waste from different sources, use of adequate natural resources, storage container mechanisms to limit mosquitoes access, proper fumigation schedule and enlighten infrastructure may reduce the burden of infection [24]. The global population is constantly facing risks of emerging infectious diseases [25]. Around the world; the key focus goal is to produce a safe and effective vaccine against dengue infection. One of the recognized registered vaccines in some countries of the world is Dengvaxia®; however, it is used with some limitations [18]. The strategic approach of the World Health Organization for 2021-2030 is to minimize, control, treat, and/or eradicate the dengue infection fatal outcome rate to 0% [26].

Objective of Review: The objective and intention of the current review are to mainly focus on and evaluate the current development and prospects for the production of safe anti-dengue viral drugs, therapy, and measures to control.

METHODOLOGY

To write a narrative review on the topic of current development and prospects for dengue control; a literature survey was conducted from 2013 to 2023 by two authors. Key-words and truncation techniques were used for the collection of relevant literature from PubMed, Directory of Open Access Journals (DOJA), BioMed Central, Google Scholar, PakMediNet, National Database of Indian Medical Journals, African Journals Online (AJOL), Bioline International and Emerald. Eighty articles on the said topic were downloaded; seventy-seven were chosen after abstracting relevant information from the studies and assessing quality, data synthesized and presented by following the PRISMA flow diagram (**Fig. 1**) [27]. The PRISMA diagram details how studies were identified, the results of abstract screening, the results of full-text eligibility assessment; the breakdown of reasons for exclusion, and details of included studies [28]. Full-text eligible articles were sixty. All the articles were evaluated for their quality, type of journal, data collection methods, statistical tests, significance values, and interpretations made.

Quality of Literature Evaluation: GRADE (Grading of Recommendation Assessment, Development and Evaluation) criteria were employed for establishing the quality of literature. GRADE is an explicit and transparent system for decision-making regarding the best available literature [29].

Evidence/Literature Inclusion Criteria: Evidence about the dengue virus, infection, prevalence, its current modes of treatments, and new developments. Literature published from 2013 to 2023.

Evidence/Literature Exclusion Criteria: Literature reported the cases of co-morbid or multiple infections, un-confirmed diagnosis of dengue infection, and literature published before 2013.

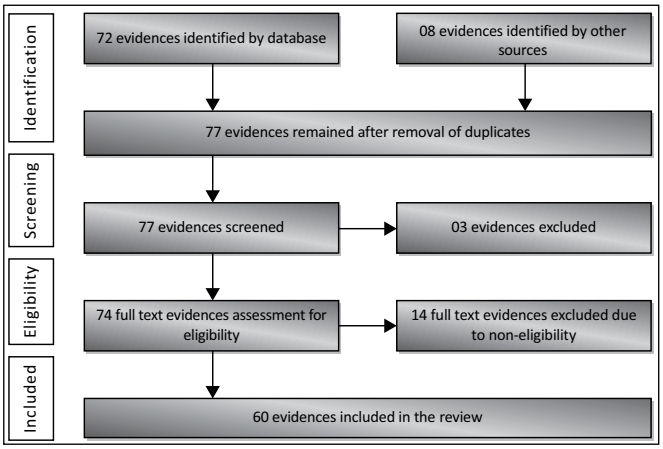

Fig. (1): PRISMA Diagram.

FINDINGS AND RESULTS OF REVIEW

Reported compounds and drugs acted against dengue virus by different mechanisms (**Table 1**).

Table 1: Compounds and drugs acted against dengue virus replication.

Study Year	First Author Name	Study Design	Drug / Compound Used	Mechanism	Outcome and Reference	Quality of Evidence [29]
2023	García-Ariza L.L.	An experimental study	M78 (indole-like structure)	Inhibition of replication	Treatment by 50 μM reduced the expression of the NS5 protein up to 70% and decreased dengue viral RNA by 1.7 times [30].	High
2023	Behrouz S.	An experimental study	N-sulfonyl peptide-hybrids	Protease inhibition	The N-terminus of peptidic inhibitors proved to be a promising and attractive strategy for further drug development against dengue virus infections [31].	Moderate
2023	Feracci M	An experimental study	AT-752 (guanosine-analogue)	RNA chain terminator	The in vitro activities of AT-752 against all four dengue virus serotypes were reported in using Huh-7 cells [32].	Moderate
2022	Patil P.	An experimental study	Carica papaya leaf extract and silver nanoparticles	Inhibition of replication	Inhibition of dengue virus was significant when silver nanoparticles and supercritical fluid extract formulations were used for *Carica papaya* [33].	High
2022	Yenuganti V.R.	An experimental study	Milk exosomes	Inhibition of replication	Goat Milk exosomes not only significantly reduce the secretion of mature virions but also reduce dengue virus replication [34].	High
2022	Piccini L.E.	An experimental study	Trifluoperazine	Inhibition of replication	Dose-dependent activity against all serotypes of dengue viruses was noted by trifluoperazine. Antiviral efficacy was exhibited in the cell lines HepG2 and A549 [22].	High
2022	Renantha R.R.	An experimental study	Juglanin and silymarin	Envelope protein inhibitors	In this study envelop proteins of dengue virus 2 were inhibited by compounds silymarin and Juglanin. These compounds have the potential to become a promising drug [35].	Moderate
2021	Shen T.J.	An experimental study	Metoclopramide	Dopamine 2 receptor antagonism	Metoclopramide has shown anti-viral efficacy in the experimental study of neural cell lines of mice with dopamine 2 receptor expression [36].	Moderate
2021	Farfan-Morales C.N.	An experimental study	Metformin [37]	Activation of AMP-activated protein kinases and reduction of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase activity	Metformin has shown an anti-dengue effect in vitro by activating AMPK (Activating-AMP-activated protein kinase) and reducing HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) activity [38].	Low
2021	Wan Y.	An experimental study	Tenovin-1	SIRT1/2 (Sirtuins) inhibitor	Tenovin-1 was found effective against dengue virus 2 (EC50 at 3.41 μM). For the other three types of dengue viruses, responses were also observed and their EC50 was at 0.97 μM, 1.81 μM, and 3.81 μM respectively [39].	High
2021	Wilson D.K.	An experimental study	Leaves extract of Psidium guajava and Justicia adhatoda	Inhibition of replication	The anti-viral activity was observed in leaves extract of *Psidium guajava* and *Justicia adhatoda* in Vero cells infected with dengue virus 2 [40].	Highv
2020	Hitakarun A.	An experimental study	Orlistat	Inhibition of replication	In a study, it is proven that orlistat inhibited the growth of dengue virus and other flavivirus [41].	Moderate
2020	Ali-Seyed M.	A review article	Methanol extracts of A. paniculata	Inhibition of replication	*A. paniculata* possesses antiviral properties including dengue with 75% of inhibition [42].	Moderate
2020	Maryam M.	An experimental study	Aqueous extract of Dryopteris crassirhizoma and Morus alba	Inhibition of replication	The study concluded that the half minimal inhibitory concentrations of extracts of *Dryopteris crassirhizoma* and *Morus alba* were 130 and 221 μg mL respectively [43].	Low
2019	Isa D.M.	An experimental study	DET2/DET4	Inhibition of virus binding and entry	The antiviral activity of DET2 and DET 4 (synthetic peptides) was noted against dengue virus 2 by binding with envelope proteins [44].	High
2019	Rothan H.A.	An experimental study	Carnosine [endogenous dipeptide (β-alanyl-l-histidine)]	Protease inhibition	Carnosine inhibited dengue virus 2 mainly by inhibiting viral genome replication and interfering with virus entry [45].	High
2019	Yang C.C.	An experimental study	BP34610	Inhibitor of virus entry	The compound BP34610 inhibits the dengue virus 2 entry into the cells with a 50% effective concentration [46].	Moderate
2018	Pu S.Y.	An animal study	Sunitinib and erlotinib	Inhibition of replication	Sunitinib/erlotinib combination alters inflammatory mediators in dengue-infected mice. These findings support the feasibility of sunitinib/erlotinib combination as a host-targeted antiviral approach [47].	High
2017	Chen H.H.	An animal study	AR-12 (Celecoxib derivative)	Inhibition of replication	AR-12 can inhibit replication of the dengue virus before or after virus infection in culture cells and mice [48].	High
2017	Yu J.S.	An experimental study	Schisandrin A	Inhibition of replication	Schisandrin A found as a potential antiviral agent against the dengue virus in vitro and in vivo [49].	High

Study Year	First Author Name	Study Design	Drug / Compound Used	Mechanism	Outcome and Reference	Quality of Evidence [29]
2017	Yu J.S.	An animal study	Celastro	Inhibition of replication	Celastrol represents a potential anti-dengue virus agent that induces IFN-α expression and stimulates a downstream antiviral response [50].	Moderate
2017	Estoppey D.	An experimental study	Cavinafungin	Inhibition of replication	Cavinafungin is a potent and selective compound against four dengue virus serotypes [51].	Moderate
2016	van Cleef K.W.R.	An experimental study	AM404	NS4B gene inhibition	Acetaminophen metabolite AM404 inhibits dengue virus replication by NS4B gene inhibition [52].	High
2016	Bryan-Marrugo O.L.	An experimental study	Fluvastatin, Atorvastatin, Pravastatin, Simvastatin	Inhibition of replication	A reduction in the dengue virus was observed in dengue-infected cells following 48-hour treatment with 10μM fluvastatin, 10μM atorvastatin, 20μM lovastatin and 20μM simvastatin, which achieved 70, 70, 65 and 55% dengue virus 2 inhibition [53].	High
2016	Watanabe S.	An animal study	Celgosivira	Accumulation of alpha-glucosidase enzymes	Celgosivir was protective against lethal infection of dengue virus 1 and 2 [54].	Moderate
2016	Leela S.L.	An experimental study	Minocycline	Inhibition of replication	Minocycline interferes with the life cycle of the dengue virus and inhibits RNA synthesis and hence protein production [55].	High
2016	Brai A.	An experimental study	Compound 16d	Inhibition of replication	Human helicase DDX3 inhibitors *e.g.* compound 16d represent the first compound to achieve broad-spectrum antiviral activity against HIV, HCV, Dengue, and WNV-infected cells by targeting a host factor [56].	Moderate
2015	Sweeney N.L.	An experimental study	Compound 25	NS3 helicase inhibition	Compound 25 [4-hydroxy-3-(5-methylfuran-2-carbonyl)-2H-pyrrol-5-one] scaffold 20 μM is the most potent pyrrolone; which inhibited the dengue virus replicons by 50% [57].	Moderate
2015	Bhakat S.	An experimental study	Nelfinavir	Protease inhibition	Nelfinavir showed slight activity against dengue virus 2; the 50% effective concentration was 3.5 μM [58].	Moderate
2015	Richard A.S.	An experimental study	Duramycin	Inhibition of entry	It is demonstrated that phosphatidylethanolamine mediates phagocytosis and viral entry. Studies proved that Duramycine inhibited this process of dengue viral entry [59].	Moderate
2015	Farias K.J.S.	An animal study	Chloroquine	Inhibition of fusion and maturation	Chloroquine was effective in replication of dengue virus 2 in Aotus monkeys and with time viremia reduction was observed compared with the controls [60].	Moderate
2015	Carocc M.	An experimental study	4-hydroxyphenyl retinamide	Inhibition of replication	The inhibition of dengue virus in vivo by 4-hydroxyphenyl retinamide suggests that it may be repurposed as a pan-Flaviviridae antiviral agent [61].	High
2014	Basavannacha-rya C.	An experimental study	Suramina	NS3 (Non-structural protein 3) helicase inhibition	Suramin inhibited dengue virus NS3 helicase activity as a non-competitive inhibitor [62].	Low
2014	Yang C.C.	An experimental study	BP13944	Protease inhibition	BP13944 likely targets the dengue virus NS3 protease. BP13944 could be considered part of a more effective treatment regime for inhibiting dengue virus in the future [63].	Moderate
2014	Varga N.	An experimental study	Construct 13.4 (Glycodendrimers)	Inhibition of entry	At low concentrations, Construct 13.4 was shown to block the uptake of dengue virus in Raji cells [64].	Very Low
2014	Soto-Acosta R.	An experimental study	Nor-dihydroguaiaretic acid	Inhibition of assembly and replication	Results suggest that Nor-dihydroguaiaretic acid inhibits dengue virus infection by targeting genome replication and viral assembly [65].	Moderate
2014	Martinez-Gutierrez M.	An animal study	Lovastatin	Inhibition of entry and assembly	Lovastatin delays infection and Increases survival rates in AG129 mice infected with Dengue Virus Serotype 2 [66].	High
2014	Boon-yasuppayakorn S.	An experimental study	Amodiaquine	Generation of free heme/ inhibition of replication	Both p-hydroxyanilino and diethylaminomethyl moieties of amodiaquine are important for their anti-dengue viral activity [67].	Moderate
2014	Cheung Y.Y.	An experimental study	Lanatoside C	Inhibition of RNA synthesis	Lanatoside C a cardiac glycoside was identified as a candidate anti-dengue compound. The data revealed that lanatoside C has an IC50 of 0.19 μM for dengue virus infection in HuH-7 cells [68].	Very Low
2013	Pambudi S.	An experimental study	SK-12	Inhibition of interaction between NS2B and NS3 (non-structural protein NS2B/NS3 serine-protease)	SK-12 was found to inhibit replication of all dengue virus serotypes at EC50 = 0.74–4.92 μM [69].	Moderate
2013	de Wispelaere M.	An experimental study	Dasatinib	NS4B inhibition	Dasatinib inhibits dengue virus growth by interfering with the replication of RNA; this inhibitory effect pertains to the manipulation of the Fyn kinase enzyme of dengue virus [70].	High
2013	Ichiyama K.	An experimental study	Curdlan sulfate	Inhibition of virus binding and entry	The binding and fusion of the dengue virus to the cell membrane is blocked by Curdlan sulfate; this process inhibits the virus replication at an early stage [71].	Moderate

DISCUSSION

It is a bleak reality that no anti-viral drug is currently licensed anywhere around the world against flavivirus; which is causing a significant burden of diseases, particularly Dengue virus. Dengue is very common nowadays and transmitted by the bite of *Aedes aegypti*, a female vector that influences more than 20% population every year across the world [72]. One-third of the world's population has concerns about dengue infection propagation which is alarming for health safety [73]. The incidences of dengue infections have increased up to 30 times within the last few decades [74]. It is noteworthy that the age factor also contributes to dengue infection incidences; people under the age of 14 and above 70 years are more susceptible to infection [75]. Dengue infection is a febrile infection and if not managed properly in time; leads to severe complications, especially in children [76]. Climate changes have strong consequences for the spreading of dengue infection across the globe. Humid and sub-humid regions, hot climatic regions having strong rainfall are favorable environments for vector growth and propagation of dengue virus. That is why climate sensitivity is an important parameter contributing to the successful growth and multiplication of parasites and miniatures [77]. Transmission of dengue infection by the flavivirus family through a complicated cycle from infected person to healthy people repeated very rapidly and is a main cause of the spread of infection worldwide [77]. The incubation period for an acute dengue infection is typically three to fourteen days. It can range from asymptomatic to life-threatening. The illness can also be categorized into three phases; critical, febrile, and recovery. The critical phase lasts for about three to seven days [78]. Fever, which can reach over 40 degrees Celsius usually appears within two to seven days. It can be accompanied by various symptoms such as nausea, vomiting, abdominal pain, and lymphadenopathy [78]. Due to the severity of the dengue infection in infected people, it can lead to gene expression at multiple levels [78].

Severe dengue infection can only managed by supportive therapy, which includes excessive administration of intra-venous fluid and painkillers particularly Acetaminophen to reduce the complications and to avoid unbearable loss of fluid in case of vascular porosity [72]. From the current review, it is revealed that structural proteins have a key role in the propagation of viruses, enhance entry chances, and assemble and secrete friendly chemicals for viral attachment; on the other hand, the non-structural viral proteins are vital for immunity of virus, its propagation and enzyme enhancement [79]. The presence of non-structural (NS1) protein in the body fluid is the main contributor to detecting the presence of dengue virus and thus helpful in effective diagnosis [80]. Many drugs are studied by targeting these proteins of the dengue virus to use as a therapy for dengue infection [39, 52, 58, 81, 82]. Natural resources are the best for humanity for the ailment of various infections. It has been observed in current study that dengue virus growth is inhibited by various mechanisms; these mechanisms include inhibition of replication by interaction with different viral ribosomal proteins [22, 30, 33, 34, 45, 48, 50, 55, 56, 61], viral protease enzyme inhibition, which is necessary for ribosomal proteins synthesis of virus [31, 45, 58, 63], termination of RNA chain [32, 68], inhibition of viral envelop proteins [35], antagonism of dopamine 2 receptor [36] to arrest viral nervous system, Activation of AMP-activated protein kinases and reduction of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase activity [38] and hence interfere with the metabolic activity of virus, SIRT1/2 (Sirtuins) inhibition [39] to produce neurodegenerative effect on virus, inhibition of virus binding and entry in host cells [44, 46, 64, 66, 71], inhibition of NS4B gene of virus which is necessary for its growth [52, 70], accumulation of alpha glucosidase enzyme [54] to suppress glucose metabolism of virus, inhibition of NS3 helicase of virus [57, 62, 69], inhibition of viral fusion with host cell membrane and maturation and generation of free heme [60, 67]. All of these mechanisms are about viral growth and replication. Interaction of these drugs may not only produce virustatic activity but also viricidal. The ultimate goal is clinical improvement against infection, which needs further research in human beings, as most of the studies are conducted either on animals or on in-vitro cell lines.

Primary natural resource such as plants plays a vital role in biodiversity to control diseases. Uptakes of fresh citrus juices and extract of papaya leaves [33] from natural sources are the best remedies temporarily during dengue infection particularly for the management of thrombocytopenia [40, 42, 43, 83, 84]. With the emergence of new infectious diseases, it is becoming difficult to develop and produce urgent, effective, safe, and potential vaccines or therapeutic agents. Currently, only one live attenuated tetravalent chimeric vaccine made by recombinant DNA technology is registered in some countries [85]. This vaccine provides long-term protection in single or multiple doses [85]. In clinical studies, it has been observed that the vaccine is more effective in individuals above 9 years old [86]. The main limitation of this vaccine is the risk of hospitalization, as observed in a 3-year long-term safety assessment [87]. In addition to live attenuated vaccines; some other vaccines are also under investigation against dengue virus infection, these vaccines include; DNA vaccines, inactivated vaccines, and recombinant sub-unit vaccines [3]. Similarly, there is no proper treatment protocol for the cure and management of dengue infection. In severe cases only temporary measurements can be taken to reduce the severity of infection; *e.g.* fluid therapy and the use of painkillers [88]. Prophylactic vaccination for high-risk populations against dengue fever is one of the rational tools to reduce the burden of infection globally. In addition, Muslim societies across the globe are very sensitive to halal incipients and excipients of

anti-dengue drugs or vaccines and other infections vaccines [89]. Unfortunately, to date, no efficacious and safe vaccine is available to reduce the rate of dengue cases below 1% in such a modernized and technical era [72]. Different studies have shown that the main reasons for the failure to develop an effective vaccine or drug against the dengue virus are; changes in structure, shape, genetic variations or recombination, diversified genome, virulence and specification for host attachment, susceptibility due to climatic diversity of flavivirus family [73].

LIMITATIONS AND CHALLENGES

The main limitation of the current review is that most of the studies are conducted either in animals as an experimental study or in-vitro cell lines, clinical data of these compounds are limited against dengue virus infection. In addition, some compounds which have shown activity against dengue viruses are already in clinical use for different therapeutic indications; *e.g.* Dasatinib, Lovastatin, Chloroquine, Duramycin, Nelfinivir, Minocycline, Sunitinib, Erlotinib, Orlistat, Metformin, Metoclopramide and Trifluoperazine. These compounds will not be acceptable for the treatment of dengue infection in clinical practice unless standardized randomized clinical trials with clear end-points are available for their efficacy and safety. The in-vitro activities against different serotypes of dengue viruses of these compounds are creating another challenge for Pharmaceutical and Biomedical scientists. These challenges include the formulation of safe, effective, stable, tolerable, and practical dosage forms. It is also noted in some studies that many drugs are effective when used in vitro, but when used in vivo, they lose their efficacy.

CONCLUSION

Dengue fever spread out as an endemic worldwide; which badly affects the health of the population of the tropical and subtropical regions. It is a major public health issue across the globe. The main contributing factors to the transmission of the dengue virus are climate change, human lifestyle, bad sanitary system, evolution in viral genetics, socioeconomic factors, devastating urbanization, uncontrolled population, and global travel and trade mechanisms. Researchers have not yet succeeded in developing any therapeutic entity or safe vaccine against dengue infection. Some natural sources are contributed to minimize the complications of dengue infection, *e.g.* fresh juice from citrus fruits and extract of *Carica papaya*. A study also reveals the effectiveness of phenothiazine derivative (Trifluoperazine) against all serotypes of dengue viruses.

RECOMMENDATIONS

The world is still facing outbreaks of dengue infection. Hence continuous efforts in the area of research are required to develop either anti-dengue therapy or a cost-effective and safe vaccine. It is suggested that the development of recombinant, live-attenuated dengue vaccine against all serotypes of dengue viruses may be safe, protective, and tolerable. Based upon the current review, it is observed that using modern techniques and technologies such as x-ray modeling, screening methodologies, and accessible databases will provide sound groundwork to develop unique antiviral therapeutic agents against dengue infection. At the moment the best approaches or strategies to prevent dengue infection are; avoiding contact with infected people, avoiding mosquito-rich areas, using proper insecticides, covering exposed body parts, changing living lifestyle, monitoring climate changes worldwide, and suitable precautionary measures.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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