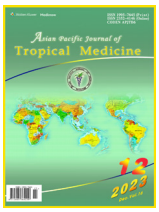

Review Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.391776

Impact Factor: 3.1

Resveratrol as an epigenetic therapy for flavivirus infection: A narrative review

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ABSTRACT

Flaviviruses are a group of positive-stranded RNA viruses that cause a broad spectrum of severe illnesses in humans worldwide. Clinical manifestations of flavivirus infections range from mild febrile illness to hemorrhage, shock, and neurological manifestations. Flavivirus infections cause a substantial global health impact, with an estimated more than 400 million cases of infections annually. Hence, an understanding of flavivirus-host interaction is urgently needed for new antiviral therapeutic strategies. In recent years, many aspects concerning epigenetic therapy for viral infections have been addressed, including methylation of the genome, acetylation/deacetylation of histone complex and microRNA regulation. In this context, we surveyed and reviewed the literature and summarized the epigenetic effects of resveratrol, a natural polyphenol with potential anti-viral properties, on flavivirus infections.

KEYWORDS: Infectious diseases; Epigenetic; Resveratrol; Flavivirus; DNA methylation; Histone; Non-histone proteins; Micro-RNA

1. Introduction

Flavivirus is a genus of more than 70 arthropod-transmitted viruses that belong to the Flaviviridae family. These viruses have caused many outbreaks and epidemics over the past few decades. The most well-known flaviviruses that result in significant social burden and economic implications are dengue virus (DENV), Zika virus (ZIKV), West Nile virus (WNV), yellow fever virus (YFV), Japanese encephalitis virus (JEV) and tick-borne encephalitis virus (TBEV)[1]. DENV, however, is the most prevalent and of significant public health concern, with estimating 390 million cases per year and 3.97 billion people at risk of infection in approximately 128 countries[2]. Clinical manifestations of dengue vary between individuals, with most infected persons are asymptomatic. Symptomatic dengue is classified as self-limiting and mild dengue fever (DF), and severe forms of disease, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). ZIKV, on the other hand, is recognized as a public health concern because of its unexpected association with severe neurological abnormalities such as microcephaly in newborns and Guillain-Barré syndrome (GBS) in adults[3]. WNV and JEV can also cause severe clinical symptoms, including encephalitis and meningitis with a significant mortality risk[4]. The fatality rate associated with encephalitis caused by TBEV infection is around 2%[5]. Given the severity of illness caused by many of these flaviviruses, effective treatment and prevention measures are urgently needed. Towards these, a good understanding of the mechanisms of virus replication and the pathogenesis of the infection are needed.

Harnessing epigenetic factors is one possible approach towards mitigating the effects of flavivirus infections. Epigenetics, is a study of heritable phenotype changes concerned primarily with the regulation of covalent modifications in histone proteins and

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How to cite this article: Chin KL, Tan KK, Bakar SA, Zainal N. Resveratrol as an epigenetic therapy for flavivirus infection: A narrative review. Asian Pac J Trop Med 2023; 16(12): 546-557.

Article history: Received 29 May 2023 Revision 27 November 2023
Accepted 18 December 2023 Available online 29 December 2023

DNA molecules, which may affect gene expression such as gene silencing and thus could alter cellular processes, including apoptosis, maintenance of stem cell pluripotency, X-chromosome inactivation and genomic imprinting without directly influencing the DNA sequence[6]. Other than the core components of histone, chromatin and DNA, the non-histone chromatin proteins and other epigenetic regulators such as the non-coding RNAs also play critical roles in epigenetic regulation[7]. Several Food and Drug Administration (FDA)-and European Medicines Agency (EMA)-approved epigenetic drugs, such as azacytidine (AZA) and decitabine (DAC), are already in use either as a monotherapy or in combination with conventional chemotherapy for the treatment of myelodysplastic syndrome (MDS)[8], acute myeloid leukemia (AML)[9] and chronic myelomonocytic leukemia (CMML)[10]. The current review; however, focused on how viruses use the epigenetic machinery to promote viral propagation or latency and immune evasion[11]. Hence, the epigenetic-targeted natural compounds such as resveratrol[12], curcumin[13] and quercetin[14] could be effective and beneficial for inhibition of virus replication and modulation of the host immune response regulation.

Resveratrol (3, 5, 4' –trihydroxy-trans-stilbene, RES) has been shown to possess antiviral properties against viruses such as enterovirus 71[15], influenza A virus[16], Epstein-Barr virus (EBV)[17], herpes simplex virus (HSV)[18], cytomegalovirus[19], respiratory syncytial virus[20], human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[21] as well as flaviviruses including dengue virus[22], Zika virus[23], hepatitis C virus (HCV)[24] and West Nile virus[25]. The compound is a natural stilbenoid polyphenol isolated initially from the roots of the white *Veratrum grandiflorum* in 1939[26]. RES is an antioxidant that is commonly present in a variety of plants, especially grapes, berries and peanuts, in response to stress, infections and ultraviolet radiation[27]. RES exists in two isomeric forms, cis- and trans-resveratrol. Its main suggested antiviral mechanisms involve suppressing viral gene expression or viral protein synthesis, as well asinhibiting various transcription and signaling pathways. A growing number of studies, however, relate RES's therapeutic effects to its involvement in epigenetic targets such as DNA[28], histone proteins (*e.g.*, H2B[29], H3[30] and H4[31]), non-histone proteins (*e.g.*, high mobility group box 1 (HMGB1)[32], nuclear factor-kappa B (NF-κb)[33] and microRNA[34]. The following review discusses the possible epigenetic mechanisms of RES in affecting flavivirus infections. It intends to propose alternative therapeutic strategies to restrict virus infection and dissemination. Four widely recognized epigenetic mechanisms that could be induced by RES and with potential to affect virus replication are 1) suppression of DNA methylation, 2) histone modification, 3) non-histone protein modification and 4) regulation of microRNA expression. These mechanisms are summarized in Table 1 and discussed in detail in the following sections.

2. Suppression of DNA methylation

DNA methylation is essential in diverse fundamental cellular processes, such as embryonic development, regulation of transcription, genome imprinting, genome stability and chromatin structure[35]. Mammalian DNA methylation is catalyzed by a family of DNA methyltransferase enzymes (DNMTs) that transfer the methyl group from S-adenyl methionine (SAM) to the fifth carbon of a cytosine residue, forming 5-methyl cytosine (5mC) mainly within CpG dinucleotides[36]. Most methylations of mammalian genomic DNA are catalyzed by the DNMT1 and DNMT3 DNA methyltransferases[37], whereas DNMT2 is a highly selective DNA and RNA methyltransferase that simultaneously methylates DNA and tRNAAsp[38].

Due to the importance of DNA methylation in regulating numerous cellular processes, abnormalities in its profile have been associated to the pathogenesis and progression of a variety of illnesses. The dysregulation of the DNA methylation system could also have significant implications on virus replication[39]. RNA viruses can methylate both host and viral genomes as a potential mechanism to mask themselves from recognition and clearance by the host immune system during latent infections[40]. The NS5 methyltransferase of flaviviruses disrupts the dynamics of the epigenome through methylation of the viral genome and *de novo* methylation of the host genome[41]. A previous study postulated that DENV induces the expression of DNA methyltransferase gene (*AaDnmt2*) to enhance its replication, whilst downregulation of *AaDnmt2* in *Wolbachia* mosquitoes inhibits DENV replication[42]. Conversely, hypomethylation of the tumor necrosis factor-alpha (TNF-α) promoter gene has been associated with the overexpression of TNF-α, which is recognized as one of the pathogenic mechanisms of DENV[43]. DENV could induce both methylation and demethylation of certain genes, facilitate its replication and contribute to its pathogenesis. ZIKV has also been discovered to alter host DNA methylation *in vitro*, which downregulates the expression of RAB GTPase activating protein 1 (RABGAP1L), involved in intracellular membrane trafficking, and interferon-stimulated genes, ISGs [*e.g.*, myxovirus resistance protein A (MxA) and ISG15], contributing to the pathogenesis of ZIKV-induced neurological disorder[39,44]. Besides, HCV's core 1b protein was found to induce DNMT1 and DNMT3b overexpression in a signal transducer and activator of transcription 3 (STAT3)-dependent manner[45]. Down-regulation of DNMT1 or DNMT3b expression in Huh7.5.1 cells severely affected cell culture-produced HCV infection, highlighting the significant role of DNMTs as host factors in HCV propagation[46]. These findings suggest that inhibition of DNMTs may represent a novel antiviral therapeutic development approach against flavivirus infections. Notably, decitabine (NCT04482621), a DNMT inhibitor, has been recently included in Phase 2 clinical trials for the treatment

Table 1. Epigenetic mechanisms of resveratrol and its effects.

Concentration of RES	Epigenetic mechanism	Target protein/ RNA	Cell line/ Animal model	Functional effects	Ref.
15 μM (combination with 5 μM pterostilbene)	DNA methylation suppression; Histone deacetylation; Histone acetyltransferase enzyme activity	DNMT HDAC HAT	MDA-MB-157 breast cancer cells	Lowering 5-methylcytosine levels at the CpG sites; Restoring ERα expression in ERα-negative breast cancer cells	[48]
10 μM	DNA methylation suppression	DNMT1	MCF7 breast cancer cells; MDA MB 231 breast cancer cells	2- to 3-folds decrease in DNMT1 levels	[49]
25 mg/kg/day	DNA methylation suppression	DNMT3b	Female ACI rats	Significant decrease in DNMT3b expression in mammary tumors; No significant change in DNMT1 protein expression in mammary tumors	[50]
15 μM	DNA methylation suppression	DNMT1	HeLa cells	Lowering DNMT1 induction by HIV-1 through disrupting the AP-1 transcription factor pathway	[51]
10 mg/kg/day	DNA methylation suppression	Cytokines	Diabetic rat	Increasing anti-inflammatory cytokines (*e.g.*, IL-10)	[52]
40 or 60 μM	Histone acetylation induction	Aacetyl-H3K9 Acetyl-H3K14 Acetyl-H4K8	J-Lat cells ACH2 cells Jurkat T cells Human PBMCs	Reactivating latent HIV by enhancing histone acetylation and activating heat shock factor 1	[68]
30 μM	Histone acetylation induction	Aacetyl-H3K9 Acetyl-H3K14 Acetyl-H4K8	HeLa cells	Enhancing HSV-2 replication by increasing histone acetylation and activating NF-κB	[69]
80 μM	SIRT-1 activation Nuclear HMGB1 retention	SIRT-1 HMGB1	Huh7 cells	Inhibiting DENV replication by upregulating ISGs through activation of SIRT-1 and retention of nuclear HMGB1	[72]
20, 40 or 80 μM	SIRT-1 activation	SIRT-1	Jurkat cells Molt-4 cells HTLV-1-transformed T cells (MT2, MT4, and C8166)	Inhibiting viral transcription and Tax activation of human T-cell leukemia virus type 1 in a SIRT1-dependent manner Obstructing the recruitment of CREB and CRTCs	[84]
25 μM; 25 mg/kg/day	SIRT-1 activation	SIRT-1	$CD4^+$ T cells C57/BL6 mice Male DBA1 mice	Suppressing T-cell activation both *in vitro* and *in vivo* Inducing peripheral T cell tolerance mediated by SIRT-1 Reducing the incidence and severity of rheumatoid arthritis	[86]
50 nM	SIRT-1 activation	SIRT-1	Mouse embryonic 3T3/NIH fibroblasts	Inhibiting TNF-α induced inflammation in a Sirt1-dependent manner; Suppressing acetylated RelA/p65 and mTOR activation induced by TNF-α.	[87]
50 mg/kg/d	SIRT-1 activation	SIRT-1	BALB/c mice	Inhibiting B cells proliferation and autoantibodies production; Suppressing $CD4^+$ T cells activation; Protecting against systemic lupus	[88]
80 μM	Nuclear HMGB1 retention	HMGB1	Huh7 cells	Inhibiting ZIKV replication by upregulating MxA and IFN-β *via* retention of nuclear HMGB1; Suppressing ZIKV-induced pro-inflammatory response	[116]
50 μM	MmiR-155 downregulation MiR-34a downregulation	MiR-155 and miR-34a	B cells	Interrupting EBV transformation; Inducing apoptosis in EBV-infected cells though blocking viral anti-apoptotic genes expression; Inhibiting EBV-induced NF-κB activation; Downregulating miR-155 and miR-34a induced by EBV	[130]
30 or 50 μM	MmiR-663 upregulation MiR-155 downregulation	MiR-663 and miR-155	THP-1 cells	Suppressing AP-1 activity by increasing miR-663 expression Inhibiting proinflammatory response partly through the downregulation miR-155	[135]

DNMT: DNA methyltransferase enzyme; HDAC: histone deacetylases; HAT: histone acetyltransferases; ERα: estrogen receptor-α; AP-1: activator protein-1; IL: interleukin; HIV: human immunodeficiency virus; HSV: herpes simplex virus; NF-κB: nuclear factor-kappa B; SIRT-1: Sirtuin-1; DENV: dengue virus; ISGs: interferon-stimulated genes; HMGB1: high mobility group box; CREB: cAMP responsive element binding protein; CRTCs: CREB-regulating transcriptional coactivators; TNF-α: tumor necrosis factor-alpha; MxA: myxovirus resistance protein A; IFN-β, interferon-beta; EBV: Epstein-Barr virus.

of coronavirus (COVID-19) pneumonia-acute respiratory distress syndrome (ARDS)[47], paving ways for evaluating the antiviral potential against other virus infections.

Numerous *in vitro* and *in vivo* studies have reported the ability of RES to suppress DNA methylation by downregulating the expression of DNMTs. For instance, the combination of 15 μM RES and 5 μM pterostilbene demonstrates a significant decrease in DNMT enzymatic activity in MDA-MB-157 breast cancer cells, which alters overall DNA methylation patterns by decreasing 5-methylcytosine levels in the CpG sites globally[48]. Additionally, immunoblotting studies revealed a 2- to 3-fold reduction of DNMT1 protein expression in human breast cancer cell lines (*e.g.*, MCF7 and MDA MB 231 cells) after cells were exposed to 10 μM RES for 96 hours[49]. In another *in vivo* study, treatment of RES (25 mg/kg/day) was found to significantly reduce DNMT3b expression in hormone-sensitive mammary tumors compared to normal mammary tissue, but had no significant change in DNMT1 protein expression[50]. Other than the protective effects of RES in cancers through inhibition of DNA methylation, induction of DNMT1 expression *via* HIV-1 Tat and Nef early proteins has also been reported to be inhibited by RES, which interferes with the transcription factor AP1 pathway[51]. In addition, one intriguing hypothesis posits that RES could potentially boost the immune response by inducing hypomethylation of immune-related genes, thereby impeding virus replication. Nevertheless, it is still constrained by insufficient research to support this claim and further investigations are needed to fully understand the effects of RES on the hypomethylation of immune genes and its impact on viral infections. RES treatment in mice has also been shown to reduce DNA methylation at the promoter region of anti-inflammatory cytokines, such as IL-10[52], suggesting that RES may help to alleviate the inflammatory response induced by virus infections. RES-induced DNA methylation suppression might have dual roles in modulating the innate immune response and alleviating the inflammatory response. Therefore, it is plausible to propose that DNMT inhibition is one of the major epigenetic mechanisms by which RES could inhibit viral replication.

3. Histone modification

Host DNA is tightly wrapped around the histone protein octamer, resulting in compact chromosomes to regulate gene transcription. Five distinct types of histone proteins have been identified: H1/H5, H2A, H2B, H3, and H4[53]. Histones can be modified to govern the intrinsic histone-DNA interactions via the acetylation or deacetylation of lysine residues by histone acetyltransferases (HATs) or histone deacetylases (HDACs). HAT-induced acetylation leads to a less compact chromatin structure, which enhances RNA polymerase accessibility and gene expression. Conversely, HDAC-induced deacetylation promotes a compact chromatin structure, limiting RNA polymerase access, hence, lowering gene expression[54].

It has been revealed that histone acetylation[55] and histone deacetylation[56] are essential for the replication and lytic reactivation of viruses, implying that histone modification is virus-specific and caution must be taken when developing therapeutic agents. In particular, JEV has been found to downregulate NF-κB expression through HDAC inhibition, hence suppressing the inflammatory response for viral immune evasion[57]. Meanwhile, prior research has demonstrated that inhibiting histone deacetylation is beneficial in suppressing the replication of flaviviruses and improving the disease outcome by reducing inflammation[58,59] since HDACs are needed for immune response induction[60]. For example, the decrease in cytokine production in DENV-infected macrophages by valproic acid (VPA), an HDAC inhibitor, has been proposed as treatment against DENV infection and preventing the progression to severe illness such as DHF/DSS[61]. Similar results were observed in an *in vivo* study where the co-treatment of an RNA polymerase inhibitor (NITD008) and a HDAC inhibitor (vorinostat or SAHA) reduced WNV replication, inflammation and virus-induced neuronal death[58]. Additionally, HDAC inhibitors, including SAHA[62], tubastain A[63], hydroxamic acids[64] and RGFP966[59] showed antiviral effects on HCV propagation. Therefore, HDAC inhibitors could be proposed as a potential therapeutic target for antivirals against flaviviruses due to their antiviral and immunosuppressive properties.

HDACs are a family of enzymes that remove acetyl groups from the ε-N-acetyl lysine amino acids on histone and non-histone proteins. HDACs are categorized into five major classes: class Ⅰ (which includes HDAC1, 2, 3 and 8); class Ⅱa (which includes HDAC4, 5, 6, 7, and 9); class Ⅱb (which includes HDAC 6 and 10); class Ⅲ (also known as Sirtuins, including SIRT1 to SIRT7); and class Ⅳ (HDAC11, the sole member)[65]. During an RNA virus infection, HDAC6 interacts with the viral sensor, retinoic acid-inducible gene Ⅰ (*RIG*–Ⅰ) and deacetylates lysine 909 of RIG-Ⅰ, thereby suppressing its RNA-sensing activity and downstream signalling pathways[66]. It has been discovered that RES inhibits all 11 classical HDACs of classes Ⅰ, Ⅱ and Ⅳ[67]. Furthermore, the suppression of RES on histone deacetylase activity has been postulated to be involved in the transcriptional repression of BRLF1 and BZLF1 promoters to limit EBV lytic protein expression[17]. In contrast, RES has also been found to have pro-viral effects enhancing HIV and HSV-2 replication by inducing histone acetylation[68,69]. These findings from prior research suggest that RES histone modification is virus-specific and involves distinct mechanisms.

On the other hand, RES also induces histone deacetylation, mainly mediated by Sirtuins, a family of NAD^+-dependent class Ⅲ HDAC. *In vitro* and *in vivo* studies have shown that RES

upregulates transcription and activity of SIRT1, consequently regulating gene expression[70]. SIRT1 is involved in various viral infections[71], flaviviruses (DENV[72], HCV[73]), and other viruses (influenza A virus[74], HBV[75], HIV[76], Kaposi's sarcoma-associated herpesvirus[77], respiratory syncytial virus[78] and SARS-CoV-2[79]). Accumulated studies have shown that SIRT1 can inhibit viral infection in some circumstances, but it can potentially enhance the replication of certain viruses. One of the proposed antiviral mechanisms of SIRT1 is that SIRT1 upregulates host immune responses, thereby restricting respiratory syncytial virus infection and pathogenesis through autophagy induction[78,80]. SIRT1 has also been reported to suppress Kaposi's sarcoma-associated herpesvirus latency by decreasing the expression of viral lytic protein replication and transcription activator[77,81]. In contrast, SIRT1 has also been discovered to interact with HBV mini-chromosome[82] and activate the peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a transcriptional coactivator[83], resulting in enhanced HBV replication. Meanwhile, SIRT1 activation by RES has been demonstrated to suppress viral transcription and Tax activation of human T-cell leukemia virus type 1 by preventing the recruitment of cAMP responsive element binding protein (CREB) and CREB-regulating transcriptional coactivators (CRTCs)[84], with similar inhibitory effects on Tat-induced HIV-1 LTR transactivation[85]. Hence, it is worth pointing out that SIRT1 activation possesses both pro-viral and antiviral properties against virus infections. Moreover, the crucial role of SIRT1 in enhancing the immune response against viral infections has been demonstrated in previous research with DENV. Notably, the downregulation of interferon-stimulated genes (*MxA* and *ISG56*) was observed in DENV-infected SIRT-1 knockdown cells compared to infected wild-type cells, highlighting the importance of SIRT-1 in augmenting an effective immune response to combat the virus[72]. RES, on the other hand, has the potential to modulate the inflammatory response triggered by virus infections. Through SIRT1 activation, RES can induce peripheral T cell tolerance[86] and downregulation of NF-κB-induced inflammatory response *via* inhibition of v-rel avian reticuloendotheliosis viral oncogene homolog A (RelA) acetylation[87], which may help to prevent excessive immune reaction during virus infections. The activation of SIRT-1 by RES has been shown to hinder the proliferation of B cells and the production of autoantibodies, thereby conferring a protective effect against systemic lupus erythematosus (SLE), an autoimmune disease[88]. However, it is important to note that RES-induced SIRT-1 activation is not universally beneficial in all contexts of virus infections. Future investigation is required to elucidate the histone acetylation/deacetylation mechanisms involved in the antiviral effects of RES against flaviviruses, and how these mechanisms might be exploited for the development of novel antiviral therapies.

4. Non-histone proteins modification-regulation of high mobility group box 1

Non-histone proteins are proteins which remained within chromatin after the histones were removed. Non-histone proteins are epigenetic targets that are involved in a wide variety of key cellular processes, such as gene transcription[89], signal transduction[90], RNA metabolism[91] and protein synthesis[92]. HMGB1 protein is a well-known example of a non-histone nucleosomal DNA-binding protein that regulates DNA transcription and nucleosome stability in nearly all cell types[93]. HMGB1 is generally distributed in a 30:1 ratio in the nucleus and cytoplasm, but this ratio is significantly lowered in response to lipopolysaccharides, radiation, and oxidative stress[94,95]. HMGB1 is a multifunctional protein that plays a variety of roles depending on its subcellular localization. The assembly of HMGB1-DNA in the cell nucleus induces DNA binding and bending, as well as chromatin remodelling[96]. Nuclear HMGB1 is subjected to several post-translational modifications such as acetylation[97], phosphorylation[98], oxidation[95,99], methylation[100] and glycosylation[101], inducing its secretion from the nucleus to the outside of the cell, where it functions as a damage-associated molecular pattern (DAMP) that initiates inflammatory reactions[102].

During viral infection including HCV[103], DENV[72], ZIKV[104], WNV[105], chikungunya virus (CHIKV)[106], HSV[107], HIV[108] and SARS-CoV-2[109], HMGB1 is transported from the nucleus to the extracellular milieu, where it acts as an alarmin to elicit inflammatory responses. Besides, the overproduction of HMGB1 in the sera of individuals infected with DENV and CHIKV was observed to be strongly linked with viral load and illness symptoms[106,110]. Extracellular HMGB1 has been shown to play a harmful role in viral infection by causing a major impact on the pathogenesis of viral infections linked with cytopathic effect (CPE) and triggering inflammatory responses, according to previous studies[105,111]. For example, extracellular HMGB1 has been implicated in the pathophysiology of DHF/DSS, most likely *via* disrupting the vascular barrier[112]. Additionally, excessive extracellular HMGB1 induced by ZIKV, WNV and JEV may cause neuroinvasion, probably through the blood-brain barrier disruption [104,105,113]. As a result, secreted HMGB1 may be considered as a biomarker for the diagnosis of flavivirus infections and inhibiting its overproduction as a therapeutic strategy for treating viral infection pathogenesis could be a feasible alternative.

RES positively upregulates SIRT1, leading to HMGB1 deacetylation, thus inhibiting the intracellular-extracellular translocation of HMGB1 and retention of HMGB1 in the nucleus[114]. The inhibition of extracellular HMGB1 release by RES-activated SIRT1 helps to reduce the inflammation-related positive feedback loop, as evidenced by the fact that extracellular HMGB1 triggers overexpression of a panel of pro-inflammatory cytokines[20,114,115]. Hence, administering

RES or anti-HMGB1 neutralizing antibody may be a strategy to alleviate the virus-induced inflammatory damage.

Previous studies have suggested that RES possesses antiviral effects against DENV[72] and ZIKV[116] through the intranuclear retention of HMGB1. Nuclear HMGB1 is proposed to be involved in the antiviral response to DENV[72], ZIKV[116], duck reovirus and duck Tembusu virus or duck plague virus[117] by binding to the promoter regions of ISGs and upregulating their expression to inhibit viral replication. Contrarily, nuclear HMGB1 has been shown to bind to viral nucleoprotein to facilitate influenza virus replication[118]. Whereas, the cytoplasmic HMGB1 has also been shown to act as a pro-viral factor during DENV and HCV replication by interacting with viral UTRs and eliciting pro-inflammatory responses[119,120]. Hence, RES's inhibitory effects on other flavivirus infections are plausible through nuclear HMGB1 retention mechanisms similar to that reported in DENV and ZIKV infections.

5. Regulation of micro–RNA expression

MiRNAs are small non-coding RNAs with a length of about 22 nucleotides that play significant roles in controlling gene transcription. More than 460 miRNAs have been identified, but the complete list of miRNAs in the human genome remains unknown. In general, miRNAs in our genome are transcribed by RNA polymerase Ⅱ[121]. Once bound to their target mRNAs, miRNAs downregulate their target gene expression post-transcriptionally by either destabilizing target mRNAs or inhibiting mRNA translation, ultimately impacting protein levels and cellular functions[122].

To date, miRNAs have been linked to various diseases, such as cancer, neurodegenerative diseases and viral infections. Numerous miRNAs have been identified to regulate viral replication, either positively or negatively, in flavivirus infections. Viruses have evolved the cellular miRNA machinery in order to aid in replication. For instance, miR-146a promotes DENV replication by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6) and dampening interferon-beta (IFN-β) induction[123]. This is similar to how miR-146a enhances JEV replication by suppressing NF-κB activation, Janus kinase (Jak)-STAT pathway and ISGs[124]. MiR-21 has also been found to facilitate DENV-2 replication in HepG2 cells and treatment with anti-miRNA-21 oligonucleotide (AMO-21) significantly reduces DENV-2 replication[125]. On the other hand, the host produces a variety of miRNAs to combat infections. For example, miR-30e* and miR-223 limit DENV replication by enhancing NF-κB-dependent IFN-β induction[126] and downregulating the microtubule-destabilizing protein stathmin 1 (STMN1)[127], respectively. The highly expressed chromosome 19 miRNA cluster (C19MC) in primary human trophoblasts, which includes miR-512-3p, miR-516b, miR-517a, and miR-525-5p, protects against ZIKV infection *via* a type Ⅲ IFN and ISGs-independent mechanism[128]. In addition, miR-532-5P suppresses the host genes *SEC14* and spectrin domains 1 (SESTD1) and TAK1-binding proteins 3 (TAB3), which are essential for WNV replication, thus, exerting antiviral action against WNV[129]. Overall, the conflicting functions of miRNAs which can either promote or hinder virus replication, highlight the intricacy of the relationship between hosts and viruses.

RES can act as a miRNAs regulator in treating both communicable and non-communicable diseases. Previous studies have suggested that RES treatment can regulate the expression of miRNA to combat viruses through SIRT1-dependent or SIRT1-independent pathways. RES, for example, downregulates the levels of miR-155 and miR-34a expressions, which in turn interrupts EBV transformation[130]. Meanwhile, elevated miR-182 and miR-217 expressions lead to a decrease in SIRT1 expression and an increase in Tat-induced HIV-1 long-terminal repeat transactivation[131,132]. Similarly, SIRT1 levels have been discovered to be inhibited by the upregulation of miR-142 expression in simian immunodeficiency virus-infected cells[133] and miR-217 expression in human cytomegalovirus-infected cells[134], respectively. In short, these findings suggest that RES's miRNA regulation of SIRT1 may suppress viral transactivation and replication *via* the SIRT1-dependent mechanism since RES is a SIRT-1 activator, as previously described. In addition to its antiviral effects, RES has been shown to modulate miRNA expression, which can influence the immune response and potentially help combat virus replication. For instance, RES induces an anti-inflammatory response by upregulating miR-663 and downregulating miR-155, leading to the downregulation of JunB and JunD proteins[135], since these proteins are components of the AP-1 transcription factor complex that regulates inflammation and immune response. Further studies, however, are required to identify additional miRNAs targeted by RES and to understand the implications of these interactions in the context of viral infections.

6. Conclusions and future prospects

Flavivirus infections have recently emerged as among the most widely distributed vector-borne diseases, affecting millions of individuals annually and putting billions more at risk for contracting the infection. Infection with a flavivirus can cause a wide range of symptoms, from asymptomatic, mild to severe infections and deaths. The disease imposed a substantial medical and economic burden onto the population especially in developing countries where the disease in endemic. Even though vaccines for several of the flaviviruses are available, there is still a number of other debilitating flavivirus infections that still do not have approved vaccines. Effective antiviral drugs to treat these flavivirus infections,

hence are urgently needed. Although several compounds have been demonstrated with anti-flavivirus properties, there is currently a lack of approved antiviral drugs specially formulated for the prevention or treatment of flavivirus infections. Among the promising alternative is an approach employing epigenetic therapy. There is a growing evidence that epigenetic plays a pivotal role in controlling various viral infections. Epigenetic modifications are in general reversible, highly adaptable and rapidly sensitive to environmental changes and other exposures[136]. RES, a polyphenol with antiviral activity, has been discovered to induce epigenetic changes which inhibited flaviviruses and other viruses replication. Epigenetic alterations implicated in flavivirus infections include DNA methylation, histone acetylation or deacetylation, non-histone modification and miRNA regulation. Epigenetic mechanisms by RES also include activation of innate immune responses, induction of T-cell tolerance, and inhibition of pro-inflammatory cytokines. These effects collectively can aid in controlling virus replication and alleviating inflammatory responses. By lowering inflammation, the detrimental consequences associated with excessive inflammation, such as haemorrhagic fever, neurological complications, and multiple organ failure, can be prevented during viral infections. Hence, immunomodulatory potential of RES through epigenetic mechanisms makes it a valuable therapeutic approach in combating virus infections. Apart from its potential as an epigenetic therapy, RES has shown high potential as an adjuvant to enhance vaccine efficacy and provide long-lasting protection against flavivirus infections. For example, co-administration of RES with pseudorabies virus vaccine increased antibody production and enhanced the antigen presentation ability of peritoneal macrophages in mice[137].

While RES in general holds potential as epigenetic therapeutic agent against flavivirus infections, it is important to consider several limitations including the substantial variations of results between studies. RES-induced epigenetic mechanisms have been found to have both proviral and antiviral properties, which could likely due to the complex and multifaceted nature of epigenetic regulation in virus infections. Another limitation is its lack of specificity in its action, which can vary depending on its concentration. This is due to the fact that RES has been shown to have effects on multiple signaling pathways and cellular processes, which can lead to unintended effects on the host. For instance, at low doses, RES has been discovered to have anti-inflammatory effects by inhibiting NF-κB and reducing the expression of pro-inflammatory cytokines[138]. Conversely, high doses of RES can result in the upregulation of pro-inflammatory cytokine expressions and apoptosis[139]. In addition, there is still a lack of clinical data on the safety of RES as an epigenetic therapy for virus infections. To overcome these limitations, more research is necessary to fully understand the underlying epigenetics mechanisms of RES, optimize its efficacy and specificity as well as assess its safety in clinical trials to avoid inadvertent side effects. In this review, attempts were made to summarize the epigenetic modifications that could take place in flavivirus infections and how the epigenetic effects of RES may be explored to limit these infections. Targeting specific epigenetic modulators to prevent and treat infections could be the future epigenomic investigations to explore new avenues for developing novel antiviral drugs.

Conflict of interest statement

We declare that we have no conflict of interest.

Funding

The author received no extramural funding for the study.

Acknowledgments

We acknowledge the funding from the Ministry of Higher Education, Malaysia for niche area research under the Higher Institution Centre of Excellence (HICoE) program (MO002-2019 & TIDREC-2023).

Authors' contribution

K.L.C. and K.K.T. conducted a comprehensive literature search and contributed to manuscript preparation. S.A.B. and N.Z. contributed to the manuscript editing, reviewing, and refining the content. All the authors have reviewed and approved the final manuscript.

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