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REVIEW ARTICLE

A comprehensive review on the antiviral activities of chalcones

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ABSTRACT

Some viral outbreaks have plagued the world since antiquity, including the most recent COVID-19 pandemic. The continuous spread and emergence of new viral diseases have urged the discovery of novel treatment options that can overcome the limitations of currently marketed antiviral drugs. Chalcones are natural open chain flavonoids that are found in various plants and can be synthesised in labs. Several studies have shown that these small organic molecules exert a number of pharmacological activities, including antiviral, anti-inflammatory, antimicrobial and anticancer. The purpose of this review is to provide a summary of the antiviral activities of chalcones and their derivatives on a set of human viral infections and their potential for targeting the most recent COVID-19 disease. Accordingly, we herein review chalcones activities on the following human viruses: Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus, human immunodeficiency, influenza, human rhinovirus, herpes simplex, dengue, human cytomegalovirus, hepatitis B and C, Rift Valley fever and Venezuelan equine encephalitis. We hope that this review will pave the way for the design and development of potentially potent and broad-spectrum chalcone based antiviral drugs.

Introduction

Nature is considered as a valuable source of medicine due to the existence of certain active ingredients and chemicals in various plant species. Numerous plant extracts were found to be useful remedies in different disease conditions [1–3]. Among the well-studied phytochemicals are chalcones. Chalcones are considered the main precursors for flavonoids and isoflavonoids biosynthesis in plants [4]. They are found in various plant species including fruits and vegetables [4]. These medicinal molecules can also be synthesised in the lab in bulk quantities [4]. A group of schemes and procedures have been described for the synthesis of these compounds. These methods include, but are not limited to, Claisen–Schmidt condensation, Aldol condensation, Suzuki reaction, Friedel–Crafts acylation, Witting reaction and photo-Fries rearrangement of phenyl cinnamate [4].

Chalcones consist of an aromatic ketone and an enone that form a variety of biological agents [5]. Their skeleton is made up of two aromatic rings with an aliphatic three-carbon chain linking them to form a linear or planar skeleton structure [5]. They are also interconnected by conjugated double bonds and possess a delocalised π-electron system on the aromatic rings [5]. Chalcones and their natural or synthetic derivatives (through some structural modifications of the chalcone rings) are known to have a wide range of numerous pharmacological actions comprising anti-inflammatory, anti-oxidant, antitumor, anti-tubercular, anti-viral, anti-malarial, anti-fungal and anti-bacterial activities [6]. Several natural and synthetic or semi-synthetic chalcones have shown great medicinal bioactivity due to their actions against diverse

targets [6,7]. Their anticancer activity was evident by targeting several molecules including P-glycoprotein (P-gp), aromatase, 5α-reductase, proteasome, vascular endothelial growth factor (VEGF) and other important factors [6,7]. Chalcones also showed promising beneficial activities against haematological, cardiovascular and obesity related diseases [6,7]. They have been reported to possess inhibitory effects on calcium (Ca^{2+})/potassium (K^+) channel, angiotensin-converting enzyme (ACE), acyl-coenzyme A, thromboxane (TXA2 and TXB2), etc. [6,7]. Their excellent anti-inflammatory actions were proposed to be due to their inhibition of different targets like lipooxygenase (LOX), cyclooxygenase (COX), interleukins (ILs), nitric oxide synthase, prostaglandins (PGs), etc. [8]. Additionally, chalcone molecules exert anti-diabetic effects through modulating agents of dipeptidyl peptidase-4 (DPP-4), peroxisome proliferator-activated receptor gamma (PPAR-Γ), α-glucosidase and tissue sensitivity [9]. Their potential anti-viral activities have been well recognised via various targets including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), topoisomerase-II, fumarate reductase, lactate dehydrogenase, several protein kinases, protein tyrosine phosphatase, human immunodeficiency virus (HIV-integrase (IN)/protease), lactate/isocitrate dehydrogenase, etc. [10].

One of the major issues with several antiviral treatments is drug resistance that can emerge through mutations, genetic modifications and phenotypic changes [11]. Thereby, the virus will no longer respond to the previous effective drug resulting in failure of controlling the disease, leading to higher risks of disease spreading, and high mortality rates [11]. Consequently, the need for new antiviral agents became essential, thus, with the proven

antiviral role of chalcones, they became a new attractive subject that have acquired the interest of the scientific community. We herein will go through different aspects of various chalcone based antiviral compounds, focussing particularly on their molecular antiviral activities and potential for treating COVID-19.

Viral infections and their therapeutic management

Viruses encompass a large cluster of pathogens that are accountable for causing severe infectious diseases and represent a major threat to the global health and economy. During 2019, the World Health Organization listed four different viruses among the 10 global health threats that require more attention, which included influenza, dengue, HIV and ebola viruses [12]. Other high-threat viral infections requiring special attention and priority were also listed and included zika, haemorrhagic fevers, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS) [12]. Subsequently, during 2020 specifically, the world has faced the greatest health pandemic of the twenty-first century after the tremendous spread of the new COVID-19 disease triggered via SARS-CoV-2 coronavirus [13]. This virus has spread to every continent and efforts to quarantine it are not yet effective [13]. Unfortunately, SARS-CoV-2 has striking negative consequences on morbidity, mortality, healthcare systems capacity and world economy [13,14]. Viral infections are associated with deleterious consequences in the host body including cell death, stimulation of inappropriate response of immune system, disruption of cell function and cellular transformation [15]. In immunocompetent patients, the majority of viral infections tend to resolve spontaneously [15]. Additionally, antivirals are used in the management of a limited number of infectious diseases in order to reduce the virulence of the virus and minimise the course of illness [16]. Vaccines are also used as a preventive measure against severe viral strains, but they are not always efficient and are still lacking for several types of viruses [17].

Managing severe viral infections requires the timely and efficient use of therapeutic antiviral interventions to control the spread of the virus and reduce disease severity. Antiviral medications act principally by targeting either viral or cellular proteins [18]. The first mechanism usually results in a specific targeted response with less side effects, but with a higher possibility for developing drug resistance [18]. The second mechanism on the other hand, while presenting with less chances of developing drug resistance, provides a broad spectrum of antiviral activity and high toxicity profile [18]. Most of the currently approved antiviral drugs function directly or indirectly by targeting different stages of the virus replication cycle as well as specific cellular and viral enzymes required for its replication [19]. These targeted viral life cycle stages involve virus attachment and adsorption, cell fusion, synthesis of viral RNA or DNA and progeny virus release [19]. Since viruses are obligate pathogens that use the host-cell machinery for their replication, finding drug targets that interact with viral replication is challenging [18,19]. Additionally, the current antivirals are associated with a group of limitations which include diminished efficacy, high toxicity, high costs and emergence of drug resistance [18]. Therefore, discovering improved antiviral alternatives targeting viral diseases is highly required, especially with the developing concern of re-emergence of new viral strains and infections.

Chalcones as potential candidates for treating viral infections

Various studies have reported that different types of chalcones can act on important targets in diseases caused by viral infections. These promising diverse antiviral bioactions, make chalcone derivatives a favourable broad-spectrum candidate for targeting the most recent viral pandemic, COVID-19 and any other potentially emerging viral diseases. Their interesting biological activities have been studied in several scientific investigations as potential pharmacological agents capable of targeting a variety of human viruses including; MERS-CoV, severe acute respiratory syndrome-related coronavirus (SARS-CoV), HIV, influenza virus, human rhinovirus, herpes simplex virus (HSV), dengue virus (DEN), human cytomegalovirus (HCMV), hepatitis B virus (HBV), hepatitis C virus (HCV), Rift Valley fever (RVF) and Venezuelan equine encephalitis virus (VEEV), through their well discovered antiviral cellular targets and based on specific chalcone skeleton design [20–30]. Figure 1 illustrates the main mechanisms of actions of chalcone derivatives that were reported in literature on different human viruses. Chalcones were shown to act on important viral molecular targets affecting different stages of viral replication cycle including; reverse transcriptase (RT) [31,32], IN [22,33–35], protease [36–38], neuraminidase (NA) [39], aminotransferases [40], superoxide dismutase, glutathione peroxidase and other associated enzymes [40]. They were also found to act on important receptors such as CXCR4 chemokine receptors [41], US28 receptor of HCMV [27] and capsid pocket inside viral protein 1 (VP1) in rhinovirus [42]. Other important activities include targeting the kinase activity of epidermal growth factor receptor (EGFR) [27], inhibition of DNA hybridisation [30], mammalian target of rapamycin (mTOR) pathway [43], blocking virus-mediated cell fusion and inhibiting the late stages of viral replication [44]. In addition, chalcones were demonstrated by some studies to act as broad-spectrum covering agents on different viral infections and were shown to possess some preventive and prophylactic potential [45]. Further clinical trials have supported the use of chalcone due to its low toxicity potential, making it an attractive option in the pharmaceutical industry [46]. Table 1 summarises the mechanisms of action of bioactive chalcone derivatives based on the viruses they were tested on, which are discussed in more details on subsequent text.

Chalcone derivatives tested on coronaviruses

Coronaviruses (CoVs) are enveloped viruses that belong to the Nidovirales order and Coronaviridae family, and are divided into four genera (α, β, γ and δ CoVs) [67]. These pathogens have been found in bats, dogs, humans, as well as other mammals [67]. There are seven species of CoVs identified to date that can induce diseases in humans [68]. Four out of them (229E and NL63 α-CoVs; HKU1 and OC43 β-CoVs) trigger mild symptoms of common cold [68]. The remaining three are β-CoVs (SARS-CoV, MERS-CoV and SARS-CoV-2) and are responsible for severe diseases [68]. SARS first appeared in 2002–2003 and SARS-CoV was identified as its causative agent [69]. This virus resulted in the viral outbreak that lasted from 2002 to 2003, which was the first pandemic of the twenty-first century originating from China and spreading to other countries [69]. As per the Centers for Disease Control (CDC), SARS spread in 26 countries leading to 774 deaths and 8098 cases of infection [70]. Around ten years later (2012), the Middle East respiratory syndrome emerged and a sixth coronavirus (MERS-CoV) was recognised in a patient in Saudi Arabia presenting with severe respiratory symptoms [71]. This virus was reported in more
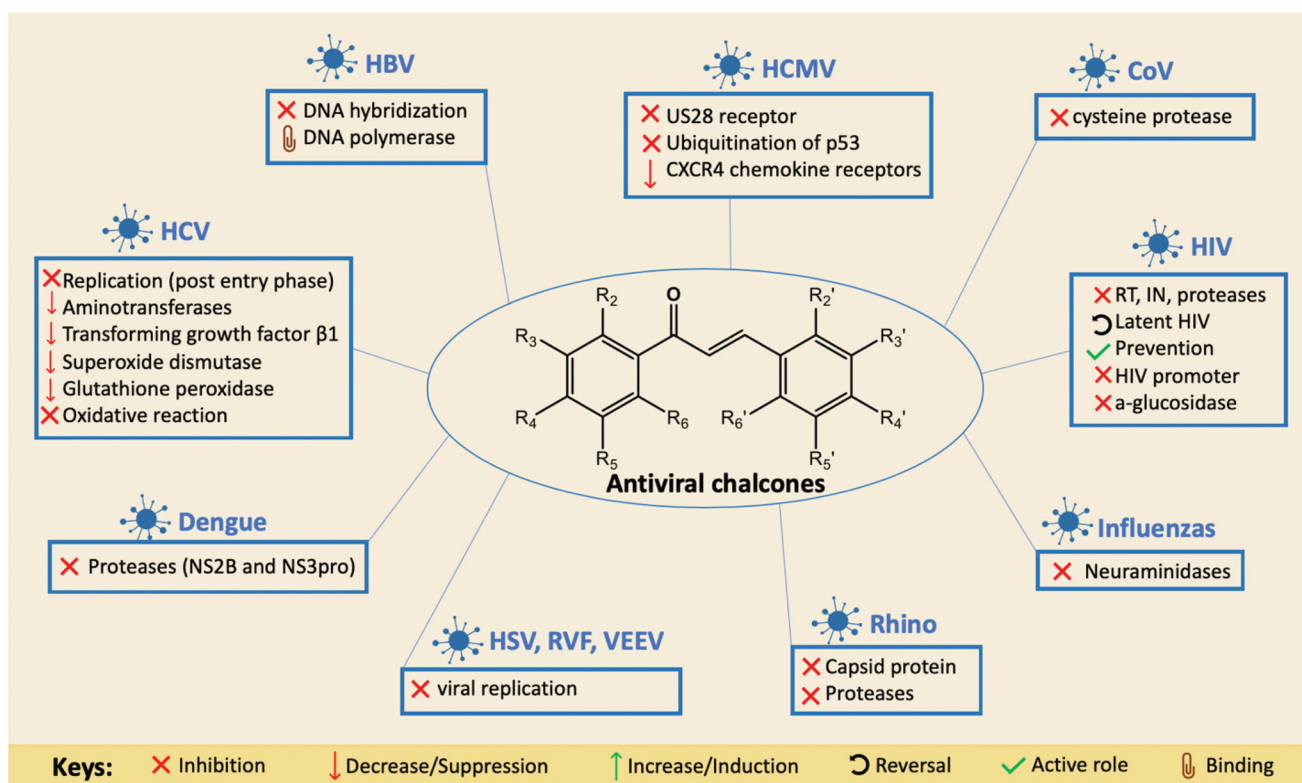
Figure 1. Mechanisms of action and targets of antiviral chalcone derivatives reported on different human viruses.

than 27 countries across the Middle East, Asia, North Africa and Europe resulting in 2040 infections and 712 deaths [71]. More recently, a seventh coronavirus (SARS-CoV-2) was identified in December 2019 in China and consequently spread worldwide resulting in a major health pandemic [13]. The disease induced by SARS-CoV-2 was referred to as COVID-19 and is very closely related to the SARS disease identified in 2002 [13]. The typical symptoms of SARS include dry cough, fever, shortness of breath and patients may progress to pneumonia in severe cases [13]. As of 10 October 2020, the World Health Organization reported that 1,056,186 COVID-19 patients have died and 36,361,054 people are infected with SARS-COV-2 [72]. A huge global effort is being undertaken in order to stop and control the current significant spread of COVID-19. There is no specific drug or vaccine to control the spread of CoVs; therefore, there is an ongoing research to identify and develop effective medications and new treatment options.
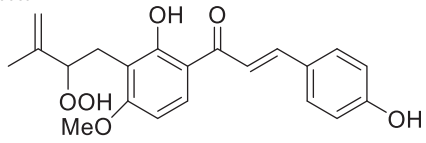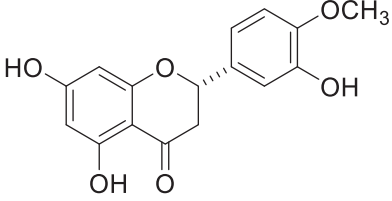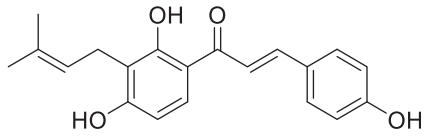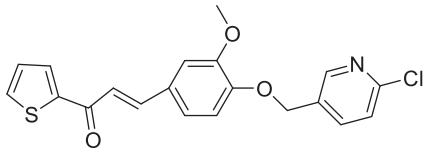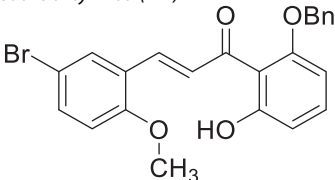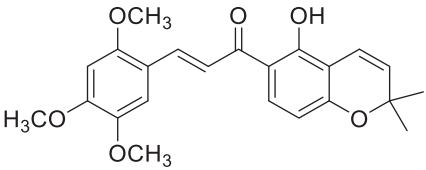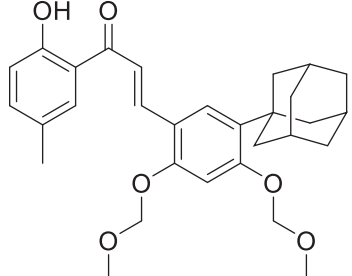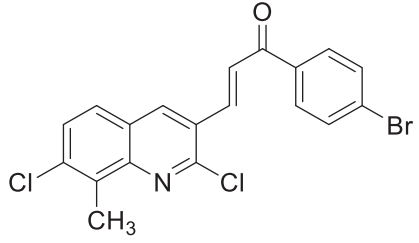
Chalcone pharmacophore represents a unique and attractive scaffold for the discovery and targeting of CoVs due to their significant anti-infective properties. Few chalcones were investigated with regards to their effect on CoVs infection, namely the SARS-CoV and MERS-CoV [20,21,30,47]. Only two studies investigated chalcones effect on SARS-CoV [21,47]. Park et al. synthesised and tested the antiviral activity of nine chalcone derivatives isolated from *Angelica keiskei* plant against SARS-CoV [47]. Among these derivatives, an alkylated chalcones with methoxy and perhydroxyl substitutions were found to have potent inhibitory activities against important targets in SARS-CoV, which are cysteine proteases (i.e. papain-like protease (PLpro) and a 3chymotrypsin-like protease (3CLpro)) [73]. Additionally, it showed an IC$_{50}$ of 11.4 μM against 3CL^{pro} and 1.2 μM against PL^{pro}. Therefore, the substantial effect of chalones against these important proteases makes them attractive molecules for the development of anti-SARS drugs. On the other hand, two studies have explored chalcones activities

against MERS-CoV [20,30]. MERS-CoV 3C-like protease (3CLpro) was explored as a target for chalones in a study published by Jo et al. [20]. They reported two chalcone derivatives, isobavachalcone and helichrysetin, that exert prominent inhibitory activity against MERS-CoV 3CLpro (IC$_{50}$: 35.85 and 67.04 μM, respectively) [20]. In the other study, chloropyridine chalcone derivative exhibited a better inhibitory activity against viral replication and cellular growth (EC$_{50}$: 3.2 μg/mL; CC$_{50}$: 5.5 μg/mL; SI$_{50}$: 1.7 μg/mL), indicating that the pyridyl functionality can enhance anti-MERS-CoV activity [30]. Taken together, chalcone derivatives can target different types of CoVs, particularly their cysteine protease enzymes. This makes them a possible candidate for treating the emerging COVID-19 disease caused by SARS-CoV-2 virus. To date, no drug or vaccine has been approved for the treatment of COVID-19 and other coronavirus diseases and research is still ongoing. Therefore, more studies should be undertaken to test chalcone derivatives as potential candidates on SARS-CoV-2 and other CoVs.

Chalcone derivatives tested on human immunodeficiency virus

Acquired immunodeficiency syndrome is a life-threatening chronic disease caused by the HIV [74,75]. HIV is classified into two subtypes (HIV-1 and HIV-2), with HIV-1 being 24 times more common than HIV-2 [74,75]. According to the World Health Organization and the Joint United Nations Program on HIV and AIDS, 39 million patients died due to the AIDS epidemic and around 37 million patients were infected with HIV by the end of 2018 [76,77]. Therefore, treating HIV efficiently and effectively is a global health issue specially with increasing concerns of patients developing drug resistance. HIV/AIDS is currently treated mainly through the use of multiple antiretroviral drugs. These drugs are classified into six classes depending on their mechanisms that target different stages of the HIV life-cycle [78]. These classes are: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside

Table 1. Bioactive chalcone derivatives tested on different viral infections.

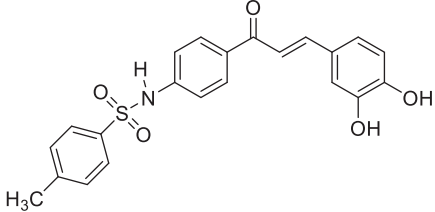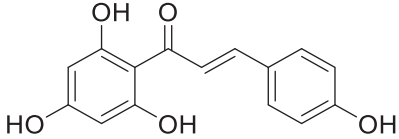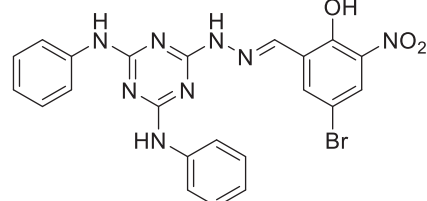| Structure	Source	Virus subtype	Mechanism of action	Ref.
Coronaviruses				
1	Natural	SARS-CoV	Anti-3CL^{pro} protease: cell-free tans-cleavage; IC$_{50}$: 11.4 μM; K_i: 16.1 μM, cell-based cis-cleavage activities; IC$_{50}$: 7.1 μM Anti-PL^{pro} protease: IC$_{50}$: 1.2 μM; K_i:1.2 μM	[47]
2	Natural	SARS-CoV	Anti-3CL^{pro} protease: cell-free cleavage; IC$_{50}$: 18.1 μM, cell-based cleavage; IC$_{50}$: 8.1 μM	[21]
3	Natural	MERS-CoV	Anti-3CLpro IC$_{50}$: 35.85	[20]
4	Synthetic	MERS-CoV	EC$_{50}$: 3.2 μg/mL; CC$_{50}$: 5.5 μg/mL; SI$_{50}$: 1.7 μg/mL	[30]
Human immunodeficiency virus (HIV)				
5	Synthetic	HIV-1	Inhibitory IC$_{50}$: 4.7 μM in TZM-bl cells; non-toxic	[45]
6	Natural	HIV-1	Strong binding against P24 protein and RT enzyme	[32]
7	Synthetic	HIV-1	Phosphorylation of CDK9 at the T-loop and formation of the Tat-SEC complex at the viral promoter	[48]
8	Synthetic	HIV-1	Potent inhibition against RT; IC$_{50}$: 0.10 μg/mL	[31]
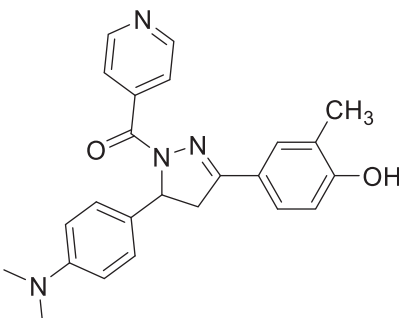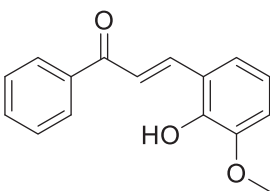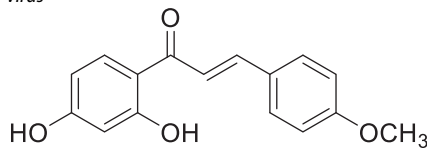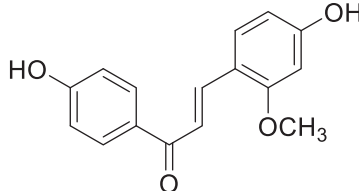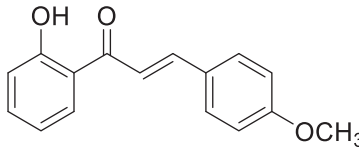
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Table 1. Continued.

	Structure	Source	Virus subtype	Mechanism of action	Ref.
9		Synthetic	HIV-1	Inhibited integrase (IN) against the IN 30 processing; IC_{50}: 7.8 μM, IN strand transfer processes; IC_{50}: 0.7 μM	[22]
10		Natural	HIV-1	Inhibitory IC_{50}: 10.7 μg/mL; EC_{50}: 0.022 μg/mL	[49]
11		Synthetic	HIV-1, HIV-2	Potent non-selective anti-HIV activity HIV-1 and HIV-2 IC_{50}: 5.7 μM	[50]
12		Synthetic	HIV-1	Active against integrase strand transfer; IC_{50}: 3.7 μM; EC_{50}: 7.3 μM	[33]
13		Natural	HIV-1	Inhibited HIV-1 replication by 77% at 15.9 μM	[51]
14		Natural	HIV-1	Suppressed TPA-induced HIV promoter activity by around 80%	[52]
15		Natural	HIV-1	Anti-protease activity; high IC_{50} value (>100 μM)	[37]
16		Synthetic	HIV-1	Anti-HIV-1; IC_{50}: >200.0 μM; EC_{50}: 64.7 μM	[53]
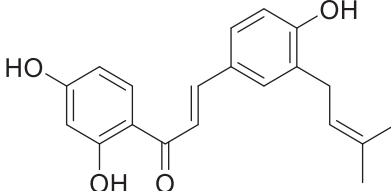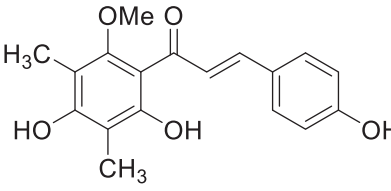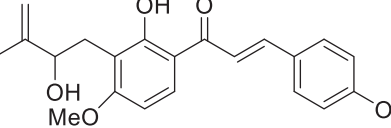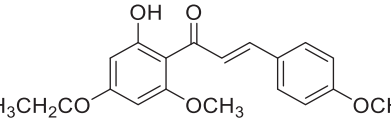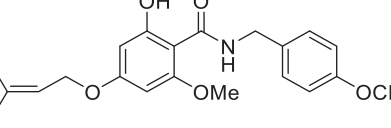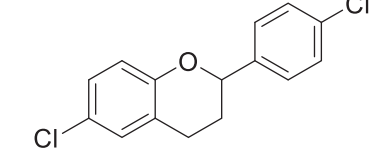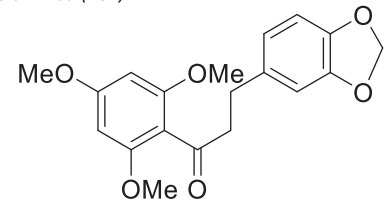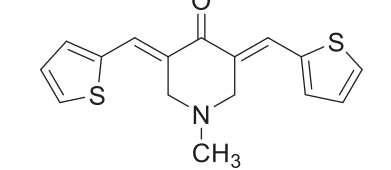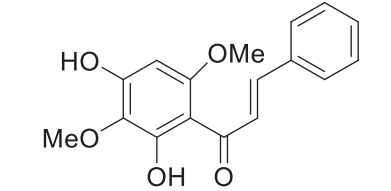
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Table 1. Continued.

	Structure	Source	Virus subtype	Mechanism of action	Ref.
17		Synthetic	HIV	Non-competitive inhibition; IC$_{50}$: 0.40 μM; K_i: 0.24 μM	[54]
18		Natural	HIV-1	Anti-protease activity; 26.8%	[38]
19		Synthetic	HIV-1	Inhibitory IC$_{50}$ value for IN-mediated 30-processing: 1.9 μM, IN strand transfer: 0.6 μM	[34]
20		Synthetic	HIV-1, HIV-2	Inhibitory IC$_{50}$: 5.7 μM against HIV-1 (IIIB) and 7.0 μM against HIV-2 (ROD)	[55]
21		Synthetic	HIV-1	Inhibitory IC$_{50}$: 2 μM against purified IN in the presence of Mn^{2+} and Mg^{2+} as cofactors; EC$_{50}$: 23 μM	[35]
Influenza virus					
22		Synthetic	H1N1	Inhibited H1N1 neuraminidase (NA) enzyme; IC$_{50}$: 2.23 μmol/L	[39]
23		Natural	H1N1, H9N2, novel H1N1, oseltamivir resistant novel H1N1	Inhibited NA from influenza viral strains; IC$_{50}$: 2.19–5.80 μg/mL	[23]
24		Synthetic	H5N1	Non-competitive inhibition; binds and holds the 150 loop of NA disrupting the binding of sialic acid in the catalytic site	[56]
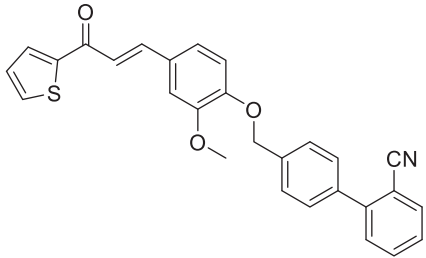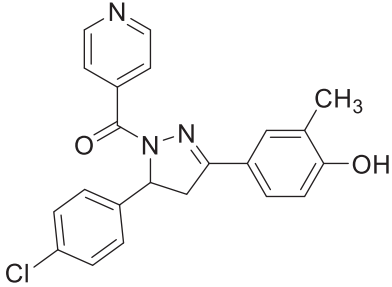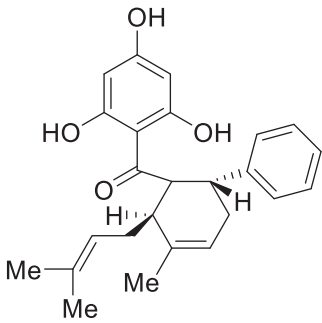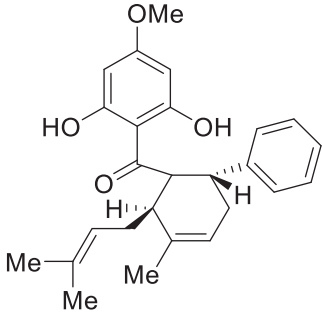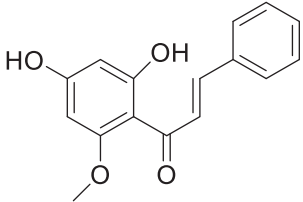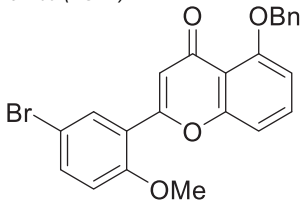
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Table 1. Continued.

	Structure	Source	Virus subtype	Mechanism of action	Ref.
25		Natural	H1N1, H9N2	Inhibited NA; IC_{50}: 21.51 and 20.03 µg/mL, respectively	[57]
26		Natural	H1N1, H9N2, novel H1N1, oseltamivir resistant novel H1N1	Inhibited NA; IC_{50}: 3.31–20.45 µM	[58]
27		Synthetic	H1N1	Inhibited NA IC_{50}:12.3 µM	[59]
Rhino virus 28		Synthetic	HRV2, HRV9	Inactivated capsid protein; IC_{50}: 0.03 µg/mL, cytotoxic concentration: 30 µg/mL	[60,61]
29		Synthetic	HRV-2, HRV-30	Inhibited the uncoating of HRV by stabilising the viral capsid protein; IC_{50}: <0.0018 µg/mL	[42]
30		Synthetic	HRV-2	Inactivated binging capsid protein; IC_{50}: 0.053 µg/mL	[62]
Herpes simplex virus (HSV) 31		Natural	HSV-1, HSV-2	IC_{50}: 15.5 µg/mL, IC_{50}: 17.0 µg/mL	[63]
32		Synthetic	HSV-1	33% reduction in the number of viral plaques; IC_{50}: 0.66 µM	[53]
33		Natural	HSV-1	The ethanol extract of the plant (P. spectabile); IC_{50} of 21.9 µg/mL	[64]
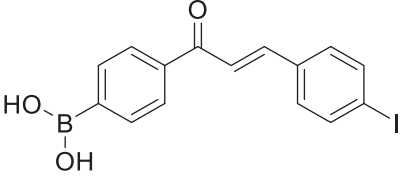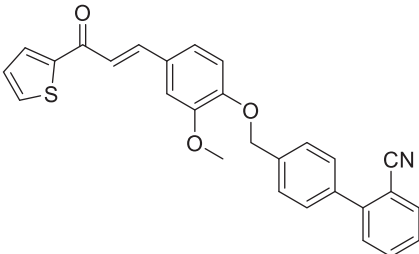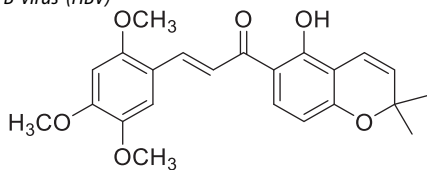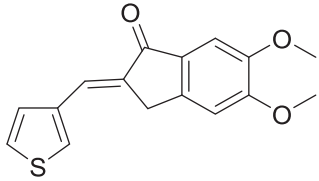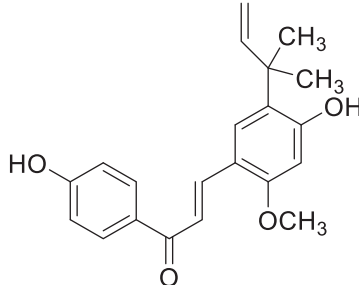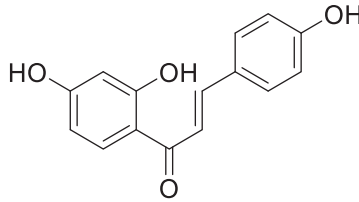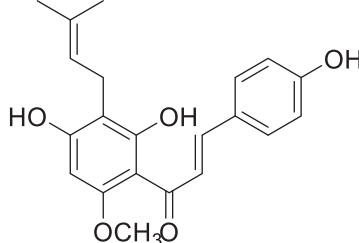
(*continued*)

Table 1. Continued.

	Structure	Source	Virus subtype	Mechanism of action	Ref.
34		Synthetic	HSV-1	EC_{50}: >6.00 μM; CC_{50}: 23.77 μM; SI_{50}: <4 μM	[30]
35		Synthetic	HSV-1, HSV-2	Minimum cytotoxic concentration: 200 μg/mL; minimum inhibitory concentration: >8 μg/mL against HSV-1 and 40 μg/mL against HSV-2	[25]
Dengue virus					
36		Natural	DEN-2	Anti-NS3 protease with the K_i: 21 μM	[26]
37		Natural	DEN-2	Anti-NS3 protease with the K_i: 25 μM	[26]
38		Synthetic	DEN-2	Anti-NS2B/NS3 proteolytic with the K_i: 377 μM	[65]
Human cytomegalovirus (HCMV)					
39		Synthetic	HCMV	Anti-US28 receptor, EC_{50}: 3.5 μM	[27]
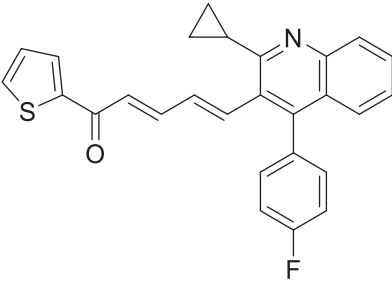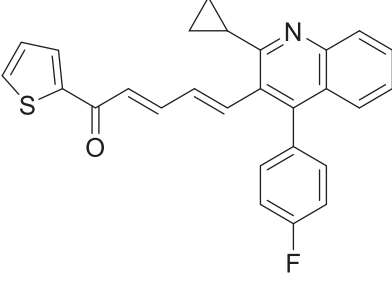
(continued)

Table 1. Continued.

	Structure	Source	Virus subtype	Mechanism of action	Ref.
40		Synthetic	HCMV	Inhibited ubiquitination of p53 in infected cells	[66]
41		Synthetic	HCMV	EC50: <0.05 µM; CC_{50}: 2.96 µM; SI_{50}: >62	[30]
Hepatitis B virus (HBV)					
42		Natural	HBV	*P. pinnata* seed extract inhibited HBV replication at 0.18 pg/mL; bound in silico to HBV DNA polymerase protein	[28]
43		Synthetic	HBV	EC_{50}: 4.2 µM, SI_{50}: >24	[30]
Hepatitis C virus (HCV)					
44		Natural	HCV genotype 2a (J6/JFH1P47)	Inhibited the post entry phase by inhibiting the HCV subgenomic RNA replication; IC_{50}: 2.5 µg/mL	[29]
45		Natural	HCV genotype 2a (J6/JFH1P47)	Inhibited the post entry phase by inhibiting the HCV subgenomic RNA replication; IC_{50}: 3.7 µg/mL	[29]
46		Synthetic	HCV genotype 1b	Regulation of apoptosis, inhibition of oxidative reaction, modulation of MTP activity	[40]

(*continued*)

Table 1. Continued.

Structure	Source	Virus subtype	Mechanism of action	Ref.
Rift Valley fever (RVF)				
47	Synthetic	RVF	EC_{50}: 0.39 μg/mL; CC_{50}: 1.2 μg/mL; SI_{50}: 3.1 μg/mL	[30]
Venezuelan equine encephalitis virus (VEEV)				
48	Synthetic	VEEV	EC_{50} >2.8 μg/mL; CC_{50} 2.8 μg/mL; SI_{50} 0 μg/mL	[30]

reverse transcriptase inhibitors (NNRTIs), chemokine receptor 5 (CCR5) antagonist, protease inhibitors (PIs), IN inhibitors and fusion inhibitors [78].

Numerous natural and synthetic chalcone derivatives and analogues were tested on different viral infections. The vast majority of them were explored on HIV infection (with major focus on HIV-1 subtype). As summarised in Table 1, the main HIV targets that were investigated with chalcone were RT [31,32], IN [22,33–35] and protease [36–38] enzymes. Some chalcones were investigated for their inhibitory potential on viral replication without specifying their exact targets [49,51]. Few chalcones were tested for their effects on RT enzyme [31,32]. For example, one study reported quinoline based chalcones as possible NNRTs [31]. Based on their findings, chloro and bromo substituted chalcones increased RT inhibition (IC_{50} values of the most active molecules were 0.10 μg/mL and 0.11 μg/mL) [31]. Chalcone derivatives were also evaluated against IN enzyme [22,33–35]. Among them, a derivative based on the chalcone pharmacophore had potently inhibited the IN mediated 3′ processing (IC_{50}: 1.9 μM) and strand transfer (ST) processes (IC_{50}: 0.6 μM) [34]. Protease enzyme is another target that was studied for chalcone anti-HIV actions [36–38]. Turkovic et al. reported the discovery of a very active chalcone derivative exhibiting a potent inhibitory activity towards protease enzyme (IC_{50} value of 0.001 μM) [36].

Other tested anti-HIV activities of chalcones included preventive approaches [45], latent HIV reversing [48], HIV promoter activity inhibition [52] and a-glucosidase inhibition [54]. In a study testing chalcones therapeutic and preventive role on HIV, a chalcone with bromo and methoxy-substitutions was found to inhibit HIV infection potently in a dose-dependent manner in different HIV clinical isolates (e.g. anti-HIV IC_{50}: 4.7 μM in TZM-bl-HIV infected cells) with no apparent toxicity [45]. The ability to prevent HIV-1 infection was also investigated in the same study, where another chalcone derivative bearing bromo- and ortho-benzyl-substitutions was reported to exert both preventive and therapeutic responses [45]. The effect on targeting latent viral reservoirs was

also explored [48]. Wu et al. investigated the effect of a new chalcone derivative [(E)-3-(5-(adamantan-1-yl)-2,4-bis (methoxymethoxy) phenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one] as a latency-reversing agent [48]. The principle of LRAs action is based on reactivating the latent proviruses and consequently eliminating them [48]. This chalcone derivative worked by activating HIV transcription by phosphorylating CDK9 at the T-loop and prompting the formation of Tat-SEC complex at the viral promoter [48]. There are no LRAs currently in the market for HIV due to their high toxicity/low efficacy profiles. Therefore, this chalcone should be further examined for possible further development. In a different article, it was reported that a chalcone derivative had affected HIV gene expression at the transcriptional level by inhibiting HIV promoter activity by 80% [52]. This significant activity was not observed on the cytomegalovirus (CMV) promoter, making this molecule selective towards the HIV promoter [52]. Additionally, alpha-glycosidase inhibition has been reported as a possible mechanism to treat HIV [79]. In a study exploring novel sulphonamide chalcone derivatives as alpha-glucosidase inhibitors, it was reported that a chalcone bearding dihydroxy substituent inhibited alpha-glucosidase non-competitively with a potent IC_{50} of 0.4 μM (inhibitory constant (K_i): 0.24 μM) [54].

HIV-2 represents another distinct subtype that is far less common compared to HIV-1 [74,75]. However, around 1.5 million people are living with HIV-2 including those with dual HIV-1 and HIV-2 infection, yet it is attracting much attention [74,75]. Only few studies investigated the role of chalcones on HIV-2 [50,55]. In a study by Casano et al., three novel chalcone derivatives were found to have specific inhibition for HIV-2 multiplication, one compound was found to be six times more selective towards HIV-2 with IC_{50} of 47.7 μM [50]. Additionally, para substitution was reported to increase the potency of this inhibition [50]. Others synthesised chalcones within the same study exerted potent non-selective activities towards both HIV-1 and HIV-2 (e.g. IC_{50}: 5.7 μM on both subtypes) [50]. However, the majority of the chalcones were reported to be selective towards HIV-1 [50].

Chalcone derivatives tested on influenza virus

Influenza is a viral infection with seasonal variations caused by RNA viruses of the Orthomyxoviridae family [80]. Influenza A and B viruses are causative factors of death of many people worldwide [80]. Influenza virus has evolved cellular mechanisms for exploiting human cell factors to boost its replication while suppressing host immune responses [80]. Identification of these cellular techniques would help to widen the number of the anti-influenza drug targets. Current targets include two proteins; the M2 ion channel and NA [81]. Neuraminidase is a large glycoprotein on the outside surface of viral particles. NA is one of the pathogenic factors and is responsible for the release of progeny virus from infected cells [82]. Despite the emergence of many inhibitors of viral NA, including rimantadine, amantadine, oseltamivir and zanamivir, drug-resistant influenza viruses have been generating rapidly [83]. Therefore, search for effective anti-influenza drugs against different influenza strains is given high priority. Throughout the developmental process of an anti-influenza screening program of natural products, numerous effective molecules were found to play a role in limiting the threat of resistant strains or enhancing the effectiveness of many anti-viral agents. NA became one of the major anti-viral targets of many natural and synthetic chalcones, as targeting it is crucial for the inhibition of the viral growth. $2',4'$-dihydroxy-4-methoxy chalcone is derived from bioactive compounds in nature and presented a high activity in inhibiting H1N1 NA [39]. In a different study, H9N2, H1N1, novel H1N1 and oseltamivir-resistant novel H1N1 cells were targeted by natural products obtained from the acetone extract of *Glycyrrhiza inflata* including isoliquiritigenin (IC_{50} (μg/mL) of 8.41 ± 0.39, 9.69 ± 0.37, 3.48 ± 0.19 and 3.42 ± 0.12, respectively) and echinantin (IC_{50} (μg/mL) of 5.80 ± 0.30, 5.70 ± 0.55, 2.49 ± 0.14 and 2.19 ± 0.06, respectively) [23]. $2'$-Hydroxy-4-methoxychalcone is also a synthetic compound designed based on quercetin and was found to effectively target H5N1 [56]. In another study, 2-hydroxy-3-methyl-3-butenyl alkyl is a synthetic product that mainly targets H1N1 with IC_{50}:12.3 μM [59]. This compound exhibited the most potent inhibitory effect of NA activity in comparison to other chalcone substitutes; 6-hydroxyl-3,7-dimethyl-octa-2,7-dien-yl > dimethylallyl > geranyl in a non-competitive inhibition manner [59]. According to another study, H1N1 and H9N2 were also inhibited by natural products extracted from the root bark of *Erythrina addisoniae* including; licoagrochalcone A, abyssinone VI and $5'$-prenylbutein [57]. (E)-4,$2',4'$-Trihydroxy-$6'$-methoxy-$3',5'$-dimethyl-chalcone, $2',4'$-dihydroxy-$6'$methoxy-$3',5'$-dimethylchalcone, $2',4'$dihydroxy-$3'$-methyl-$6'$-methoxychalcone and $2,2',4'$-trihydroxy-$6'$methoxy-$3',5'$-dimethylchalcone are natural C-methylated products isolated from *Cleistocalyx operculatus* buds that exhibited major inhibition of the viral NAs from H1N1 and H9N2 strains [58].

Chalcone derivatives tested on rhino virus

The rhinovirus is a common viral infectious pathogen in humans that is a predominant agent of the common cold and upper respiratory tract infections [84]. Rhinovirus infection prefer to proliferate in warm temperatures of 33–35 °C, mainly in the nose [85]. It belongs to the Picornaviridae family; which are small nonenveloped viruses with a single-stranded RNA [84]. There are three species of rhinovirus (A, B and C) and include around 160 serotypes differentiated according to their surface proteins [86]. Current antiviral agents against this virus were formed to target cell susceptibility by preventing virus binding and attachment, viral replication, virus uncoating and production of protein [86].

Chalcones have been tested on a number of specific targets including binding sites, capsid pocket and viral proteases inside VP1, the latter was found to be the main effective target of several anti-rhinovirus chalcones. Ro 09-0410, was the main chalcone and one of the first isolated compounds [24,60,61]. However, upon further testing on humans through clinical trials, it did not significantly reduce the incidence of infection or illness; therefore, several attempts have been made to produce various synthesised analogues related to Ro 09-0410 compound [24]. The goal of identifying anti-rhinovirus agents was to develop compounds with higher therapeutic ratio to limit viral infectivity. Chalcone Ro 09-0410, $4',6$-dichloroflavan (DCF) and RMI-15,731(1-[5-tetradecyloxy-2-furanyl]-ethanone), were suggested by several studies for directly inactivating the virus [62]. However, the binding site of the aforementioned compounds on the capsid was found to have slight conformational differences among viral serotypes [62]. A minor change in the binding site was proposed since chalcones can bind to the DCF resistant rhino virus type, and no cross-resistance was seen between RMI and DCF [62]. In another study, amide analogues where developed and among them; Ro 09-0535 ([4-methoxy-3H]) with IC_{50} of 0.0018 μg/mL, Ro 09-0696 (chalcones derivatives with methoxy (OMe) substitution) with IC_{50} of <0.0018 μg/mL, and Ro 09-0881 was shown to be 4.5–12 times more effective on several serotypes of the virus than Ro 09-0410 or other agents that target the capsid protein [42]. An earlier study reported synergistic activities among certain drug combinations. DCF (dichloroflavan), chalcone Ro-09-0410, enviroxime and HuIFN (human interferon)-alpha 2, HuIFN-beta, HuIFN-beta X 401 and HuIFN-gamma, showed an activity against rhinovirus type 2 (RV2) and rhinovirus type 9 (RV9) [87]. The combinations of HuIFN-gamma or HuIFN-alpha and enviroxime were of special interest [87]. These results indicate that similar drug combinations are worthy of future clinical studies. Subsequent investigations emphasised the importance of closely monitoring the development of drug-resistant viruses during chemotherapy and antiviral treatment, as a single change in an amino acid is sufficient for the emergence of drug viral resistance [88]. However, another study reported that use of chalcones is beneficial despite drug resistance. The study reported that chalcone Ro 09-0410 was capable of decreasing rhino virus infectivity in humans who were challenged with a drug resistance mutant. In the same study, a drug-dependent virus had completely lost its capability of infecting humans [89]. Further studies should be conducted to determine the mechanism of action by which chalcones can overcome or reduce the extent of drug resistance.

Chalcone derivatives tested on herpes simplex virus

Herpes simplex virus belongs to the Herpesviridae family and is associated with various types of diseases [90]. The most prevalent types that are associated with human infections are HSV-1 followed by HSV-2 [91]. In 2016, it was estimated that 3.7 billion people were living with HSV-1 and 491.5 million individuals had HSV-2 [91]. Latent HSV-1 infections can reactivate causing severe illnesses in all age groups including neonates [90]. These infections include conjunctivitis, cutaneous or genital herpes, keratitis, eczema herpeticum or encephalitis [90]. On the other hand, HSV-2 can cause aseptic meningitis, genital herpes and devastating neonates infections [92]. HSV infections are managed through the use of antiviral agents, with acyclovir being the first-line treatment option [92]. There is a range of promising virus and host-cell specific targets for HSV treatment [93]. Examples include, viral

polymerase and helicase–primase or host cell related targets such as cyclin-dependent kinases and cyclooxygenase-2 [93].

Various natural and synthetic chalcone derivatives were tested against HSV focussing mainly on their inhibitory potency on viral replication [25,30,53,63,64,94]. A chalcone derivative isolated from *Millettia leucantha* has shown moderate inhibitory activity against HSV-1 and HSV-2 (IC_{50}: 15.5 μg/mL against HSV-1 and IC_{50}: 17.0 μg/mL against HSV-2) [63]. In another study, a biphenyl substituted cyano chalcone derivative has also shown a good inhibition against HSV-1 (EC_{50}: >6.00 μM) [30]. In a third study by Ali et al., a group of chalcone derivatives were tested for their broad spectrum activities against different viruses [25]. Among them, 5-(4′-chlorophenyl)-3-(4″-hydroxy-3″-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-4-pyridyl methanone had the best replication inhibitory activity against HSV-1 and HSV-2 (minimum cytotoxic concentration: 200 μg/mL; minimum inhibitory concentration: >8 μg/mL against HSV-1 and 40 μg/mL against HSV-2) [25]. This chalcone derivative has shown promising broad spectrum activities against other viruses including vesicular stomatitis, vaccinia, para-influenza-3, sindbis, reovirus-1, coxsackie and Punta Toro viruses [25]. This is one of select studies investigating the role of chalcone derivatives as broad spectrum antiviral agents [25,30,94]. Therefore, more studies investigating chalcone derivatives against multiple virus subtypes are highly required in order to distinguish broad spectrum chalcones from those having specific activities against certain viruses. Additionally, more research should be done focussing on chalcones effects on more specific HSV targets.

Chalcone derivatives tested on dengue virus

Dengue is an infection caused by the Arthropod-borne DEN [95]. It can present as dengue fever (DF) or dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) [96]. Dengue virus belongs to the Flaviviridae family and is caused by four variants of viruses including DEN-1, DEN-2, DEN-3 and DEN-4 [96]. Dengue present 3–14 days after the infection with symptoms of high fever, muscle and joint pains, and rash, with expected recovery taking 2–7 days [96]. It is also considered an endemic disease in more than 100 countries [97]. Flaviviridae family and DEN consist of a single positive-sense 1-kb RNA [96]. Translation of the genome results into a single polyprotein made of three structural and seven non-structural (NS) proteins [98]. This polyprotein yields a sequential order C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5 [98]. Upon gene expression, proteolytic processing of the synthesised polyprotein whether co- or post-translational is required [99]. This processing results in the *cis* and *trans*-cleavage of polyprotein precursor by both host proteases or virus protease complex NS2B/NS3 alongside its cofactor NS2B [99]. Although the efficacy of vaccines like the recently developed ChimeriVax is currently under evaluation, to date; there is no known vaccine approved for human use as a protective measure against dengue [100]. However, there are a number of evolving promising therapeutic strategies against this disease.

Dengue virus protein targets were examined in several trials and including virus protease (NS2B-NS3pro), methyltransferase (MTase), helicase (NS3 helicase), virus envelope and protein RNA-dependent RNA polymerase (RdRp) [101]. Despite several trials, NS3pro became an important and attractive target for potential therapeutic agents in addition to some chalcone compounds which were used in such trials against DF/DHF [101]. 4-Hydroxypanduratin A is a natural product that was tested against dengue-2 virus and showed a competitive inhibition towards NS3 protease [26]. In another study, panduratin A was also shown to

behave similarly with the K_i value of 25 μM [26]. Cardamonin, also known as dihydroxymethoxychalcone, is a synthetic compound that exhibited a non-competitive inhibition against DEN-2 NS2B/NS3 activities [65]. There are two proposed mechanisms by which dengue virus (DENV2) NS2B/NS3 protease is targeted for inhibition [102]. A promising compound can either destabilise electronic density to the catalytic triad residues NS3-ASP75, NS3-HIS51 and NS3-SER135 [102]. Conversely, this enzyme can be inhibited by a ligand which can also interrupt the C-terminal movement of NS2B, which is needed for conversion between the open and closed conformations [102]. Upon exploring these binding sites by multiple molecular dynamics simulations, chalcones were found to be one of the top potential drugs acting via both aforementioned inhibitory mechanisms [102]. Nevertheless, further investigations on the allosteric pocket is needed for more drug discovery potentials.

Chalcone derivatives tested on human cytomegalovirus

Although there is currently a number of available drugs for cytomegalovirus (HCMV) infection treatment, the side effects of these medications including their toxicity and directed teratogenicity make their use in certain populations like pregnant women contraindicated [103]. Moreover, drug resistance is considered an important problem in this disease management, especially in patients who are immunocompromised and are in severe need for such medications. There are several recent promising trials for antiviral medications that are able to combat HCMV infections with less drawbacks including toxicity and resistance. The genome of HCMV, is made of double stranded DNA that encodes for specific receptors, vital G protein coupled receptors (vGPCRs), of which US28 receptor is considered an attractive target [104]. The US28 receptor processes a ligand-independent signalling pathways in which it can activate cascades to facilitate virus survival, invasion, oncogenesis and variety of diseases including cardiovascular disease through these constitutive signalling pathways [104]. The potential role of US28 receptor in viral pathogenesis establishes a potent infection in immunocompromised hosts as well as immunocompetent hosts through latent infections that facilitate the viral dissemination and invasiveness [104].

Known biological activities of flavonoids and their abundance in plants makes them attractive candidates for targeting HCMV virus as they are generally considered as effective and potentially safe antivirals for use in different patients; however, validation of their safety in specific populations like pregnant women are further needed [105–107]. Of those flavonoids, chalcones became an ideal platform for their relatively easy synthesis and their biological effects in inhibiting a number of known enzymes; therefore, they became a potential tool for the treatment of HCMV infections [105]. 5-(Benzyloxy)-2-(5-bromo-2-methoxyphenyl)-4H-chromen-4-one, is one of these chalcones that was found to inhibit the US28 receptor of HCMV with an EC_{50} of 3.5 μM [27]. In 2004, xanthohumol 1, a prenylated chalcone showed moderate antiviral activity against HCMV through its action in downregulating CXCR4 chemokine receptors [41]. Other chalcones were also found to be effective in targeting the kinase activity of EGFR and thus preventing HCMV entry into cells and limiting cellular activation [27]. HCMV infection also induces an upregulation of p53, this process is a common target of trans-4-iodo, 4′-boranyl-chalcone as ubiquitination of p53 in infected cells is inhibited by the chalcone [66]. In a study, biphenyl substituted cyano derivative was found to be effective against both resistant and non-resistant strain with high potency [30]. Thus, due to their unique structure, strong

activity and potential low toxicity profile, chalcones are expected to be further involved in future investigations as antiviral agents against HCMV.

Chalcone derivatives tested on hepatitis B virus

Hepatitis B virus is a virus that attacks the liver and induces hepatitis B infection [108]. It is a small DNA virus that belongs to the Hepadnaviridae family [108]. Hepatitis B is usually a short-term infection; however, for some patients, it may transform into a chronic illness [108]. Chronic hepatitis B is associated with serious complications like liver cancer and cirrhosis [108]. As of 2015, the World Health Organization reported that around 257 million individuals were living with chronic hepatitis B infection and that 887,000 died of it [109]. There are some medications that can help with the management of hepatitis B including nucleoside/nucleotide analogues and interferon-based therapy [110]. However, none of them is effective in eradicating the infection [110]. The best preventive strategy is hepatitis B vaccination [110]. Various studies have tested different types of molecules as potential treatment options for hepatitis B, including chalcone derivatives.

Few studies only investigated chalcones role on HBV [28,30]. Patil et al. synthesised a group of substituted aryl/heteroaryl derived thienyl chalcones and reported that the more rigid, less bulky thiophenylindenone derivative was the most potent at inhibiting DNA hybridisation in vitro (EC$_{50}$: 4.2 μM; good selectivity index: >24) [30]. These results demonstrate that chalones can be a potentially good candidates for inhibiting the replication of DNA viruses. In a study by Mathayan et al., they investigated the anti-HBV effects of the *P. pinnata* seeds, which contains some chalcone derivatives [28]. At a concentration of 5 mg/mL, *P. pinnata* extract significantly inhibited HBV replication (virus concentration of 0.18 pg/mL; $p < .001$) with no apparent toxicity [28]. On the other hand, molecular docking studies showed that two chalone derivatives (isopongachromene and glabaarachalcone) present in *P. pinnata* bind to the HBV DNA polymerase protein [28]. However, further studies are needed in order to confirm the real effects of chalcone derivatives in vitro by isolating and testing them separately from the plant extract, especially with the promising virtual screening study results that merit further in vitro confirmation.

Chalcone derivatives tested on hepatitis C virus

Hepatitis C virus is a member of the Flaviviridae family [111]. The heterogenicity of the viral genetic material has been used to classify the HCV virus into seven genotypes and more than 67 subtypes [111]. The viral genome consists of a single stranded positive-sense RNA [111]. This genetic material/genome is used to create a precursor (poly protein), which is made up of three thousands amino acids that need to be processed in the post-translational phase by the intracellular proteases in order to form mature proteins including core, E1, E2, a putative ion channel p7, in addition to NS proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B [111]. These structural and NS proteins are essential for the viral pathogenesis and aid in its infectivity, carcinogenesis and several other pathological processes [111]. Besides its well-known effects on liver metabolic processes including lipids and glucose metabolic disorders, it has been well-known for being one of the major causative agents of chronic hepatitis, cirrhosis and hepatocellular carcinomas [111]. There are a number of standard agents used for the treatment of HCV infection including pegylated interferon regiments, ribavirin and other direct-acting agents [111]. The need for alternative drugs development for HCV infection treatment became a well-studied topic due to clinical and economic purposes. The cost of these medications as well as drug resistance emergence is commonly encountered. In this regard, complementary medicine aims to develop antiviral agents that are strong and effective inhibitors of HCV infection.

Chalcones and their compounds have been studied as effective substitutes because of their ability to inhibit viral translation and replication of HCV. Plants like *Glycyrrhiza uralensis* and *G. glabra* have been considered as good candidates in medicinal plants evolution [29]. Several chalcones extracted from the aforementioned plants have been examined for their activity as anti HCV medications [29]. A well discovered target is the mTOR pathway through the inhibition of ribosomal protein 6 (rps6) phosphorylation and its kinase [43]. Licochalcone A and isoliquiritigenin are natural products targeting HCV genotype 2a (J6/JFH1P47) with an IC$_{50}$ of 2.5 mg/mL and 3.7 mg/mL, respectively [29]. Their activity is witnessed through the inhibition of HCV virus subgenomic RNA replication and protein synthesis [29]. Xanthohumol (XN) is another well-known chalcone for its biological activities in protecting the liver by antiviral mechanisms [40]. XN activity was monitored in HCV infected cells, and was shown to significantly decrease aminotransferases, transforming growth factor β1 expression and hepatic steatosis score in cells exposed to XN in comparison to their control [40]. XN was also shown to significantly decrease the activity of superoxide dismutase, glutathione peroxidase and other associated enzymes [40]. Therefore, XN is capable of affectively decreasing hepatic damage through the inhibition of oxidative reaction and manipulating the apoptosis pathways [40]. Upon further investigations, it was shown to decrease liver fibrosis through its inhibitory activity on stellate cell function [40]. Studies on medicinal plants are promising and can potentially yield more effective agents against HCV infective strains including resistant ones.

Chalcone derivatives tested on Rift Valley fever

Rift Valley fever virus (RVFV) is an arbovirus that belongs to the Phenuiviridae family and is transmitted mainly through mosquitoes [112]. RVFV is accountable for a zoonosis disease which affects mainly domesticated animals in sub-Saharan Africa including cattle, sheep, camels and goats alongside animals in other countries [113]. Humans can also get infected with RVFV through bites from infected mosquitoes or contact with infected animals' blood or body fluids [113]. However, transmission of RVFV through human-to-human contact was not documented to date [113]. Similar to other arboviral infections such as dengue, zika and chikungunya, RVF infection by RVFV is emerging globally [114]. According to the CDC, there is no available approved antiviral medications against RVF and the disease is usually self-limiting [115]. However, severe cases can only be managed through supportive care [115]. Therefore, identifying therapeutic options that are specific to RVFV is urgently needed. Some synthetic chalcone analogues were explored for their anti-RVFV activities [30,94]. Interestingly, a cyclopropylquinoline analogue was found to be 28 times more potent (EC$_{50}$: 0.39 μg/mL) as compared to the conventional antiviral drug, ribavirin (EC$_{50}$: 11 μg/mL) in terms of inhibiting RVFV viral replication [30]. However, more investigations are needed to identify specific RVFV molecular targets of chalcone derivatives. Particularly, host-cell related pathways (e.g. transcriptional and mitochondrial processes) utilised by RVFV for its replication, are promising therapeutic targets for anti-RVFV drug development [116].

Chalcone derivatives tested on Venezuelan equine encephalitis virus

Venezuelan equine encephalitis virus belongs to the Togaviridae family and affects both equines and humans [117]. VEE outbreaks are known throughout Latin America and examples of affected countries include Venezuela, Peru, Colombia, Costa Rica, Ecuador, Mexico, El Salvador, Panama, as well as USA [117]. Around 14 subtypes of VEEV were identified with subtype I varieties A, B and C being the most associated with epidemics in humans and equids [117]. VEE is mostly misdiagnosed as dengue infection which makes the estimation of its specific burden on health and economy more difficult [117]. VEEV may cause encephalitis in humans and common signs and symptoms of VEE involve headache, fever, tremors, nausea and vomiting [118]. The main management strategy to control VEE is through vaccination against VEEV [117]. However, there is no FDA-approved drug available for targeting this virus. Patil et al. have investigated the role of a group of chalcone derivatives on VEEV [30]. The most potent in inhibiting VEEV viral replication was a cyclopropylquinoline analogue (EC_{50} >2.8 μg/mL) [30]. Unfortunately, its cytotoxic concentration has a similar potency (CC_{50} 2.8 μg/mL), making it unselective towards the virus as compared to the host cell (SI_{50} 0 μg/mL) [30]. Other investigated chalcone derivatives have all shown the same unselectively (SI_{50} 0 μg/mL). Therefore, more attempts to improve the structure of these derivatives are needed.

Conclusions

Viral infections are one of the most common human diseases and are considered the leading cause of a variety of illnesses with high morbidity and mortality. A great number of antivirals were developed and are widely used around the world. Despite their broad range of coverage, the rapidly evolving antiviral resistance limits their efficacy to combat viral infections. In addition to high rate of drug resistance development and emergence of new viral strains, the need for alternative antivirals has increased over the years necessitating the extraction and synthesis of novel antiviral agents, of which chalcones became one of the main candidates. Chalcones are widely biosynthesised in plants and play a significant role in defending the body against pathogens and insects. Numerous chalcone derivatives were investigated for their antiviral activities and found to possess interesting and remarkable effects on modulating several anti-infective molecular targets which makes chalcone derivatives a potentially effective and safe broad spectrum antiviral agents. However, additional investigations should be conducted in order to study chalcones specific mechanisms and targets in vitro and in vivo as most reports thus far were conducted in vitro, without further determining their specific molecular targets. In addition, there are very limited clinical studies on chalcones as antiviral therapies. Therefore, in order to establish the viability of chalcones as potential antiviral agents in human diseases more in vivo investigations are needed.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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