

Original Research Article

An Update Comprehensive Review on the Antiviral Activities of Chalcone Analogs

Rozin Moghimi¹, Homayon Jafari Moghadam¹, Fereshteh Talebi², Sepideh Abrishami³,
Mohammad Mahboubi-Rabbani^{1*}

^{1*} Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

² Student Research Committee, Hormozgan University of Medical Science, Bandar Abbas, Iran

³ Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Since ancient times, the world has experienced several viral epidemics, the most recent one was the COVID-19 pandemic. The emergence of new viral infections has led to a need for newer therapeutic approaches that can overcome the limitations of conventional antiviral drugs. Natural open-chain flavonoids called chalcones can be synthesized in laboratories and are present in a variety of plants. Numerous investigations have demonstrated the pharmacological actions of these tiny chemical compounds, which include antiviral, anti-inflammatory, antibacterial, and anticancer properties. This article provides an overview of the antiviral characteristics of chalcones and their derivatives against several human viral infections, with potential use in the COVID-19 pandemic. This article reviews chalcones' work on human viruses such as Hepatitis B and C, Rift Valley fever, Human Immunodeficiency, Influenza, Human Rhinovirus, Herpes Simplex, Dengue, Human CMV, and Venezuelan Equine Encephalitis. This review could lead to the development of chalcone-based antiviral medicines that are both efficacious and versatile.

Keywords: Chalcones; viral infections; COVID-19; HIV; influenza virus; HSV; hepatitis B virus; rhino virus; dengue virus

*Corresponding author email address: Mohammad Mahboubi-Rabbani,
jrsorouh@gmail.com;

Introduction

Nature is a valuable source of medicines due to its many plant species and their active chemicals. Many plant extracts have been discovered to be effective treatments for many medical diseases [1-3]. Chalcones are one class of well-researched phytochemicals. Chalcones are thought to be the primary building blocks for plants' production of flavonoids and isoflavonoids [4]. Numerous plant species, including fruits and vegetables, contain them [4]. Large-scale lab production of these therapeutic compounds is also possible [4]. The synthesis of these chemicals has been described using a variety of plans and techniques. Claisen–Schmidt condensation, Aldol condensation, Suzuki reaction, Friedel–Crafts acylation, Wittig reaction, and photo-Fries rearrangement of phenyl cinnamate are a few of these techniques [4].

Chalcones are biological agents in various forms. They consist of an enone and an aromatic ketone [5]. They have a linear or planar skeleton structure composed of two aromatic rings joined by an aliphatic three-carbon chain [5]. A delocalized π -electron system is present on the aromatic rings, and they are linked by conjugated double bonds [5]. A wide range of pharmacological actions, including anti-inflammatory, anti-oxidant, antitumor, anti-tubercular, antiviral, anti-malarial, anti-fungal, and antibacterial properties, are known to be present in chalcones and their natural or synthetic derivatives (via certain structural modifications of the chalcone rings) [6]. Several chalcones, whether natural, synthetic or semi-synthetic, have demonstrated significant medical bioactivity due to their ability to target a variety of targets [6-7]. The targeting of many molecules such as P-glycoprotein (P-gp), aromatase, 5α -reductase, proteasome, vascular endothelial growth factor (VEGF) and other key components has demonstrated their anticancer potential [6-7]. Chalcones have also shown encouraging protective effects against obesity-related, cardiovascular and haematological disorders [6-7].

According to reports, they inhibit the acetyl-coenzyme A, thromboxane (TXA₂ and TXB₂), calcium (Ca²⁺)/potassium (K⁺) channel, and angiotensin-converting enzyme (ACE) [6-7]. It was suggested that their potent anti-inflammatory properties stemmed from their inhibition of various targets, including prostaglandins (PGs), cyclooxygenase (COX), lipooxygenase (LOX), interleukins (ILs), nitric oxide synthase, and others [8]. Chalcone compounds also have anti-diabetic effects by influencing tissue sensitivity, peroxisome proliferator-activated receptor gamma (PPAR-C), dipeptidyl peptidase-4 (DPP-4), and α -glucosidase [9]. Numerous targets, such as glycerol-dehyde-3-phosphate dehydrogenase (GAPDH), fumarate reductase,

lactate dehydrogenase, several protein kinases, protein tyrosine phosphatase, human immunodeficiency virus (HIV-integrase (IN)/protease), lactate/isocitrate dehydrogenase, etc., have helped to recognize their potential antiviral properties [10].

Medication resistance is a serious issue with many antiviral treatments, as it can arise from mutations, genetic changes, and phenotypic changes [11]. As a result, the virus will stop responding to the prior medication that worked, which will make it impossible to control the illness and increase the danger of disease spreading and high death rates [11]. The scientific community has become interested in chalcones due to their demonstrated antiviral role, which has made them an interesting subject. As a result, the demand for new antiviral drugs has become critical. This article will cover a variety of chalcone-based antiviral medications, focusing on their potential application in the management of COVID-19 and their molecular antiviral characteristics.

Viral infections and their therapeutic management

A vast group of organisms known as viruses are to blame for the development of serious infectious diseases, which pose a serious risk to both world health and the economy. The Influenza, HIV, Ebola viruses, and dengue were among the ten global health concerns that the World Health Organization identified in 2019 as needing greater attention [12]. The list also includes Zika, Middle East respiratory syndrome coronavirus (MERS-CoV), Hemorrhagic fevers, and Severe acute respiratory syndrome (SARS) as high-threat viral illnesses that needed immediate attention and priority [12]. In 2020, the world witnessed the most severe health crisis of the twenty-first century, mainly because of the quick spread of the unique COVID-19 virus, which was brought on by the coronavirus SARS-CoV-2 [13]. Attempts to confine this virus have not yet proven successful because it has spread to every continent [13]. Regrettably, the capability of healthcare systems, global economy, morbidity, and mortality are all severely impacted by SARS-CoV-2 [13, 14]. The host body can suffer harmful effects from viral infections, such as cell death, immune system responses that are not suitable, disturbance of cell activity, and cellular metamorphosis [15]. Most viral infections in immunocompetent individuals resolve on their own [15]. To lessen the severity of the infection and slow down the progression of the sickness, antivirals are also employed in the treatment of a small number of infectious disorders [16]. Although they are now insufficient for a number of virus types,

vaccinations are also employed as a preventive approach against highly contagious forms of the virus [17].

Therapeutic antiviral interventions must be used promptly and effectively to manage severe viral infections to stop the virus's transmission and lessen the severity of the illness. The main way that antiviral drugs work is by specifically attacking viral or cellular proteins [18]. The initial mechanism typically produces a focused react with fewer adverse effects, but it increases the risk of medication resistance [18]. Conversely, the secondary system has a high toxicity profile and a wide range of antiviral efficacy, but it also has a lower likelihood of acquiring drug resistance [18].

The majority of antiviral medications that are now on the market work either directly or indirectly by focusing on several viral and cellular enzymes that are necessary for the virus to replicate, as well as various phases of the virus replication cycle [19]. The targeted virus's attachment and adsorption, cell fusion, RNA or DNA synthesis, and viral progeny discharge are all included in the previously described stages of the life cycle [19]. Since viruses are obligatory pathogens that multiply by exploiting the host cell's machinery, it is challenging to find therapeutic targets that interact with viral replication [18,19]. Furthermore, there are several drawbacks to the antivirals that are already on the market, such as reduced effectiveness, significant toxicity, high price, and the emergence of medication resistance [18].

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Furthermore, there are a number of drawbacks to the antivirals that are already on the market, such as decreased efficacy, high toxicity, high cost, and the development of medication resistance [18]. Consequently, it is imperative to find better antiviral options that target viral diseases, particularly in light of the growing concern over the reemergence of novel viral strains and infections.

Chalcones as potential candidates for treating viral infections

Numerous investigations have revealed that various forms of chalcone can operate on significant aims in virally induced illnesses. Derived Chalcones are a favorable wide-ranging contender for attacking the most recent COVID-19 virus pandemic, as well as any future viral infections that might arise, as a result of their encouraging variety of antiviral bioactions. Chalcones have attracted attention for their potential as pharmacological agents against a range of human viruses, including 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). This interest stems from their ability to target specific cellular sites involved in viral activity [21,22].

The primary methods of action of chalcone derivatives that have been documented in the literature on several human viruses are depicted in Figure 1. Reverse transcriptase (RT) [23,24], IN [25-28], protease [29-31], neuraminidase (NA) [32], aminotransferases [33], superoxide dismutase, glutathione peroxidase, and other related enzymes [33] are among the significant viral molecular targets that chalcones have been demonstrated to modulate. Important receptors such the US28 receptor of HCMV [34], the capsid pocket inside viral protein 1 (VP1) in rhinovirus [35], and CXCR4 chemokine receptors [36] were also discovered to be impacted by them. Targeting the kinase activity of the epidermal growth factor receptor (EGFR) [34], limiting DNA hybridization [22], blocking the mammalian target of rapamycin (mTOR) pathway [37], preventing virus-mediated cell fusion, and suppressing the last stages of viral replication [38] are additional significant actions. Furthermore, chalcones have been proven in certain trials to have some prophylactic and preventative potential and to function as broad-spectrum covering agents on many viral infections [39]. Chalcone's low potential for toxicity has been confirmed by additional clinical trials, which makes it a desirable option for the pharmaceutical business [40]. Based on the viruses that were used for testing, Table 1 summarizes the mechanisms of action of bioactive chalcone derivatives; these viruses are covered in more detail in the text that follows.

Chalcone derivatives tested on coronaviruses

The four genera of enclosed viruses known as coronaviruses (CoVs) are α , β , γ , and δ CoVs. They are members of the Nidovirales order and Coronaviridae family [41]. These diseases have

been discovered in humans, dogs, and other mammals in addition to bats [41]. As of right now, seven species of coronavirus have been shown to cause illness in humans [42].

Among them, four (229E and NL63 α -CoVs; HKU1 and OC43 α -CoVs) cause mild cold symptoms [42]. Severe diseases are caused by the enduring three β -CoVs (SARS-CoV, MERS-CoV, and SARS-CoV-2) [42]. SARS-CoV was found to be the cause of the disease when it initially manifested in 2002–2003 [43]. This virus was the cause of the 2002–2003 viral outbreak, which started in China and expanded to other nations. It was the first pandemic of the twenty-first century [43]. According to The Centers for Disease Control (CDC), SARS was disseminated to 26 countries, resulting in 8098 cases of infection and 774 deaths [44].

In 2012, approximately ten years later, A person in Saudi Arabia displaying severe respiratory symptoms was identified to have a sixth coronavirus (MERS-CoV) and the Middle East respiratory syndrome [45]. There have been reports of this virus in over 27 countries in the Middle East, Asia, North Africa, as well as Europe; as a result, there have been 2040 infections and 712 fatalities [45]. More recently, a significant pandemic was caused by the seventh coronavirus (SARS-CoV-2) that was discovered in China in December 2019 and then spread over the world [13]. COVID-19, the name given to the SARS-CoV-2-induced illness, is strongly associated with the 2002 SARS diagnosis [13]. Typical SARS signs and symptoms include fever, shortness of breath, and dry cough; in more severe cases, pneumonia may develop in the patients [13]. The World Health Organization stated that as of October 10, 2020, 36,361,054 people had contracted SARS-COV-2 and 1,056,186 COVID-19 patients had perished [46]. The present considerable spread of COVID-19 is being stopped and controlled through massive global efforts. Since there isn't a single medication or vaccine that can stop the spread of CoVs, research is constantly being done to find and create new and efficient treatments.

The robust anti-infective characteristics of the chalcone pharmacophore render it a distinct and attractive structure for identifying and targeting Coronaviruses (CoVs). A small number of chalcones, specifically the SARS-CoV and MERS-CoV, were studied concerning their impact on CoV infection [21, 22, 47, 48]. The effect of chalcones on SARS-CoV was only examined in two investigations [47, 48]. Nine chalcone variants extracted from the *Angelica keiskei* botanical source were synthesized and evaluated for their antiviral efficacy against SARS-CoV by Park et al.[48] The study revealed that some derivatives, specifically alkylated chalcones

with methoxy and perhydroxyl replacements, exhibited strong inhibitory effects on cysteine proteases, specifically papain-like protease (PLpro) and 3chymotrypsin-like protease (3CLpro). It also displayed IC_{50} values of $1.2 \mu M$ against PL^{pro} and $11.4 \mu M$ against 3CL^{pro}.

Accordingly, Chalcones have a strong effect against these important proteases, making them attractive chemicals for the development of anti-SARS drugs. Conversely, two investigations have examined chalcones' anti-MERS-CoV capabilities [21, 22]. In a study by Jo et al [21], MERS-CoV 3C-like protease (3CLpro) was investigated as a potential target for chalcones. They discovered that MERS-CoV 3CLpro is significantly inhibited by two chalcone derivatives, isobavachalcone and helichrysetin (IC_{50} : 35.85 and 67.04 μM , respectively) [21]. The results of the other investigation showed that the pyridyl attribute can improve anti-MERS-CoV activity, the chloropyridine chalcone derivative shows a better ability to inhibit both viral replication and cellular growth. (EC_{50} : 3.2 $\mu g/mL$; CC_{50} : 5.5 $\mu g/mL$; SI_{50} : 1.7 $\mu g/mL$) [22].

When combined, chalcone derivatives have the ability to specifically target the cysteine protease enzymes of various CoV species. As a result, they could be explored as potential treatments for the recently emerged COVID-19 disease caused by the SARS-CoV-2 virus. Research is ongoing, but there is currently no approved drug or vaccine to treat COVID-19 or any other coronavirus disease. Chalcone derivatives should therefore be tested further as viable possibilities against SARS-CoV-2 and other CoVs.

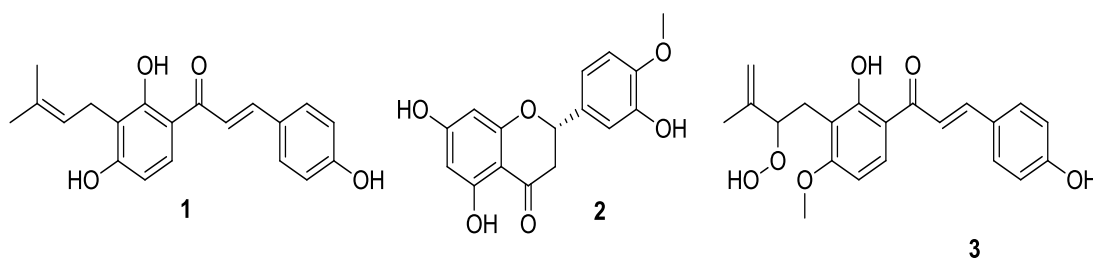


Fig. 1: 1: Anti-3CLpro IC_{50} : 35.85 μM [21]. 2: Anti-3CLpro protease: cell-free cleavage; IC_{50} : 18.1 M, cell-based cleavage; IC_{50} : 8.1 M [47]. 3: Mechanism of action: Anti-3CLpro protease: cell-free trans-cleavage; IC_{50} : 11.4 M; K_i : 16.1 M, cell-based cis-cleavage activities; IC_{50} : 7.1 M Anti-PLpro protease: IC_{50} : 1.2 M; K_i : 1.2 M [48].

Chalcone derivatives tested on human immunodeficiency virus

HIV, which stands for Human Immunodeficiency Virus, is responsible for causing AIDS, or Acquired Immunodeficiency Syndrome, a chronic condition that can ultimately lead to death

[49-50]. HIV-1 and HIV-2 are two types of HIV, which HIV-1 is 24 times more prevalent than HIV-2 [49-50]. According to the World Health Organization and the Joint United Nations Program on HIV and AIDS, by the end of 2018, approximately 37 million people had HIV infections and 39 million people had died from the AIDS epidemic [51-52]. As a result, properly and efficiently treating HIV is a global health priority, particularly in light of growing worries about individuals becoming resistant to medication. Nowadays, antiretroviral medications are the major treatment for HIV/AIDS. Depending on their mechanisms and the phases of the HIV replication cycle they target, these medications are classified into six classes [53]. These include the following classes: chemokine receptor 5 (CCR5) antagonists, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), IN inhibitors, and fusion inhibitors [53]. Numerous synthetic and natural compounds, derived from chalcones, have been experimented with against a range of viral infections. Most of the research conducted evaluated HIV infection, with a main focus on the HIV-1 subtype. The primary HIV targets that were studied with chalcone were the enzymes RT [23-24], IN [25- 26- 28], and protease [29-31], as listed on the last page. Without identifying their precise targets, the inhibitory potential of some chalcones on viral propagation was studied [54-55]. The impact of a few chalcones on the RT enzyme was investigated [23-24] Quinoline-based chalcones, for instance, were mentioned in one study as potential NNRTs [23]. Their results showed that RT inhibition was boosted by chloro and bromo-substituted chalcones (IC_{50} values of the most active compounds were 0.10 and 0.11 $\mu\text{g/mL}$) [23]. Chalcone derivatives were also tested for their impact on the IN enzyme [25-28].

One of these, a derivative developed from the chalcone pharmacophore, demonstrated significant inhibition of both the strand transfer (ST) process (with an IC_{50} of 0.6 μM) and IN-mediated 3' processing (with an IC_{50} of 1.9 μM) [28]. Another target investigated for chalcone's anti-HIV properties is the protease enzyme [29-31]. Turkovic and his colleagues found a potent chalcone derivative that strongly inhibited the protease enzyme, with an IC_{50} value of 0.001 μM [29].

Chalcones have shown anti-HIV properties through preventive measures [39], latent HIV reversal [56], inhibition of HIV promoter activity [57], and α -glucosidase inhibition [58]. In a study on using chalcones to fight HIV, scientists found that one particular type, with Bromo and methoxy substitutions, could effectively and safely block HIV infection at different doses

in various HIV strains. For instance, it showed an anti-HIV IC₅₀ of 4.7 μ M in TZM-bl-HIV infected cells [59]. The research also explored the potential for preventing HIV-1 infection. They discovered that a distinct chalcone derivative, containing Bromo- and ortho-benzyl substitutions, could offer both preventive and therapeutic benefits [39].

It was also investigated how focusing on latent viral reservoirs would affect this [56]. Wu et al. examined a novel chalcone derivative, described by its chemical structure [(E)-3-(5-(adamantan-1-yl)-2,4-bis(methoxymethoxy)phenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one], to evaluate its efficacy as a latency-reversing agent [56]. Reactivating latent proviruses and eradicating them is the basic mechanism by which LRAs work [56]. This chalcone derivative boosted HIV transcription by activating CDK9 and aiding in the formation of the Tat-SEC complex at the viral promoter [56]. Currently, there are no HIV-related LRAs available on the market because of their high toxicity and poor effectiveness profiles.

As a result, more research on this chalcone is necessary to see whether it can develop further. A chalcone derivative was found to have an 80% inhibitory effect on HIV promoter activity, which in turn altered HIV gene expression at the transcriptional level [57]. This chemical is selective for the HIV promoter because it did not exhibit this considerable action on the cytomegalovirus (CMV) promoter [57]. Furthermore, alpha-glycosidase suppression has been suggested as a potential HIV treatment strategy [59]. A study on new sulphonamide chalcone derivatives as alpha-glucosidase inhibitors found that a chalcone with a dihydroxy substituent effectively blocked alpha-glucosidase in a non-competitive manner, showing strong activity with an IC₅₀ of 0.4 μ M and a Ki of 0.24 μ M [58]. HIV-2 is an alternate subtype that is significantly less widespread than HIV-1 [49-50]. Nonetheless, although 1.5 million people—including those who are dually infected with HIV-1 and HIV-2—live with HIV-2, it is receiving a lot of attention [49-50]. The impact of chalcones on HIV-2 was the subject of very few investigations [60]. In a study conducted by Casano et al., three newly identified chalcone derivatives were found to selectively inhibit the growth of HIV-2. One of the compounds had an IC₅₀ of 47.7 μ M, increasing its preference for HIV-2 by six fold [60]. It has also been observed that para substitution increases the potency of this inhibition [60]. In the same investigation, other synthesized chalcones demonstrated strong non-selective activity against HIV-1 and HIV-2 (IC₅₀: 5.7 μ M on both subtypes, for example). Nonetheless, it was noted that most chalcones were HIV-1 selective [60].

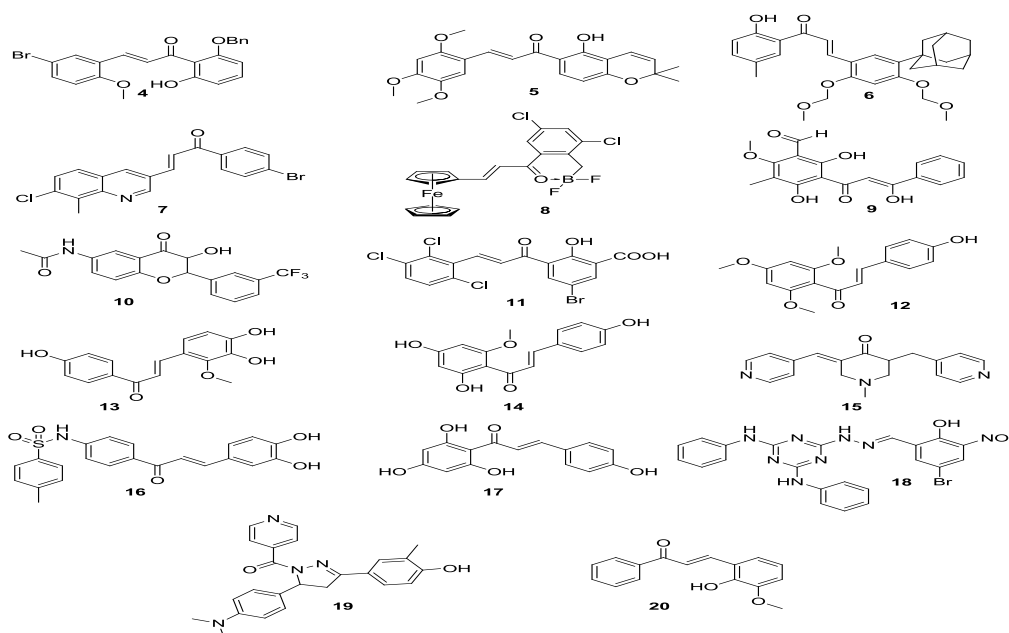


Fig. 2: 4: IC_{50} : 4.7 μM in TZM-bl cells; non-toxic [39]. 5: Mechanism of action: Strong binding against P24 protein and RT enzyme [24]. 6: Mechanism of action: Phosphorylation of CDK9 at the T-loop and formation of the Tat-SEC complex at the viral promoter [56]. 7: Mechanism of action: Potent inhibition against RT; IC_{50} : 0.10 $\mu g/mL$ [23]. 8: Inhibited integrase (IN) against the IN 30 processing; μC_{50} : 7.8 μM , IN strand transfer processes; IC_{50} : 0.7 μM [25]. 9: Inhibitory IC_{50} : 10.7 $\mu g/mL$; EC_{50} : 0.022 $\mu g/mL$ [54]. 10: Potent non-selective anti-HIV activity HIV-1 and HIV-2 IC_{50} : 5.7 μM [60]. 11: Active against integrase strand transfer; IC_{50} : 3.7 μM ; EC_{50} : 7.3 μM [26]. 12: Inhibited HIV-1 replication by 77% at 15.9 μM [55]. 13: Suppressed TPA-induced HIV promoter activity by around 80% [57]. 14: Anti-protease activity; high IC_{50} value ($>100 \mu M$) [30]. 15: Anti-HIV-1; $IC_{50} > 200.0 \mu M$; EC_{50} : 64.7 μM . 16: Non-competitive inhibition; IC_{50} : 0.40 μM ; K_i : 0.24 μM [58]. 17: Anti-protease activity; 26.8% [31]. 18: Inhibitory IC_{50} value for IN-mediated 30-processing: 1.9 μM , IN strand transfer: 0.6 μM [28]. 19: Inhibitory IC_{50} : 5.7 μM against HIV-1 (IIIB) and 7.0 μM against HIV-2 (ROD). 20: Inhibitory IC_{50} : 2 μM against purified IN in the presence of Mn^{2+} and Mg^{2+} as cofactors; EC_{50} : 23 μM [27].

Chalcone derivatives tested on influenza virus

Influenza occurs seasonally due to RNA viruses from the Orthomyxoviridae family. Many deaths worldwide are caused by the influenza A and B viruses. To increase its reproduction and inhibit host defensive responses, the influenza virus has developed cellular mechanisms to take advantage of characteristics seen in human cells. Finding these cellular methods could aid in expanding the pool of potential anti-influenza medication targets. Two proteins are currently

targets: NA and the M2 ion channel. On the outside of viral particles lies a big glycoprotein known as neuraminidase. The pathogenic factor NA is in charge of the virus's progeny being released from cells under infection. The development of numerous inhibitors of viral NA, for instance, zanamivir, oseltamivir, amantadine, and rimantadine, hasn't stopped the fast generation of drug-resistant influenza viruses. As a result, finding anti-influenza medications that work against many influenza strains is a top goal. During the development of an anti-influenza screening program for natural products, many powerful compounds were found to aid in diminishing the risk from resistant strains or enhancing the effectiveness of various antiviral treatments.

Because NA plays a vital role in halting viral growth, it has become a key focus of various natural and synthetic chalcones as antiviral targets. Derived from naturally occurring bioactive substances, 2',4'-dihydroxy-4-methoxy chalcone shows significant inhibitory effects against H1N1NA [32]. In an alternative investigation, natural products derived from the acetone extract of *Glycyrrhiza inflata* were found to target H9N2, H1N1, novel H1N1, and oseltamivir-resistant novel H1N1 cells. These products included isoliquiritigenin (IC_{50} (lg/mL) of 8.41 ± 0.39 , 9.69 ± 0.37 , 3.48 ± 0.19 , and 3.42 ± 0.12 , respectively), and echinatin (IC_{50} (lg/mL) of 5.80 ± 0.30 , 5.70 ± 0.55 , 2.49 ± 0.14 and 2.19 ± 0.06 , respectively). Another artificial substance that was created based on quercetin is 2'-Hydroxy-4-methoxychalcone, which has been shown to efficiently target H5N1.

2-hydroxy-3-methyl-3-butenyl alkyl is an artificial compound that H1N1 is its prime objective and has an IC_{50} of $12.3 \mu M$, according to another study [48]. Compared to other chalcone alternatives, this chemical demonstrated the strongest NA activity inhibition; in a non-competitive manner, 6-hydroxy-3,7-dimethyl-octa-2,7-dienyl > dimethylallyl > geranyl [48]. Another study found that natural compounds such as licoagrochalcone A, abyssinone VI, and 5'-prenylbutein that were taken from the root bark of *Erythrina addisoniae* similarly suppressed H1N1 and H9N2.

Compounds with natural C-methylation, derived from *Cleistocalyx operculatus* buds, exhibit significant inhibition against the viral NAs of both H1N1 and H9N2 strains. These include several chalcones such as (E)-4,2',4-trihydroxy-6'-methoxy-3',5'-dimethylchalcone, 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.

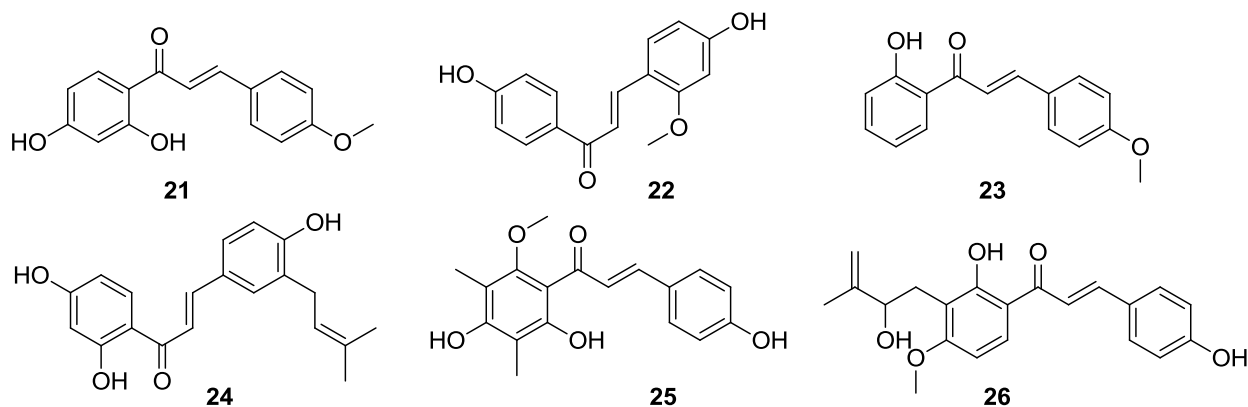


Fig. 3: 21: Inhibited H₁N₁ neuraminidase (NA) enzyme; IC₅₀: 2.23 μmol/L [32]. 22: Inhibited NA from influenza viral strains; IC₅₀: 2.19–5.80 μg/mL. 23: Non-competitive inhibition; binds and holds the 150 loops of NA disrupting the binding of sialic acid in the catalytic site. 24: Inhibited NA; IC₅₀: 21.51 and 20.03 μg/mL, respectively. 25: Inhibited NA; IC₅₀: 3.31–20.45 μM [58]. 26: Inhibited NA IC₅₀:12.3 μM [48].

Chalcone derivatives tested on rhinovirus

One of the most prevalent viral pathogens that causes colds and upper respiratory infections in people is the rhinovirus. This virus prefers to proliferate in warm environments, primarily in the nose, between 33 and 35 C [20]. It is a member of the Picornaviridae family of tiny, single-stranded RNA viruses that are not enveloped. Rhinoviruses come in three varieties, A, B, and C, and comprise over 160 serotypes that are distinguished based on surface proteins. To target cell susceptibility, current antiviral medicines against this virus were developed to block virus binding and attachment, replication, uncoating, and protein synthesis. Chalcones have been investigated against many particular targets, such as capsid pockets, binding sites, and viral proteases within VP1. It was discovered that the latter target was the most effective target of multiple anti-rhinovirus chalcones. The primary chalcone and one of the earliest isolated chemicals was Ro 09-0410. Nevertheless, after additional testing in human clinical trials, it failed to substantially lower the rate of infection or disease. As a result, numerous attempts have been made to create other synthetic analogs of the Ro 09-0410 molecule. Finding anti-rhinovirus agents was about finding chemicals that could reduce the infectivity of the virus by having a higher therapeutic ratio. Several investigations recommended using chalcone Ro 09-0410, 4,6-dichloroflavan (DCF), and RMI-15,731(1-[5-tetradecyloxy-2-furanyl]-ethanone) to directly inactivate the virus. Nonetheless, it was discovered that different viral serotypes had

somewhat different conformations at the site where the previously mentioned chemicals bind on the capsid. Since chalcones can bind to the rhinovirus type that is resistant to DCF and there was no evidence of cross-resistance between RMI and DCF, a slight modification to the binding site was suggested. A different study produced amide analogs, such as Ro 09-0535 ([4-methoxy-3H]) with an IC_{50} of 0.0018 mg/mL, Ro 09-0696 (chal-cone derivatives with methoxy (OMe) substitution) with an IC_{50} of <0.0018 mg/mL, and Ro 09-0881, which was found to be 4.5–12 times more effective than Ro 09-0410 or other agents that target the capsid protein [35].

Synergistic activity between specific medication combinations was found in a previous investigation. Rhinovirus types 2 (RV2) and 9 (RV9) were demonstrated to be active against DCF (dichloroflavan), chalcone Ro-09-0410, enviroxime, and HuIFN (human interferon)-alpha 2, HuIFN-beta, HuIFN-beta X 401, and HuIFN-gamma. Particularly interesting were the pairings of HuIFN-gamma or HuIFN-alpha with enviroxime. These findings suggest that additional clinical research on comparable medication combinations is warranted. The following studies underscored the significance of closely observing the establishment of drug-resistant viruses during antiviral therapy and chemotherapy, since medication viral resistance might arise from a single amino acid alteration. Despite drug resistance, chalcone usage is beneficial, according to another study. According to the study, chalcone Ro 09-0410 can reduce the infectivity of the rhinovirus in persons who have been challenged with a medication-resistance mutation. A drug-dependent virus in the same study had lost its ability to infect people. To find out how chalcones work to overcome or lessen the severity of drug resistance, more research needs to be done.

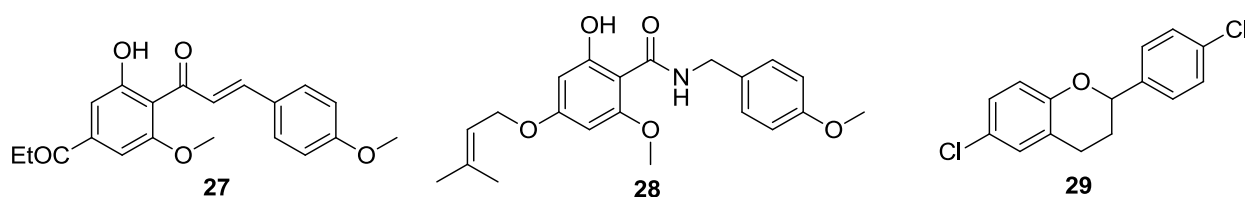


Fig. 4: 27: Inactivated capsid protein; IC_{50} : 0.03 $\mu\text{g/mL}$, cytotoxic concentration: 30 $\mu\text{g/mL}$. 28: Inhibited the un-coating of HRV by stabilizing the viral capsid protein; IC_{50} < 0.0018 $\mu\text{g/mL}$. 29: Inactivated binding capsid protein; IC_{50} : 0.053 $\mu\text{g/mL}$

Chalcone derivatives tested on herpes simplex virus

One member of the Herpesviridae family is the Herpes simplex virus which is linked to several illnesses. HSV-1 and HSV-2 are the two prevailing kinds linked to infections in humans [91]. It was projected in 2016 that 491.5 million people had HSV-2 and 3.7 billion people had HSV-1. Severe diseases in all age categories, including neonates, can result from the reactivation of latent HSV-1 infections. Conjunctivitis, genital or cutaneous herpes, keratitis, eczema herpeticum, or encephalitis are some of these infections. However,

HSV-2 can also result in vaginal herpes, aseptic meningitis, and severe neonatal infections. Antiviral medications are used to treat HSV infections, with acyclovir serving as the first line of treatment.

For the therapy of HSV, some interesting host-cell-specific and viral targets exist. Viral polymerase and helicase–primase are two examples, as are targets associated with host cells such as cyclin-dependent kinases and cyclooxygenase-2.

The prime focus of testing different synthetic and natural chalcone derivatives against HSV was to determine how effective they were at preventing the virus from replicating [23]. A chalcone derivative from *Millettia leucantha* has been shown to moderately inhibit both HSV-1 and HSV-2, with reported IC_{50} values of 15.5 $\mu\text{g/mL}$ for HSV-1 and 17.0 $\mu\text{g/mL}$ for HSV-2. A biphenyl substituted derivative of cyano chalcone has also demonstrated strong suppression against HSV-1 (EC_{50} : >6.00IM) in another investigation [22].

A third investigation conducted by Ali et al. examined the broad-spectrum activity of a set of chalcone derivatives against several viruses. Five of them (four-chlorophenyl)-3-(4-hydroxy-3-methylphenyl) The most effective replication inhibitory activity against HSV-1 and HSV-2 was exhibited by -4,5-dihydro-1H-1-pyrazolyl-4-pyridyl methanone (minimum cytotoxic concentration: 200 $\mu\text{g/mL}$; minimum inhibitory concentration: >8 $\mu\text{g/mL}$ against HSV-1 and 40 $\mu\text{g/mL}$ against HSV-2). This chalcone derivative has displayed promising wide-ranging activity against several viruses, including vesicular stomatitis, vaccinia, para-influenza-3, sindbis, reovirus-1, coxsackie, and Punta Toro viruses. This study is among a few looking into the potential of chalcone derivatives as an all-purpose antiviral drug [22].

Accordingly, to differentiate broad-spectrum chalcones from those with accurate actions targeting specific viruses, additional research on chalcone derivatives against many virus

subtypes is necessary. Furthermore, more studies on the impact of chalcones on more particular HSV targets ought to be conducted.

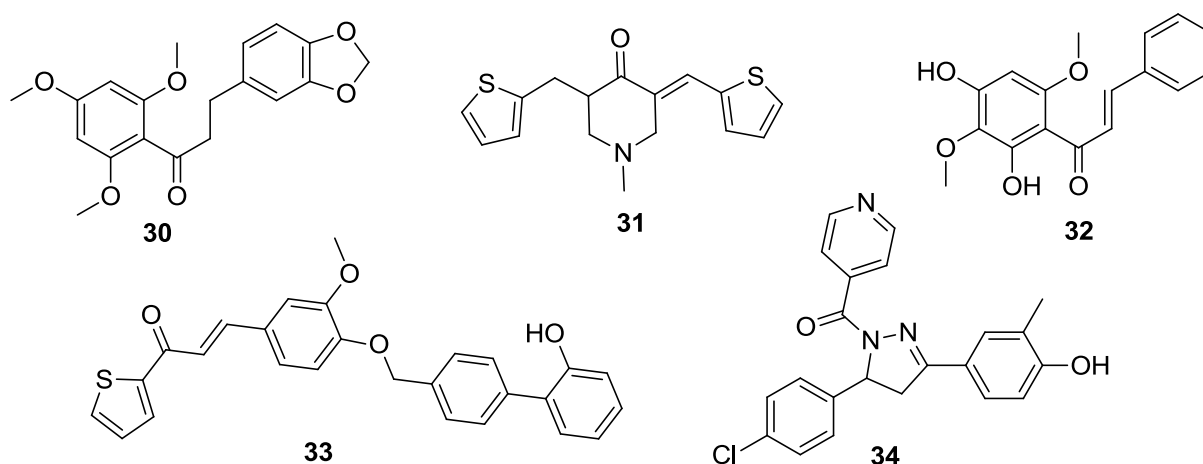


Fig. 5: 30: IC_{50} : 15.5 $\mu\text{g/mL}$, IC_{50} : 17.0 $\mu\text{g/mL}$. 31: 33% reduction in the number of viral plaques; IC_{50} : 0.66 μM . 32: The ethanol extract of the plant (*P. spectabile*); IC_{50} of 21.9 $\mu\text{g/mL}$. 33: EC_{50} > 6.00 μM ; CC_{50} : 23.77 μM ; SI_{50} < 4 μM [22]. 34: Minimum cytotoxic concentration: 200 $\mu\text{g/mL}$; minimum inhibitory concentration > 8 $\mu\text{g/mL}$ against HSV-1 and 40 $\mu\text{g/mL}$ against HSV-2.

Chalcone derivatives tested on dengue virus

The arthropod-borne DEN is the source of dengue infection. Dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS) are possible presentations. Four virus variants—DEN-1, DEN-2, DEN-3, and DEN-4—cause the dengue virus, which is a member of the Flaviviridae family [96]. Dengue symptoms include a high fever, rash, and muscle and joint pain that appear 3–14 days after the infection; recovery is anticipated to take 2–7 days. In addition, it is regarded as an endemic illness in over 100 nations. A single positive-sense 1-kb RNA makes up the DEN and the Flaviviridae family. A single polyprotein consisting of three structural and seven non-structural (NS) proteins is produced by the translation of the genome. A sequential order of C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5 is produced by this polyprotein. Proteolytic processing of the synthesized polyprotein, whether co- or post-translational, is necessary after gene expression. The polyprotein precursor is cis- and trans-cleaved as a result of this processing by the virus protease complex NS2B/NS3 and its cofactor NS2B, as well as by host proteases. There is currently no vaccination known to be licensed for use in humans as a preventive measure against dengue, despite the effectiveness of modern vaccines like ChimeriVax being evaluated.

Nonetheless, several innovative and promising treatment approaches are being developed to combat this illness. Several investigations looked at the protein targets of the dengue virus, which included protein RNA-dependent RNA polymerase (RdRp), viral protease (NS2B-NS3pro), methyltransferase (MTase), helicase (NS3 helicase), and virus envelope. Despite multiple experiments, NS3pro emerged as a significant and appealing target for possible therapeutic drugs, along with certain chalcone compounds that were employed in these trials to treat DF/DHF. 4-A natural substance called hydroxypandaratin A showed a competitive inhibition towards NS3 protease when tested against the dengue-2 virus.

Pandaratin A was also demonstrated to act similarly with a K_i value of 25 μM in another investigation. Dihydroxymethoxychalcone, another name for cardamonin, is a synthetic substance that inhibits DEN-2 NS2B/NS3 activities non-competitively. Dengue virus (DENV2) NS2B/NS3 protease is thought to be inhibited by two different pathways. One possible compound includes NS3-ASP75, NS3-HIS51, and NS3-SER135 residues, which can all have their electronic density destabilized by it. On the other hand, a ligand that likewise blocks NS2B's C-terminal motion, which is required for the transition between the open and closed conformations, can inhibit this enzyme. Chalcones were discovered to be among the best possible medications operating via both of the aforementioned inhibitory mechanisms after their binding sites were investigated by several molecular dynamics simulations. More research is needed to explore the allosteric pocket further and identify more opportunities for drug discovery.

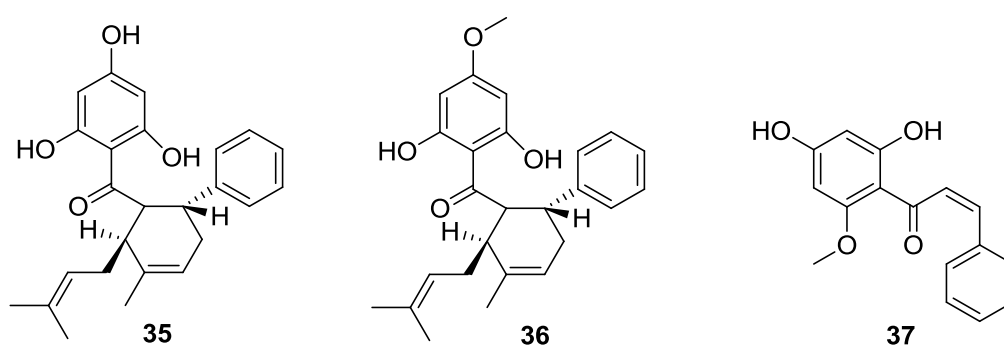


Fig. 6: 35: Anti-NS3 protease with the K_i : 21 μM . 36: Anti-NS3 protease with the K_i : 25 μM . 37: Anti-NS2B/NS3 proteolytic with the K_i : 377 μM .

Chalcone derivatives tested on human cytomegalovirus

While there are several treatments available presently to treat cytomegalovirus (HCMV) infections, their usage is prohibited in specific populations, including pregnant women, due to their toxicity and directed teratogenicity. Furthermore, drug resistance is seen as a significant issue in the therapy of this illness, particularly in individuals with impaired immune systems who require these medications desperately. Recent studies on antiviral drugs that can treat HCMV infections with fewer side effects, such as toxicity and resistance, are encouraging. The US28 receptor is seen as an appealing target for the double-stranded DNA genome of HCMV, which encodes for particular receptors known as vital G protein-coupled receptors (vGPCRs). The US28 receptor employs inherent signaling pathways to trigger cascades that support virus survival, invasion, oncogenesis, and various diseases like cardiovascular conditions. The US28 receptor's potential contribution to viral pathogenesis through latent infections, which enhance viral spread and invasiveness, results in significant infections in both individuals with a strong immune system and those with compromised immunity. Flavonoids are promising options for addressing the HCMV virus due to their known natural functions and prevalence in plant species. Although they are generally thought to be effective and potentially safe antivirals for use in a variety of patients, more research is needed to confirm their safety in particular populations, such as pregnant women. Among those flavonoids, chalcones emerged as a promising candidate for the remedy of HCMV infections due to their relatively simple manufacturing and pharmacological actions of blocking several recognized enzymes. One of these chalcones, 5-(Benzyloxy)-2-(5-bromo-2-methoxyphenyl)-4H-chromen-4-one, was reported to block the HCMV US28 receptor with an EC_{50} of $3.5\mu\text{M}$ [34]. By downregulating CXCR4 chemokine receptors, xanthohumol 1, a prenylated chalcone, demonstrated moderate antiviral efficacy against HCMV in 2004 [36]. It was discovered that additional chalcones were also successful in blocking EGFR's kinase activity, which in turn limited cellular activation and prevented HCMV from invading cells [34]. Additionally, HCMV infection causes overexpression of p53; this mechanism is a typical aim of trans-4-iodo and 4'-boranyl-chalcone because the chalcone inhibits the ubiquitination of p53 in infected cells. A study revealed that a cyano derivative with a biphenyl substitution had high effectiveness against both resistant and non-resistant strains [32]. In this manner, chalcones are anticipated to be further investigated as antiviral medicines against HCMV in the future due to their distinct structure, powerful activity, and maybe low toxicity profile.

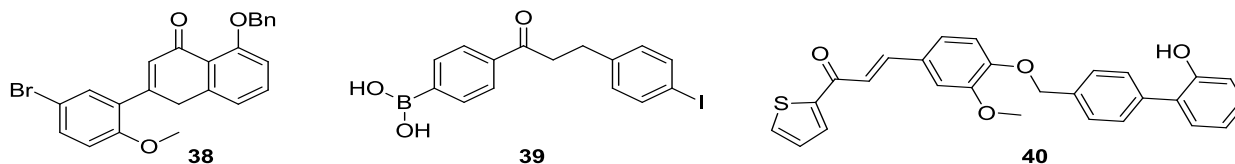


Fig. 7: 38: Anti-US28 receptor, EC_{50} : $3.5 \mu\text{M}$ [34]. 39: in infected cells. 40: $EC_{50} < 0.05 \mu\text{M}$; CC_{50} : $2.96 \mu\text{M}$; $SI_{50} > 62$ [22].

Chalcone derivatives tested on hepatitis B virus

The virus known as the hepatitis B virus targets the liver and causes hepatitis B infection. It is a little DNA virus that is a member of the family Hepadnaviridae. Hepatitis B often only lasts a short while, but in certain cases, it can become chronic. Serious side effects like liver cancer and cirrhosis are linked to chronic hepatitis B. According to data from the World Health Organization, 887,000 people died from chronic hepatitis B infection in 2015, out of an estimated 257 million people living with the condition. Nucleoside/nucleotide analogs and interferon-based therapy are two drugs that can aid in the treatment of hepatitis B [110]. But none of these can completely eradicate the illness. The hepatitis B vaccine is the most effective preventative measure. Studies have examined a variety of compounds, including chalcone derivatives, as possible hepatitis B treatments. Only a few research [22-24] looked into the role of chalcones on HBV. A series of substituted aryl/heteroaryl derived thienyl chalcones were synthesized by Patil et al [22]. They found that the stiffer, less bulky derivative of thiophenylindenone was the most effective in inhibiting DNA hybridization in vitro (EC_{50} : $4.2 \mu\text{M}$; good selectivity index: >24). These findings show that chalcones may make excellent candidates for preventing DNA virus replication. Mathayan et al. conducted a study to examine the anti-HBV properties of *P. pinnata* seeds, which are known to contain certain chalcone derivatives [24]. *P. pinnata* extract showed no discernible toxicity at 5 mg/mL and strongly suppressed HBV replication (virus concentration of 0.18 pg/mL ; $p < .001$) [34]. However, two chalcone derivatives found in *P. pinnata*, isopongachromene and glabaarachalcone, have been shown to interact with the HBV DNA polymerase protein through molecular docking experiments [24]. More research is needed to understand the real effects of chalcone derivatives in laboratory conditions by isolating and examining them from the plant extract. This is especially important given the promising results from virtual screening, which highlight the need for further validation in the lab.

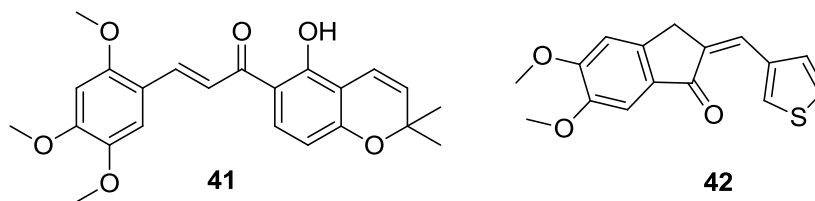


Fig. 8: 41: *P. pinnata* seed extract inhibited HBV replication at 0.18 pg/mL; bound in silico to HBV DNA polymerase protein [24]. 42: EC₅₀: 4.2 μM, SI₅₀ > 24 [22].

Chalcone derivatives tested on hepatitis C virus

The family Flaviviridae includes the hepatitis C virus. The HCV virus has been categorized into seven genotypes and over 67 subtypes due to its genetic variability. A single-stranded positive-sense RNA makes up the viral genome. The virus's genetic material is used to generate a precursor called a polyprotein, spanning 3,000 amino acids. During the post-translational phase, intracellular proteases break down this precursor into mature proteins, such as core, E1, E2, NS proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B), and a potential ion channel called p7. These NS and structural proteins support the pathogenesis of the virus by promoting its infectivity, carcinogenesis, and several other pathological processes. HCV is renowned for its role in causing cirrhosis, hepatocellular carcinomas, and chronic hepatitis, as well as its notable effects on liver metabolic processes, including complications with lipid and glucose metabolism. To treat HCV infection, ribavirin, pegylated interferon regimens, and other direct-acting medications are commonly employed. For both therapeutic and financial reasons, the necessity of developing alternative medications for addressing HCV infection has drawn extensive research attention. The price of these drugs as well as the evolution of drug resistance are frequent problems. Complementary medicine seeks to create antiviral drugs that effectively and potently block HCV infection in this way. Chalcones and related derivatives have been investigated as potential effective replacements due to their capacity to impede HCV replication and viral translation. In the progression of herbal medicine, plants such as *Glycyrrhiza uralensis* and *G. glabra* have been recommended as feasible choices. The effectiveness of several chalcones extracted from the plants as mentioned above as anti-HCV drugs has been investigated. By inhibiting the phosphorylation of ribosomal protein 6 (rps6) and its kinase, the mTOR pathway is a well-identified target [37]. Natural compounds, namely licochalcone A and isoliquiritigenin, with respective IC₅₀ values of 2.5 mg/mL and 3.7 mg/mL, target HCV genotype 2a (J6/JFH1P47). Their action is demonstrated by the suppression of

protein synthesis and HCV virus subgenomic RNA replication. Another well-known chalcone is xanthohumol (XN), which is renowned for its biological properties that protect the liver through antiviral processes [33]. When XN activity was observed in HCV-infected cells, it was observed that XN exposure dramatically reduced the expression of transforming growth factor β 1, aminotransferases, and the score for hepatic steatosis when compared to control cells [33]. Moreover, it has been demonstrated that XN dramatically reduces the activity of related enzymes such as glutathione peroxidase, superoxide dismutase, and others [33]. Thus, by inhibiting oxidative reactions and modifying the pathways leading to apoptosis, XN can effectively reduce liver damage. Further research revealed that it inhibits the action of stellate cells, which reduces liver fibrosis [33]. Research on therapeutic plants is encouraging and may lead to the development of more potent medications to combat HCV infectious strains, including resistant ones.

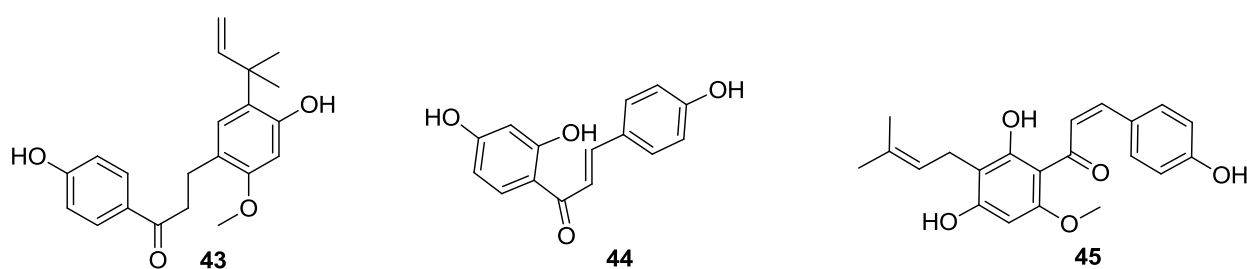


Fig. 9: 43: Inhibited the post entry phase by inhibiting the HCV subgenomic RNA replication; IC_{50} : 2.5 μ g/mL. 44: Inhibited the post entry phase by inhibiting the HCV subgenomic RNA replication; IC_{50} : 3.7 μ g/mL. 45: EC_{50} : Regulation of apoptosis, inhibition of oxidative reaction, modulation of MTP activity [33].

Chalcone derivatives tested on Rift Valley fever

The principal mode of transmission for the Rift Valley fever virus (RVFV) is through mosquitoes. This virus, categorized within the Phenuiviridae family, is considered an arbovirus. A zoonosis illness that mostly affects domesticated animals in sub-Saharan Africa, such as cattle, sheep, camels, and goats, as well as animals in other nations, is attributed to RVFV. RVFV can also infect humans through mosquito bites or contact with bodily fluids or blood from infected animals. Nevertheless, there is currently no evidence of RVFV transmission between people. RVF illness caused by RVFV is spreading around the world, much like other arboviral infections including dengue, zika, and chikungunya. The CDC

mentions that there is no licensed antiviral drug for treating RVF, and the illness often goes away by itself.

However supportive treatment is the only way to treat severe cases. It is therefore vital to find treatment alternatives that are unique to RVFV. The anti-RVFV properties of a few synthetic chalcone analogues were investigated [22]. Remarkably, it was discovered that a cyclopropylquinoline analogue was 28 times more effective at inhibiting RVFV virus replication (EC_{50} : 0.39 $\mu\text{g/mL}$) than ribavirin, the standard antiviral medication (EC_{50} : 11 $\mu\text{g/mL}$) [22]. Additional studies are required to specify the exact molecular sites that chalcone derivatives affect in RVFV. In particular, host-cell-related pathways (such as transcriptional and mitochondrial activities) that Rift Valley fever virus uses for replication present a viable avenue for the creation of anti-RVFV drugs.

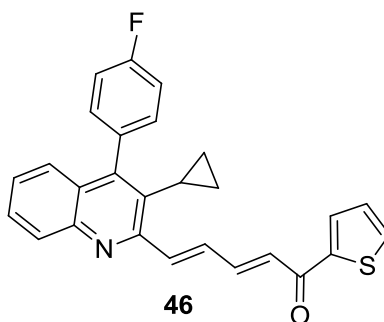


Fig. 10: EC_{50} : 0.39 $\mu\text{g/mL}$; CC_{50} : 1.2 $\mu\text{g/mL}$; SI_{50} : 3.1 $\mu\text{g/mL}$ [22]

Chalcone derivatives tested on Venezuelan equine encephalitis virus

The Togaviridae family of viruses includes the Venezuelan equine encephalitis virus, which infects both people and horses. Latin America is known to have seen VEE outbreaks; afflicted nations include the USA, Venezuela, Peru, Colombia, Costa Rica, Ecuador, Mexico, El Salvador, and Panama. There are about 14 subtypes of VEEV, the most closely linked to human and equine epidemics being subtype I variants A, B, and C. Estimating the precise impact of VEE on health and the economy is more challenging because it is frequently misinterpreted as dengue infection. Human encephalitis may result from VEEV, and common symptoms of VEE include fever, tremors, headaches, vomiting and nausea.

Vaccination against VEEV is the primary management technique to control VEE. Nevertheless, no FDA-approved medication is currently available to combat this virus. A

collection of chalcone derivatives and their impact on VEEV have been studied by Patil et al.[22] The cyclopropylquinoline analogue with an EC_{50} of >2.8 $\mu\text{g/mL}$ was the most effective in suppressing the reproduction of the VEEV virus [22]. Unfortunately, compared to the host cell (SI_{50} 0 $\mu\text{g/mL}$), its cytotoxic concentration has a similar potency (CC_{50} 2.8 $\mu\text{g/mL}$), making it unselective towards the virus [22]. All other chalcone compounds investigated showed the same non-selectivity (SI_{50} 0 $\mu\text{g/mL}$). Further efforts are therefore required to improve the structure of these derivatives.

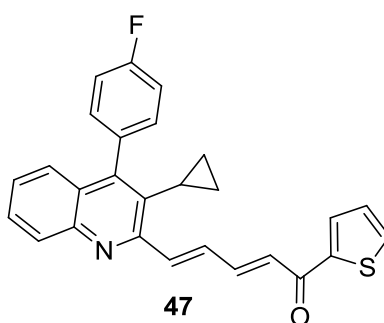


Fig. 11: Mechanism of action: $EC_{50} > 2.8$ $\mu\text{g/mL}$; CC_{50} 2.8 $\mu\text{g/mL}$; SI_{50} 0 $\mu\text{g/mL}$ [22].

Conclusions

One of the most prevalent ailments affecting people nowadays, viral infections are thought to be the main culprit behind several conditions with significant morbidity and death rates. Numerous antivirals have been created and are in widespread use worldwide. Their ability to effectively combat viral infections is limited by the fast-increasing antiviral resistance, despite their vast range of coverage. Chalcones have emerged as a leading possibility for novel antiviral agents due to the high pace of drug resistance development and the appearance of new virus strains. Over time, the need for alternative antivirals has increased, necessitating the extraction and synthesis of these agents.

Chalcones are extensively biosynthesized in plants and are important in protecting the body from insects and infections. After being thoroughly examined for their antiviral properties, some chalcone derivatives were discovered to have intriguing and noteworthy effects on regulating some anti-infective molecular targets. This suggests that chalcone derivatives may be a safe and effective class of broad-spectrum antiviral medicines. As most findings to date have been in vitro and have not further determined the precise molecular targets of chalcones,

more research should be done to explore the mechanisms and targets of chalcones both in vitro and in vivo.

Furthermore, there are extremely few clinical investigations of chalcones as antiviral medications. Therefore, more in vivo research is required to determine the viability of chalcones as possible antiviral medicines in human illnesses.

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