Antiviral Activity of Approved Anti-inflammatory Drugs and Prospects for Drug Repurposing: A review

ABSTRACT

Drug discovery and development are lengthy and expensive processes that face serious challenges. A new compound must not only produce the desired response with minimal side effects but must also demonstrate better activity than existing drugs. Thus, modification of existing drugs is easier than discovery of new drugs. Furthermore, the rate of development of new antiviral agents has declined significantly in recent decades, and pathogenic viruses have become more serious and have developed resistance against antiviral drugs. Hence, owing to multidrug resistance, severe side effects, and the emergence of new virus types, there is an urgent need for the development of new alternative or synergistic antiviral drugs with minimal side effects. Anti-inflammatory drugs represent a group of drugs with broad clinical applications and remain one of the most widely used medications worldwide. They can relieve the most common symptoms of viral infections (pain and fever). Thus, many researchers have screened for antiviral activities among the marketed anti-inflammatory drugs against different types of viral infections, based on the observed antiviral activity in different preclinical and clinical studies. This mini-review article summarizes preclinical studies (*in silico*, *in vitro*, and *in vivo*) that evaluated the antiviral activity of approved anti-inflammatory drugs.

Keywords: Drug repurposing; antiviral activity; anti-inflammatory drugs; approved drugs.

INTRODUCTION

The rate of discovery and development of antiviral agents has declined significantly in recent decades, and pathogenic viruses have become serious and have been continuously developing resistance to marketed antiviral agents, imposing a frightening medical problem

worldwide [1,2]. Furthermore, antiviral agents face serious challenges owing to a reduction in the number of newly approved drugs and a lack of knowledge about the pathways and mechanisms of these diseases[3,4]. "The pandemic coronavirus disease (COVID-19) has affected more than 29 million persons and caused more than 0.6 million deaths worldwide up to date; this great interest in drug repurposingled to a rush to repurpose existing drugs, despitethe underlying evidence base of variable quality"[5,6]. "In addition, a new compound must not only produce the desired response with minimal side effects but must also demonstrate a better effect than existing therapy" [7].

"Drug repurposing is the best strategy for developing effective therapies for human viral infections and obtaining faster clinical benefits. Thus, using already-approved drugs would reduce the time and costs associated with conducting clinical studies"[8-10]."Nevertheless, drug repurposing has become an interesting strategy for recognizing drugs against the emergence of new infectious diseases, including viral infections, such as Zika and Ebola virus"[5,11,12]."In addition, the early rapid spread of SARS-CoV-2 and the lack of specific therapies against COVID-19 have encouraged off-label testing of repurposed approved drugs"[12-15]. The mini-review will be outlined in sections that summarize studies conducted to assess the antiviral activity of drugs originally approved for their anti-inflammatory activities. This mini-review was structured according to virus families, and the potential targeted pathways for the antiviral activities of the approved anti-inflammatory drugs are shown in Figure 1 and Table 1.

Table 1. Suggested possible mechanism for antiviral activity of approved anti-inflammatory drugs

Drug	**Mechanism of action**	**Virus**	**Type of the study**	**Reference**
Non-steroidal anti-inflammatory drugs				

Aspirin	Activate p38 and mitogen-activated protein kinase	Hepatitis C virus	*In vitro*	[16]
		Dengue viruses	*In vitro*	[17]
		Japanese encephalitis virus	*In vitro*	[17]
	Reduce viral-induced reactive oxygen species (ROS)	Cytomegalovirus	*In vitro*	[18]
	Inhibit virus entry (reduce the level of virus receptor claudin-1)	Hepatitis C virus	*In vitro*	[19]
	Reduce expression of proapoptotic factors and reduce onset of viral caspase activation	Avian influenza virus-A	*In vitro*	[20]
	Inhibit Nuclear factor kappa B (NF-kB)	Avian influenza virus-A	*In vitro*	[20]
Indomethacin	Block viral RNA production	SARS-CoV	*In vitro*	[21]
Naproxen	Block nucleoprotein attachment with RNA genome	SARS-CoV-2	*In silico, In vitro*	[22]
Corticosteroids				
Budesonide	Block nuclear import of viral preintegration complex	Human immunodeficiency virus	*In vitro*	[23]
	Inhibit nuclear import of virus integrase protein	Human immunodeficiency virus	*In vitro*	[23]
Dexamethasone	Activate glucocorticoid receptor (GCR)-dependent autophagy	Rhinovirus 1B	*In vitro*	[24]
Prednisolone	Inhibit long terminal repeat (LTR) activity	Human immunodeficiency virus	*In vitro*	[25]
Antihistamines				
Azelastine	Target sodium taurocholate co-transporting polypeptide	Hepatitis B virus	*In silico*	[26]
	Inhibit virus main protease (Mpro)	SARS-CoV-2	*In silico*	[27]
Carbinoxamine	Block viral endocytosis	Influenza A virus	*In vitro*	[28]
Chlorpheniramine	Block viral endocytosis	Influenza A virus	*In vitro*	[28]
Cyproheptadine	Inhibit clathrin-dependent endocytosis	Hepatitis C virus	*In vitro*	[29]
Desloratadine and loratadine	Inhibit viral-induced intercellular adhesion molecule 1 (ICAM-1) up-regulation	Rhinovirus	*In vitro*	[30]
	Inhibit Nuclear factor kappa B (NF-kB)	Rhinovirus	*In vitro*	[30]

Hydroxyzine	inhibit viral entry at a post binding step	Hepatitis C virus	*In vitro*	[31]
Disease-modifying antirheumatic drugs				
Leflunomide	Prevent tegument acquisition by viral nucleocapsids	Cytomegalovirus	*In vitro*	[32]
Janus kinase inhibitors				
Tofacitinib	block of Janus activating kinase	Human immunodeficiency virus	*In vitro*	[33]
Ruxolitinib	block of Janus activating kinase	Human immunodeficiency virus	*In vitro*	[34]
Leukotriene receptor antagonists				
Montelukast	obstruct virus infection at the adsorption step	Zika virus, Dengue virus, Yellow fever virus	*In vitro*	[35]
	Inhibit RNA-dependent RNA polymerase (RdRp)	SARS- CoV- 2	*In silico*	[36]
	Inhibit virus main protease (Mpro)	SARS- CoV- 2	*In silico*	[36]

1. Drugs acting on *Herpesviridae*viruses

Some anti-inflammatory drugs, namely aspirin, leflunomide, piroxicam, and montelukast, have been studied against some strains belonging to the *Herpesviridae* family using *in vitro* and *in vivo* models, and have shown the ability to inhibit herpes virus infections or their effect on the body. Aspirin, which acts as a cyclooxygenase inhibitor as well as a direct reactive oxygen species (ROS) scavenger, can reduce human cytomegalovirus (CMV)-induced ROS, probably through both of these activities [18].

Leflunomide which is an anti-rheumatoid drug also in previous *in vitro* studies demonstrated activity against CMV production through its active metabolite which can interfere with protein phosphorylation [32]. Further experiments confirmed the *in vivo* antiviral activity of leflunomide against CMV in both human fibroblasts and endothelial cells, and it is considered a

promising substitute for ganciclovir-sensitive and-resistant CMV infections because of its cost and easy administration [36].

Herpes simplex is another member of the *Herpesviridae* family that is sensitive to anti-inflammatory drugs, such as piroxicam and montelukast. The antiviral effects of piroxicam against herpes simplex virus type 1 (HSV1) were demonstrated in *in vitro* studies using plaque reduction assays; it has an effect on the virus at the beginning step of viral replication and slows down the infection of host cells [37]. Moreover, montelukast which acts as a leukotriene receptor antagonist was documented to have *in vitro* antiviral activity against HSV-1, it was shown that HSV viral infectivity dramatically decreased after montelukast administration, similar to the changes in the apoptotic/necrotic response [38].

2. Drugs acting on *Flaviviridae* viruses

Anti-inflammatory drugs were studied against some strains belonging to the family *Flaviviridae* using *in vitro* and *in vivo* models, including aspirin, flurbiprofen, chlorcyclizine, hydroxyzine, cyproheptadine, ketotifen, azelastine, and rupatadine, which may have antiviral activity against some strains belonging to the family *Flaviviridae*. Our findings are presented in the following subsections.

2.1. Anti-Hepatitis C virus action

The effect of aspirin on the hepatitis C virus (HCV) has been documented and suggested to be due to the inhibition of COX-2 expression, which is mediated in part by the activation of p38 and mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MEK1/2) mitogen-activated protein kinases (MAPKs) [16]. Another study suggested that the action could be mediated partially through the modulation of inducible nitric oxide synthase (iNOS), since aspirin showed the ability to reduce iNOS expression by downregulating promoter activity,

mRNA, and protein levels, while simultaneously decreasing HCV expression [39]. Furthermore, aspirin was found to inhibit the entry of HCV pseudoparticle (HCVpp) and infectious HCV by reducing the expression levels of the hepatitis C virus receptor claudin-1 expression levels [19].

Chlorcyclizine showed a potent inhibitory effect against HCV infection, as it was able to inhibit HCV infection in human hepatoma cells and primary human hepatocytes. It also significantly inhibited infection with HCV genotypes 1b and 2a in *in vivo* experiments [40]. Additionally, hydroxyzine displayed high *in vitro* potency and low toxicity as an antiviral against HCV, and the drug effectively inhibited viral entry at a post-binding step [31]. Cyproheptadine and ketotifen, which display activity against HCV, were noted to have a tricyclic lipophilic moiety and a tertiary amine, suggesting that they might inhibit clathrin-dependent endocytosis and the entry of several viruses, including HCV. However, further *in vitro* studies showed that ketotifen had almost no activity against HCV genotype 1a (H77) pseudotyped particle entry, whereas cyproheptadine had selective inhibitory activity for H77pp entry at high concentrations [41,42].

2.2. Anti-Dengue virus action

Aspirin also showed the ability to restrict dengue virus (DEN-2) and inhibit its triggered apoptosis. It has been suggested that the mechanism by which aspirin suppresses flavivirus infection may involve the activation of p38 mitogen-activated protein (p38 MAP) kinase rather than blocking the nuclear factor κB (NF-κB) pathway [16]. In addition, the effects of rupatadine were assessed *in vitro* using the DEN-2 model, which showed a significant reduction in endothelial permeability and significantly inhibited the increased hematocrit in dengue-infected mice in a dose-dependent manner [43].

2.3. Anti-Japanese encephalitis virus activity

Aspirin also showed the ability to restrict Japanese encephalitis virus replication by the same mechanism as discussed in the section on its effect on DEN-2, as it caused activation of p38 MAP and blocked the NF-κB signaling pathway in the infected cells [17].

2.4. Anti-Zika virus action

In vitro and *in vivo* studies have demonstrated the antiviral efficacy of montelukast against Zika virus (ZIKV) infection by irreversibly inhibiting viral infectivity by disrupting the integrity of the virions to release viral genomic RNA [34].

3. Drugs acting on the *Hepadnaviridae* viruses

Among members of this family, the hepatitis B virus (HBV) is the most well-known member, and the drug azelastine has demonstrated the ability to target sodium taurocholate co-transporting polypeptide (NTCP), which plays a role in the HBV infection process both *in silico* and *in vitro* in HepG2.2.15 cells [26].

4. Drugs acting on *Paramyxoviridae* viruses

Some studies found that roflumilast and dexamethasone, as anti-inflammatory drugs, had antiviral activity against some strains belonging to the *Paramyxoviridae* family. An *in vitro* study found that roflumilast N-oxide (RNO) inhibited respiratory syncytial virus (RSV) infection of well-differentiated HBE (WD-HBE) cells and mitigated the cytopathological changes associated with this virus by preventing the loss of ciliated cells and markers, reducing the increase of MUC5AC and CLCA1, and inhibiting the increase of the proinflammatory cytokines IL-13, IL-6, IL-8, TNF-α, and ICAM-1. Additionally, RNO reversed the reduction of some defense factors against oxidative stress, such as nuclear factor erythroid 2–related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and glutathione peroxidase (GPx) mRNA levels and consequently restored the total antioxidant capacity (TAC) and reduced H_2O_2 formation [44]. However, clinical

observations have shown that dexamethasone has clinical benefits in the treatment of RSV infection [45,46].

5. Drugs acting on *Coronaviridae* viruses

In an attempt to find an effective treatment for the COVID-19 using recycling method some approved anti-inflammatory drugs including azelastine, naproxen, carbinoxamine maleate (CAM), and S-(C)-chlorpheniramine maleate (SCM), ciclesonide and indometacin; were studded against some strain belonging to *Coronaviridae* family.

Azelastine exhibited antiviral activity against the SARS-CoV-2 virus in an *in vitro* study in Vero cells, both in preventive and treatment settings, and it showed the ability to block viral replication in SARS-CoV-2 infected reconstituted human nasal tissue [47]. The drug also showed *in silico* ability to interact with the SARS-CoV-2 virus main protease (Mpro), which is known to be essential for the coronavirus replication cycle through post-translational processing of RNA machinery[48]. Experiments have demonstrated the *in vitro* antiviral activity of naproxen against SARS-CoV-2 by diminishing viral replication and nucleoprotein binding with RNA [16,42]. Additionally, an *in silico* study showed the activity of montelukast against COVID- 19, which suggested its repurposing potential, and described the mechanism of action that would likely need to be conferred by *in vitro* studies. Competitive inhibition has been observed at the enzymatic sites of RNA-dependent RNA polymerase (RdRp) and Mpro [35].

The virucidal activity of chlorpheniramine was tested against a SARS-CoV-2 strain in Vero 76 infected cells. This study demonstrated a strong virucidal effect against SARS-CoV-2 in a nasal spray containing chlorpheniramine, which was observed as a significant reduction in the viral titer and log reduction value after treatment with a single concentration of nasal spray [49].

Ciclesonide was also able to suppress SARS-CoV-2 replication *in vitro*, and it was documented that corticosteroid ciclesonide resulted in a concentration-dependent decrease in the viral RNA replication-transcription complex in cells [50]. Additional studies have demonstrated the antiviral activities of indomethacin both *in vitro* and *in vivo* against several coronavirus strains at concentrations higher than those required for COX inhibition, and found that indomethacin diminished virus titers, replication, and blocked viral RNA production [21,51].

6. Drugs acting on *Picornaviridae* viruses

Members of the *Picornaviridae*family have also been used to evaluate the antiviral activity of approved anti-inflammatory drugs, including budesonide, desloratadine, loratadine, levocetirizine, dexamethasone, aspirin, and D-penicillamine. Although budesonide alone or in combination with formoterol reduced early innate antiviral immune responses by inhibiting both early pro-inflammatory cytokines and key aspects of the type I IFN pathway, the clinical consequences of their effect on anti-viral immunity are not clear [52]. In contrast, budesonide antiviral activity against human rhinovirus (HRV) was documented in both *in vitro* experiments and *in vivo* animal models, and its antiviral activity was suggested to be due to the activation of GCR-dependent autophagy [53]. This conflict could probably be resolved by considering that the direct antiviral effect of budesonide is more prominent than its indirect effect on viral infection by inhibiting early innate antiviral immune responses.

Regarding the antiviral activity of desloratadine and loratadine, a study was carried out to investigate their effect on HRV-induced ICAM-1 expression, mRNA up-regulation, and promoter activation *in vitro*; the cultured primary bronchial or transformed (A549) respiratory epithelial cells were pretreated with desloratadine and loratadine for 16 hours and infected with RHV type16 for 8 hours. Both drugs at the concentration level (0.1-10 μmol/L) inhibited HRV-

induced ICAM-1 upregulation in both primary bronchial and transformed (A549) respiratory epithelial cells and inhibited ICAM-1mRNA induction caused by RHV infection in a dose-dependent manner. They also completely inhibited RHV-induced ICAM-1 promoter activation. Desloratadine also inhibited HRV-induced NF-κB activation [30].

Levocetirizine also inhibited the production of intercellular adhesion molecule (ICAM)-1 and secretion of interleukin IL-6 and IL-8, which may have beneficial effects on the pathophysiologic changes related to HRV infection, and the effect of levocetirizine on HRV infection was investigated in vitro using primary human nasal epithelial cells and A549 cells. The results indicated that levocetirizine inhibited the HRV-induced increase in ICAM-1 mRNA and protein levels as well as HRV-induced expression of IL-6 and IL-8 mRNA and protein levels. The viral titer was also reduced by levocetirizine, as measured by culture in MRC-5 cells. Levocetirizine treatment also reduced the increased NF-κB expression observed during HRV infection. Levocetirizine inhibited the expression of Toll-like receptor 3 (TLR-3) mRNA and protein expression. These findings indicate that levocetirizine inhibits HRV replication and HRV-induced upregulation of ICAM-1, IL-6, IL-8, TLR3 expression, and NF-κB activation in HNEC and A549 cells [54].

Aspirin also showed activity against HRV, which affects the respiratory tract [55]. Dexamethasone demonstrated antiviral activity against HRVs through glucocorticoid receptor (GCR)-dependent autophagy activation in both HeLa cells and HRV1B infected mice, associated with a dose-dependent increase in cell viability, indicating that HRV1B viral replication was reduced. In addition, HRV1B-infected mice treated with dexamethasone showed evidence of reduced inflammation and moderate histological score [24]. However, clinical observations have shown that dexamethasone has clinical benefits in the treatment of RSV infection [45,46].

Further experiments involving another member of the *Picornaviridae*family, poliovirus, showed that the antiviral activity of D-penicillamine against poliovirus replication in the early stage, decreased the cytopathic effect of poliovirus, and slowed down viral RNA and protein synthesis [56].

7. Drugs acting on *Retroviridae* viruses

The antiviral effects of budesonide, prednisolone, tofacitinib, and penicillamine against strains of the *Retroviridae* family were evaluated using *in vitro* and *in vivo* models. Budesonide was able to result in a significant reduction in the presence of specific nuclear forms of HIV DNA (two-long terminal repeats DNA circles (2- LTR circles)), which is essential for viral replication, suggesting that the drug works by blocking HIV integrase, and potentially HIV preintegration complex, and nuclear import [23].

An *in vitro* study documented a reduction in HIV-1 replication in PBMC cell culture, and flow cytometric analysis revealed a 50% reduction in the long terminal repeat (LTR) and driven green fluorescent protein activity in GHOST cells, indicating that LTR plays an important role in directing viral gene expression. Collectively, these findings indicated that prednisolone suppressed both HIV-1 viral load and CCL2 mRNA expression [25].

Furthermore, an *in vitro* study of tofacitinib revealed its activity against HIV when combined with ruxolitinib through the blockade of Janus activating kinase (JAK), which is considered a possible mechanism to slow virus replication in lymphocytes and macrophages, replication of drug-resistant HIV-1, and reactivation of latent HIV-1, and has the potential to reset the immunological milieu in HIV infected individuals [33].

D-penicillamine and L-penicillamine also displayed selective *in vitro* antiviral activity against human T-lymphotropic virus (HTLV-III/LAV) with low toxicity on T cell protective

effects, which encouraged the use of D-penicillamine for the clinical treatment of AIDS [57]. These findings are in line with the clinical observation that D-penicillamine had a dose-dependent antiviral activity against HIV expression, but it was stated that immunological suppression limits the use of D-penicillamine in a population already displaying immune compromise, although it is reversible [51,58]. Another *in vivo* study revealed that this drug had the ability to suppress HTLV-III/LAV expression [59].

8. Drugs acting on *Orthomyxoviridae* viruses

Some anti-inflammatory drugs, such as aspirin, dextromethorphan, ketotifencarbinoxamine, chlorpheniramine, and naproxen, showed *in vitro* and *in vivo* antiviral activity against some Orthomyxoviridae viruses. Regarding aspirin, the influenza virus is another target for its antiviral effect; it inhibited both *in vitro* and *in vivo* with no toxic side effects or the tendency to induce resistant virus variants [20]. Its action was suggested to involve the reduced expression of proapoptotic factors, subsequent inhibition of caspase activation, and the blockade of caspase-mediated nuclear export of viral ribonucleoproteins, which could also prevent cytokine storm events by inhibiting NF-κB [20,60]. In addition, naproxen exhibited remarkable antiviral activity against influenza A and B viruses both *in vitro* and *in vivo*, blocking nucleoprotein attachment to the RNA genome, which antagonizes the nuclear export of the viruses, which is mediated by chromosome region maintenance 1 protein (CRM1), hindering duplication of influenza B viruses and declining virus titers [61].

Antihistamine drugs have also shown efficacy against some influenza A virus strains. One study assessed the antiviral activities of approved drugs against target cellular proteins during the influenza life cycle. Out of 15 candidate compounds, four were able to inhibit infection by 10- to 100-fold without causing toxicity, *in vitro*. One of these drugs was

ketotifenwhich displayed a 50% effective dose between 5 and 50 μM, not only for the classic H1N1 PR8 strain but also for a pandemic H1N1 and a seasonal H3N2 strain [56]. Also after screening an FDA-approved drug library containing 1280 compounds by cytopathic effect (CPE) reduction assay, it was found that two antihistamines (carbinoxamine maleate and S-(C)-chlorpheniramine maleate) have potent antiviral activity against influenza A (H7N9) infection with IC50 of 3.56 and 11.84 mM, respectively [62].

Further studies showed that carbinoxamine maleate and chlorpheniramine maleate could also inhibit infection by other influenza A viruses, including influenza A/Shanghai/37T/2009 (H1N1), influenza A/Puerto Rico/8/1934 (H1N1), influenza A/Guizhou/54/1989 (H3N2), and one influenza B virus; B/Shanghai/2017 (BY). The results from mechanistic studies indicate that both drugs could inhibit influenza virus infection by blocking viral entry into the target cell, the early stage of the virus life cycle. However, carbinoxamine maleate and chlorpheniramine maleate neither blocked virus attachment, characteristic of hemagglutinin, nor virus release, characteristic of neuraminidase activity. Such data suggest that these two compounds may interfere with the endocytosis process [28].

9. Drugs acting on *Adenoviridae* viruses

Anti-inflammatory drug montelukast showed *in vitro* anti-adenoviruses activity, as the results of a study that evaluated the relationship between montelukast and viral pathogens suggest the possible antiviral activity of montelukast against *in vitro* human adenovirus isolate. The data suggested that montelukast might decrease the lytic capability of this virus, taking into account that adenovirus is capable of lysing infected cells during the viral replicative cycle, and it can directly initiate an inflammatory response by damaging host tissues, supporting the hypothesis that montelukast has an antiviral effect or at least anti-adenoviruses activity [38].

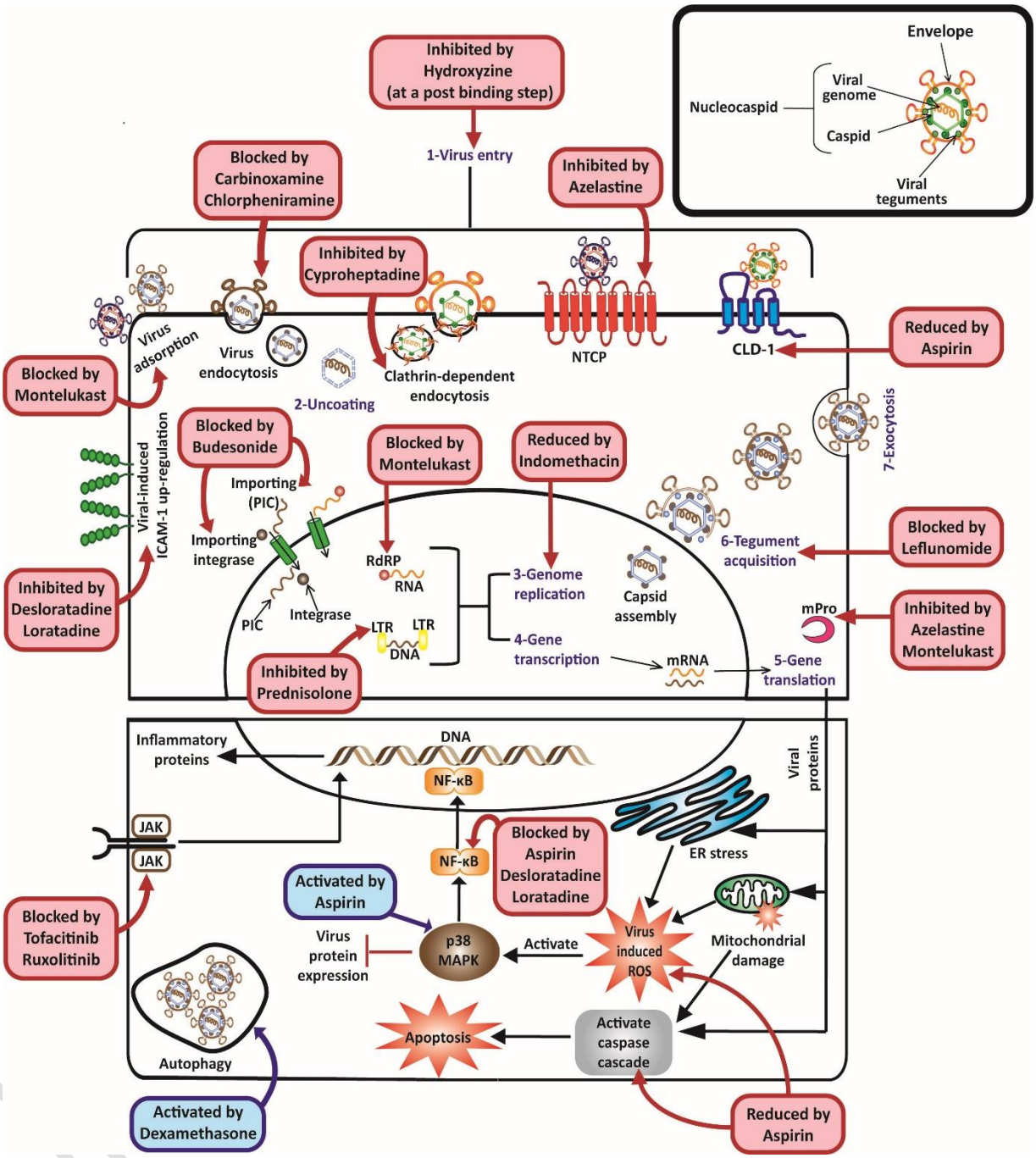

Figure 1. Targets for antiviral activity of approved anti-inflammatory drugs. CLD-1; Claudin-1 receptor, ICAM-1, Intercellular Adhesion Molecule 1, JAK; Janus kinase, LTR; long terminal repeat, Mpro; main protease, NF-κB; Nuclear factor kappa-light-chain-enhancer of activated B cells, NTCP; sodium taurocholate co-transporting polypeptide, p38 MAPK; p38 mitogen-activated protein kinases, PIC; pre-integration complex, RdRP; RNA-dependent RNA

polymerase.

CONCLUSION AND PERSPECTIVES

Viral infections are usually associated with an inflammatory response that might be localized or systemic and may range from mild to fatal response according to the type of the viral infection and the characteristics of the patient, knowing that encourages trying to find anti-inflammatory drugs with intrinsic antiviral activities, since it will be effective in both getting rid of the pathogen and reducing the disorders resulting from the infection meanwhile. Accordingly, in this mini-review, the studies that investigated the antiviral activity of approved anti-inflammatory drugs were collected and summarized, as they may have the benefit of bypassing the unwanted effects, especially if they demonstrated antiviral effects at a dose lower or within the range used for the anti-inflammatory effects, with emphasizing on the findings that suggested the mechanism of antiviral action of the studied drugs, as they may help in antiviral drug discovery.

Many anti-inflammatory drugs showed antiviral effects in *in vitro*, *in silico*, or *in vivo* studies or observed in clinical findings against a wide range of viruses, including steroidal and NSAIDs, antihistamines, disease-modifying antirheumatic drugs, and leukotriene receptor antagonists. It could be noted that aspirin had a special focus in the studies investigating the antiviral activity of anti-inflammatory drugs, and many mechanistic studies were conducted clarifying that aspirin may have multiple mechanisms by which it exerts its wide spectrum of antiviral effects, including effects on inhibiting viral entry or indirectly as its inhibitory effect on viral-induced reactive oxygen species. Other NSAIDs such as indomethacin and naproxen mainly affect viral replication, by inhibiting viral RNA production or transcription. On the other

hand, corticosteroids showed the ability to cause autophagy-dependent antiviral effects or a direct inhibitory effect on viral replication.

Antihistamine drugs, mainly affect the viral entry step in different steps, including down-regulating viral receptors on the host cells, preventing endocytosis, and inhibiting viral entry at a post-binding step. Other anti-inflammatory drugs also showed considerable antiviral effects, such as the antirheumatic drug leflunomide which prevents, tegument acquisition by viral nucleocapsids, and Janus Kinase inhibitors which exert their antiviral effect indirectly by the same mechanism by which they exert their anti-inflammatory effect, and the leukotriene receptor antagonist montelukast, which was showed the ability to inhibit viral entry and interact with some viral enzymes. Taken collectively, the findings summarized previously could be considered in further preclinical and clinical studies for rearrangement and using anti-inflammatory drugs during viral infections according to the suitability of the situation and the mechanism of their effect.

Due to the epidemiological importance of viral diseases and the difficulties faced in controlling them,limitations in antiviral drugs in addition to drug resistance, and the emergence of new viral types; the search for new drugs and antiviral therapeutic options is essential and urgent, also clinical research ultimately improve patient care,therefore is a pressing need for translating the reviewed studies in practical clinical trials.

In pandemic situations, when it is nearly impossible to design and implement a new drug, previously designed approved drugs could help, however, no clear evidence of severe adverse effects in patients who used anti-inflammatory drugs was reported, on the other hand, anti-inflammatory drugs are commonly prescribed in viral infections besides, antiviral agents based on their safety profiles and long term use, because the majority of the selected FDA-

approvedanti-inflammatoryare over the counter (OTC) medicines in developing countries, this eases their intensive consumption by the public to treat mild to moderate infections. However, little is known about the antiviral activity of these predefined FDA-approved drugs, in addition,the antiviral screening revealed that the tested drugs exhibited promising in vitro antiviral activities with a high selectivity besides their safety profiles it would be valuable for drug repurposing.

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