REVIEW

Compounds with anti-influenza activity: present and future of strategies for the optimal treatment and management of influenza

Part II: Future compounds against influenza virus

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Summary

In the first part of this overview, we described the life cycle of the influenza virus and the pharmacological action of the currently available drugs. This second part provides an overview of the molecular mechanisms and targets of still-experimental drugs for the treatment and management of influenza.

Briefly, we can distinguish between compounds with anti-influenza activity that target influenza virus proteins or genes, and molecules that target host components that are essential for viral replication and propagation. These latter compounds have been developed quite recently. Among the first group, we will focus especially on hemagglutinin, M2 channel and neuraminidase inhibitors. The second group of compounds may pave the way for personalized treatment and influenza management. Combination therapies are also discussed.

In recent decades, few antiviral molecules against influenza virus infections have been available; this has conditioned their use during human and animal outbreaks. Indeed, during seasonal and pandemic outbreaks, antiviral drugs have usually been administered in mono-therapy and, sometimes, in an uncontrolled manner to farm animals. This has led to the emergence of viral strains displaying resistance, especially to compounds of the amantadane family. For this reason, it is particularly important to develop new antiviral drugs against influenza viruses. Indeed, although vaccination is the most powerful means of mitigating the effects of influenza epidemics, antiviral drugs can be very useful, particularly in delaying the spread of new pandemic viruses, thereby enabling manufacturers to prepare large quantities of pandemic vaccine. In addition, antiviral drugs are particularly valuable in complicated cases of influenza, especially in hospitalized patients.

To write this overview, we mined various databases, including Embase, PubChem, DrugBank and Chemical Abstracts Service, and patent repositories.

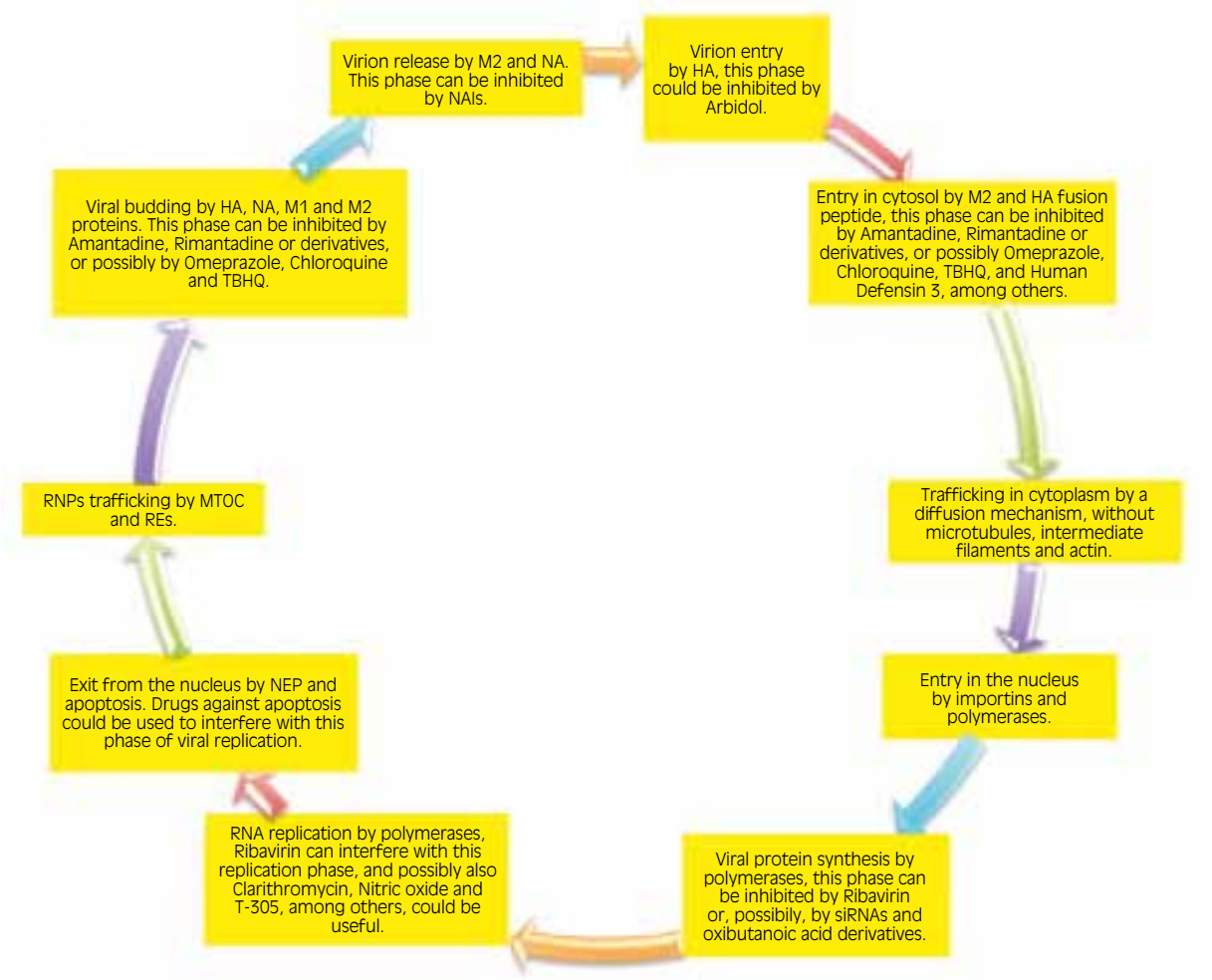
In the first part of this overview [1], we described the life cycle of the influenza virus and the pharmacological action of the currently available drugs. In this second part, we will overview the molecular mechanisms and the targets of still-experimental drugs for the treatment and management of influenza. Figure 1 shows the attack points of several potential antiviral drugs.

Antiviral drug research is a particularly active field and new approaches have been developed. Briefly, we can distinguish between compounds with anti-influenza activity that directly target influenza virus proteins or genes, and molecules that target host components that are essential to viral replication and propagation. Among the former group, we will focus especially on hemagglutinin (HA), Matrix protein 2 (M2) and neuraminidase (NA) inhibitors (HAIs, NAIs). The latter molecules have been implemented quite recently and may pave the way for personalized treatment and management of influenza. Moreover, it is expected that the inhibition of host factors (such as single molecules) and/or complex mechanisms (such as intracellular signaling cascades and pathways) may act against different influenza virus strains and may be less prone to the emergence of drug resistance than the inhibition of viral components [2, 3]. Therapies that combine two or more compounds belonging to the same group or different groups are also discussed.

To write this overview, we mined various chemical databases, including Embase [4], PubChem [5, 6], DrugBank [7] and Chemical Abstracts Service (CAS) [8], as well as patent repositories and clinical trials registries [9]. We also scanned extant reviews and consulted the gray literature (books, proceedings, conference abstracts, posters and congress communications) in order to increase coverage of the anti-influenza drugs included in the present article. With regard to the search strategy, we used a mining approach similar to that described in Eyer and Hruska [10]. No time or language filters were applied.

To the best of our knowledge, this article constitutes the most comprehensive and up-to-date overview of anti-influenza compounds in the literature. It can be used

Fig. 1. The attack points of several antiviral drugs are shown, with a particular focus on future potential compounds and strategies against influenza virus. Abbreviations: HA: hemagglutinin; M: Matrix protein; M1: Matrix type 1 protein; M2: Matrix type 2 protein; MTOC: microtubule-organizing center; NA: neuraminidase; NAIs: neuraminidase inhibitors; NEP: nuclear export protein; REs: recycling endosomes; RNA: ribonucleic acid; RNP: ribonucleoprotein; siRNA: short interfering RNA; TBHQ: Tert-butyl-hydroquinone.



also as a working bibliography and a mapping review for scholars doing research in the field.
Along with this paper, a database is currently being designed and developed and will be accessible at the CIRI-IT institutional website [11].

Entry and Attachment Inhibitors

Effective antiviral compounds that interfere with the attachment and entry of the influenza virus into the host cell include triterpenoids [12] such as glycyrrhizic acid (GA) [13], glycyrrhizin (GR) [14], glycyrrhetinic acid [15] and further derivatives extracted from licorice and present in some Chinese medicaments. GR is the most active of these molecules and can repress the replication of H3N2 and H5N1, as well as of several viruses [16]. It can be delivered as an approved parenteral GR preparation (Stronger Neo-Minophafen C, SNMC), and glutamyl-tryptophan can be added in order to increase its activity [17, 18]. GR is able to inhibit entry of the virus into the host cell, and reduces the level of pro-inflammatory molecules such as chemokine (C-X-C motif) ligand type 10 (CXCL10), interleukin 6 (IL6), CC chemokine ligand type 2 (CCL2), and CC chemokine ligand type 5 (CCL5) [19, 20]. It also exerts an anti-apoptotic action. In addition, GR hinders monocyte recruitment and has anti-oxidant activities, inhibiting the formation of influenza virus-induced reactive oxygen species (ROS) [21]. It extensively modulates gene expression, activating interferon-gamma (IFN-gamma) and reducing the expression of Nuclear factor kappa B (NFκB), c-Jun N-terminal kinase (JNK), and p38. Furthermore, GR reduces high-mobility-group box type 1 (HMGB1) [22]. Promising glycyrrhizin derivatives include spacer-linked 1-thioglucuronide analogues [23]. GA inhibits influenza virus growth and replication in embryonated eggs [24]. Moreover, it can be used as an adjuvant in the preparation of anti-influenza vaccines [25].
Other triterpenoids [26], such as the saponins and uralsaponins M-Y from the roots of *Glycyrrhiza ura-*

lensis [27], exhibit anti-influenza and anti-HIV activities. Moreover, saponins can be used as vaccine adjuvants [28-31] and modulate the expression of cytokines and chemokines [32, 33]. Further triterpenoid derivatives share broad antiviral actions [34-38].

Dextran sulphate (DS) is a negatively charged sulphated polysaccharide. Besides inhibiting virus entry and attachment, it represses HA-dependent fusion activity [39-41] and NA-dependent activity [42]. However, mutations conferring resistance to DS are described in the literature [43]. Oxidized dextran can be administered as a prevention [44-46].

Other sulphated molecules include the sulphated syalil lipid NMS03, which is effective against IAV, Human Metapneumovirus (HMPV) and picoRNAvirus. It is assumed that it interferes with fusion, but the precise nature of its mechanism is still unknown [47].

Another potential fusion inhibitor is BTA9881, which has shown promising activity against RSV [48, 49].

Lysosomotropic agents, such as concanamycin A [50-53], the macrolide antibiotic bafilomycin A1 [54, 55], saliphenylhalamide [56], N,N'-Dicyclohexylcarbodiimide [52], and chloroquine [57-64], inhibit vacuolar ATPase (V-ATPase) and reduce endosome acidification and lysosome number. They act on the CME pathway, but are unable to block clathrin caveolae-independent endocytosis. It should be stressed that the anti-influenzal activity of these compounds strongly depends on the pH of the cellular environment and that some scholars have reported conflicting findings about their *in vivo* effectiveness [65].

Extract from milk thistle seeds, known as silymarin, a complex mixture of flavonolignans, and its main component silibinin are active against influenza [66]. Also silybin and its derivative can block virus entry and regulate autophagy, repressing the formation of oxidative stress species and triggering activation of the extracellular signal-regulated kinase (ERK)/p38 mitogen-activated protein kinase (MAPK) and IκB kinase (IKK) cascades [67]. Other silybin derivatives include silybin fatty acid conjugates, which have strong anti-oxidant properties [68].

Compounds from *Melaleuca alternifolia* (tea tree) oil (TTO) concentrate (MAC) [69, 70] have a broad antimicrobial activity. *In silico* simulations have shown that these compounds can interfere with virus entry and fusion of the influenza virus [71, 72].

Other potential compounds include *Amaryllidaceae* alkaloids from *Lycoris radiate*, such as lycorine, hippeastrine, hemanthamine and 11-hydroxy vittatine, which can also inhibit the nuclear-to-cytoplasmic export of the ribonucleoprotein (RNP) complex [73].

Curcumin is able to inhibit virus entry and HA [74]. It also has antioxidant, anti-inflammatory, anticancer, antiviral, antibacterial and antidiabetic properties, among others [75]. Curcumin acts against a large array of targets [76]. Curcumin is also active against other viruses [75, 77]. Rajput and collaborators showed that animals on a diet enriched in curcumin displayed an improved immune response [78]. Surprisingly, curcumin derivatives do not exhibit anti-influenza activity [79].

LADANIA067, extracted from the leaves of the wild blackcurrant (*Ribes nigrum folium*) [80, 81], has shown antiviral activities both *in vivo* and *in vitro*, without having any effect on influenza virus metabolism or growth/proliferation.

Fattiviracin A1 is a recently discovered antiviral [82]. Besides inhibiting both IAV and IBV, it is active against HIV, HSV and VZV [83].

Lignans exert a good anti-influenza activity [84, 85] Germacrone is a molecule purified from *Rhizoma curcuma*. It can be effectively combined with oseltamivir [86].

Akt inhibitors are also effective entry inhibitors. These include peptide "Akt in", which may be TCL1- or TCL1b-based, MK2206 [87, 88] and Ma-xing-shi-gan-tang (MXSGT), a traditional Chinese herbal decoction [89]. Everolimus, an inhibitor of the PI3K-Akt-mTOR pathway, is also a valuable tool against influenza [90].

Among anti-attachment drugs, Fludase (DAS181) has potential anti-influenza virus properties [91-103]. This medication, which has proved capable of inhibiting human and avian influenza viruses in pre-clinical studies, acts by mimicking NA and destroying the molecules of sialic acid receptors on the host cell surface. It is also effective against NA-resistant influenza strains [92, 93, 103].

HA Inhibitors

An effective class of HAIs is that of the amide derivatives [104-107].

Gossypol is a natural phenolic aldehyde extracted from the cotton plant and blocks the dehydrogenase family enzymes [108, 109]. Its antiviral properties emerged during a 1970 study, in which an experimental model of influenza pneumonia was used [108]. In particular, chiral (+)-gossypol is more active than (–)-gossypol [110, 111].

Another antiviral against HA is Entry Block-peptide (EB-peptide), a peptide derived from fibroblast growth factor 4 (FGF4) [112]. EB-peptide can inhibit virus entry and attachment, being effective even when administered post-infection. Besides repressing influenza viruses, EB-peptide is also active against other viruses [113]. It can also be used as an adjuvant in the formalin-inactivated influenza whole-virus vaccine, triggering phagocytosis of influenza virions. Other peptides similar to EB-peptide are the FluPep (FP) peptides, such as FP1 (Tkip) and FP2-FP9 [114]. Tkip was designed as a mimetic of the suppressor of the cytokine signaling (SOCS) protein, which is involved in mediating the immune response to influenza. Furthermore, peptide NDFRSKT has strong antiviral properties, but with unknown therapeutic characteristics [115, 116].

Other molecules which bind to HA are collectins (CLs) [117]. Human CLs and bovine conglutinin, CL-

43 and CL-46 confer protection against influenza infection [118-122].
A related group of molecules is the ficolins (such as H-ficolin and L-ficolin), present at high concentrations in serum and in bronchoalveolar secretions [123]. They bind not only to HA but also to NA in vitro models [124]. These proteins can be engineered in such a way as to become more active against influenza virus; for example, Chang and collaborators designed recombinant chimeric lectins consisting of mannose-binding lectin (MBL) and L-ficolin [125]. However, because of their role in the inflammatory response, their potential use in humans requires more complete analysis. Recently, agglutinins such as NICTABA, UDA [126] and protectins like protectin D1 [127-130] have been found to have anti-influenza propriety [131].
An interesting compound, which binds to specific high-mannose oligosaccharides of HA is Cyanovirin-N (CVN) [132]. In 2003, O'Keefe *et al.* demonstrated its potent *in vitro* antiviral activity against a wide range of IAVs and IBVs, including NA-resistant strains, though resistance induced by mutations that affect the glycosilation site of HA seems to arise quite naturally [133].
Clarithromycin (CAM), able to inhibit influenza virus replication *in vitro* and in cell cultures, appears to have 3 mechanisms of action against type A seasonal Influenza virus. It was recently showed that CAM reduces the expression of human influenza virus receptors on the mucosal surface of the airways, reduces the production of nuclear factor-kB (NF-kB), and increases pH inside the endosomes [134, 135].
Norakin (Triperiden) is an anticholinergic drug that interacts with HA [136, 137]. This interaction may be indirect, being mediated by an increase in the internal pH in the pre-lysosomal compartment [138-140]. However, strains resistant to Norakin have been described [141-144]. Also Norakin derivatives seem to be effective antiviral compounds [145].
Another interesting compound is nitazoxanide [146-151], useful for the treatment of protozoal and bacterial infections and is active against hepatitis and influenza viruses or rotaviruses. Further thiazolides act at the post-translational level by selectively blocking the maturation of viral HA at a stage preceding that of resistance to endoglycosidase H digestion, thus interfering with HA intracellular trafficking and insertion into the host plasma membrane, which is a key step in the correct assembly and exit of the virus from the host cell.
Bacillus intermedius ribonuclease (BINASE) shows a good anti-influenza activity. BINASE and HA interact with sialic acid on the cell surface and penetrate into the host cell. Subsequently, viral RNA is released and cleaved by BINASE [152, 153].
High mannose-binding lectins (HMBL) are powerful influenza and HIV inhibitors [154].
Rutin, quercetin, and related compounds, extracted from elderberry fruit (*Sambucus nigra L.*) [155-161] are other HA inhibitors. Xylopine and rosmaricin have an amine group that interacts with HA [162, 163].
Theaflavins (TFs) from black tea have a strong anti-influenza activity, inhibiting HA and reducing the level of IL6, thus exerting an anti-inflammatory and anti-apoptotic action [164-166].

M2 Inhibitors

M2 inhibitors can be basically divided into 2 groups. The first includes compounds derived from the leads of amantadine and rimantadine and its hydroxylated derivatives [167-172]. The second includes non-adamantane derivatives, which are promising drugs against influenza viruses [173]. Some of these compounds have been specifically designed for some important mutants of the M2 ion channel of IAV [174-177].
Regarding molecules putatively capable of blocking the ion pump, Gasparini and coworkers recently conducted a field investigation into the effect of omeprazole family compounds (OFC) [178] on Influenza-like Illness (ILIs). The results showed that subjects treated with omeprazole family compounds displayed a lower risk of catching ILI (OR_{adj} = 0.29, 95% CI: 0.15-0.52) than non-treated subjects. Molecular docking and molecular dynamics (MD) simulations, which are a common method of searching for new potential drugs, seem to confirm these findings [179]. The M2 Protein – Protein Data Bank (PDB) code *3C9J* [180] – was simulated as being embedded in a dipalmitoylphosphatidylcholine (DPPC) membrane in complex, with its ligands amantadine and rimantadine being used as positive controls and omeprazole as a putative ligand. The thermodynamic integration method was used in order to estimate binding free energies of the ligands. Free-energy calculations imply omeprazole as a potent anti-viral drug. Also another study has suggested the antiviral properties of omeprazole against Ebolavirus [181].
Polyamines such as spermine [182, 183], spermidine and putrescine have recently been identified as intrinsic rectifiers of potassium channels. Indeed, the M2 protein has a binding site for polyamines, which is different from the amantadine binding site [184]. Polyamines have quite recently been exploited in designing anti-influenza vaccines [185, 186].
Spiropiperidine M2 inhibitor and its derivatives appear promising in acting against amantadine-resistant viruses; in particular, spiropiperidine-9 seems to be the most active [187].
Among natural products, pinanamine derivatives [188] and 24-E-ferulate [188] have a good influenza activity.

Endosomal and lysosomal inhibitors

Substituted salicylanilides appear promising antiviral agents [190-193]. In particular, Niclosamide [192], which is approved for human use against helminthic infections, besides being active against influenza viruses, has also shown anti-neoplastic and broad antiviral ef-

fects, being active against SARS-related coronavirus and Human Rhinovirus (HRV).
Lysosomotropic agents [50-64] have also been already discussed. Further compounds include molecules obtained from TTO [69-72], which have already been mentioned.

Protease inhibitors

The cleavage of HA can be blocked not only by anti-M2 protein compounds, but also by inhibition of the necessary proteases [194]. Given the great importance of the proteases in the viral replication cycle, many authors [195, 196] have directed their research towards anti-protease medications that could block, or at least mitigate, the consequences of HA cleavage. HA can also be blocked by natural products such as Hepatocyte growth factor activator inhibitor 2 (HAI-2) [197]. Several anti-protease drugs have been studied in *in vitro* models, animals and humans, such as Camostat mesilate [198], epsilon-aminocapronic acid [199], leupeptin [200] and Aprotinin [201], which has been approved for topical use in a small-particle aerosol formulation in Russia. A theoretical advantage of antiviral activity against enzymatic activities of the host is that these molecules would not lead to the selection of resistant viral variants.
Other molecules can interfere with the mechanism of fusion of the endosomal and viral membranes [202]. Indeed, numerous small molecules that block virus infectivity by inhibiting the conformational changes required for HA-mediated membrane fusion have been identified. Russell *et al.* [194] have demonstrated that TBHQ (*Tert-butyl-hydroquinone)* stabilizes the neutral pH structure and, in this way, presumably, inhibits the conformational rearrangements required for membrane fusion. Furthermore, Leikina *et al.* [203] have demonstrated that human β-defensin 3, a lectin, can inhibit HA-mediated influenza viral fusion.
Regarding the compounds targeted against the transcription and replication of vRNA, one of the first drugs developed is Ribavirin (RIB). RIB, also known by the trade name "Virazole", is a nucleoside analog [204]. Its mechanism of action is not completely known. However, Inosine 5'-monoposphate dehydrogenase (IMPDH) appears to be the principal target of the molecule. This inhibition diminishes the intracellular concentration of GTP (Guanosine-5'-triphosphate), and this is thought to stop viral protein synthesis and limit vRNA replication. Crotty *et al*. also demonstrated that RIB is a lethal vRNA mutagen [205]. However, the need for high doses of the drug in order to have obtain good clinical results has limited the use of RIB as an anti-influenza drug, and a recent revision of the literature by Chan-Tack *et al.* suggests that there are no conclusive results on the beneficial use of Virazole for the treatment of influenza [206]. RIB can also be delivered as a liposome encapsulated with muramyl tripeptide (MTP-PE) [207].
α(1)-antitrypsin (AAT) [208] is a serine protease inhibitor of elastase and proteinase-3 (PR-3). This protein is produced by the liver and its expression increases particularly during the acute-phase response. It also has immunomodulatory, anti-inflammatory and tissue-protective properties, reducing influenza-related complications and morbidities. As an immunomodulator, AAT mediates the maturation and differentiation of dendritic cells (DCs) and T regulatory cells (T_{reg}s), activating the IL1 receptor antagonist (IL1RA) and inducing IL10 release. Moreover, it exerts an anti-apoptotic effect, inhibiting caspases-1 and -3. The role of AAT in inhibiting influenza viruses is consistent with the clinical observations that subjects with AAT deficiency are exposed to the risk of severe influenza-related complications and should therefore be vaccinated [209, 210].
Stachyflin, acetylstachyflin and its phosphate esther or oxo derivatives [211, 212] exert their inhibitory activity on a variety of HA subtypes of IAV (H1, H2, H5 and H6, among others) but have no activity on H3 subtype IAV or on IBV [213-217]. The metabolites of stachyflin and its derivatives include compounds such as *cis*-fused decalin [214]. Stachyflin compounds can be delivered intranasally or orally, using PEG 400 as vehicle [211]. However, some amino acid substitutions confer resistance to stachyflin [212].
BMY-27709, a salicylamide derivative, and its analogues are other useful compounds [218, 219].
Thiobenzamide derivatives have a good activity profile. In particular, the axial disposition of the thioamide moiety has proved to be crucial to inhibitory activity [220].
Ulinastatin [221] is a protease inhibitor, which also protects lysosome integrity. Its use has been suggested for the treatment of avian influenza [221] and severe influenza-related complications, such as encephalopathy [222] and acute respiratory distress syndrome (ARDS) [223, 224]. Indeed, a recently published meta-analysis has shown that this drug is effective in managing acute lung injury (ALI) and ARDS [225].
The ubiquitin-specific peptidase type 18 (USP18) protease inhibitor ISG15 is another promising molecule [226]. ISG15 is part of the interferon-regulated cellular cascade. USP18 was found to be one of seven genes which predict a response to influenza virus [227]. This finding was reproduced by Liu and collaborators [228].

Polymerase inhibitors

Other antiviral strategies have been directed against the viral RNA polymerase [229, 230]. The trimeric polymerase complex has multiple enzymatic activities and can thus be targeted at different sites of action. For instance, nucleoside/nucleotide compounds have been developed against other viruses, namely HIV, HBV, etc.
A historical compound is moroxydine [231-233]. It is also active against HSV and VZV.
The most thoroughly studied of these molecules is Favipiravir (T-705). *In vitro* studies have demonstrated the high antiviral potency of the drug and mouse studies have demonstrated its protective efficacy against a wide

range of influenza viruses A and B. This molecule also seems to be effective against other viruses [234-238].
More recently, other compounds directed towards anti-nucleasic activities have been studied, such as the series of hydroxypyridinone, which appears to have antiviral activity in cells [230].
On studying 33 different kinds of phytochemicals, other scholars have identified a family of drugs called marchantines, which appear to interact with the PA subunit of the endonuclease [239].
An attractive strategy for developing anti-polymerase compounds appears to be that of interfering with the subunit binding interfaces of PB1 and PA, which are very well conserved in different Influenza virus strains [240]. Thus, these compounds would reduce the transcriptional activity of the viral RNA polymerase. One such promising compound is AL18, which is also active against human cytomegalovirus [241].
Furthermore, the recent definition of the PB1/PB2 binding interface by means of crystallography [242] has prompted researchers to study synthetic peptides, such as peptide 1-37 and peptide 731-757, which seem to inhibit the interaction between PB1 and PB2 [243-247].
Azaindole VX-787, an inhibitor of PB2 [248-251], is able to interfere with the cap-snatching activity of the polymerase complex of the influenza virus. The small GTPase Rac1 inhibitor NSC23766 exhibits a similar activity profile [252].

Nuclear pathway inhibitors

Leptomycin B (LMB) inhibits nuclear export signal (NES)-mediated vRNP export, as well as NES-receptor CRM1/exportin-1 (XPO-1); however, it is somewhat toxic [253].
Verdinexor (KPT-335) [254] is a new-generation XPO-1 antagonist that is well tolerated in animal models and seems to be effective against both IAV and IBV. It is a selective inhibitor of nuclear export (SINE).

NP inhibitors

Given the fundamental importance of the NP in modulating the replication cycle of the virus, many authors have investigated strategies for preventing its production. Moreover, molecules that prevent the functional polymerization of the NP monomers have also been studied, such as, for example, Nucleozin (NCZ) [255]. It also blocks viral RNA and protein synthesis and targets vRNP nuclear export and its cytoplasmatic trafficking. As a final result, fewer and smaller influenza viral particles are released. NCZ derivatives include a quite effective compound, namely 3061 (FA-2), which has been shown to inhibit the replication of the influenza A/WSN/33 (H1N1) virus, though NP-mutant strains have displayed resistance to this drug [256].
Jiang and collaborators screened a peptide library and discovered that the NP-binding proline-rich peptide was particularly effective against influenza viruses [257].
Another interesting molecule is the interferon-inducible Mx1 protein [258, 259].
Cycloheximide (CHX), which is also active against enterovirus-71 (EV-71), coxsackievirus B, and actinomycin D, are quite effective chemicals [260-262].
Intriguingly, clinically licensed anti-cyclooxygenase-2 (COX-2) Naproxen also appears to inhibit the functional polymerization of NP monomers. Its derivatives, such as naproxen A and C0, also appear quite promising [263].
Another drug directed against the NP is Ingavirin, which has been licensed in Russia. Indeed, Ingavirin interacts with the transport of newly synthesized NPs from the cytoplasm to the nucleus [264-272]. It is also active against parainfluenza virus, adenoviruses and human metapneumovirus [273].

NA inhibitors

NAIs include peramivir and lanimamivir derivatives [274-289].
Baicalin induces autophagy and acts against both NA [290] and NS1 [291-293].
Isoscutellarein is another compound that inhibits influenza virus sialidase. Its derivative is also active against influenza [294, 295].

NS1 inhibitors

Another potential strategy against influenza is to block the NS1 protein, a non-structural protein that is very important during the viral replication cycle. Indeed, the NS1 protein down-regulates the cellular production of IFN α/β. Furthermore, it has been demonstrated that NS1 also modulates other crucial aspects of influenza virus replication, namely viral RNA replication, viral protein synthesis, and general host-cell physiology [1, 296]. Finally, NS1 probably has an anti-apoptotic function in the early phases of replication. The meaning of apoptosis during influenza A virus replication is ambiguous, although it is usually considered to be a cellular antiviral defense that limits virus replication. Therefore, influenza viruses have acquired different ways of procrastinating this seeming host strategy [1]. Nonetheless, cellular pro-apoptotic factors favor the effective replication of influenza viruses, and some viral proteins, such as NA and PB1-F2, carry out pro-apoptotic tasks [1, 297]. Furthermore, some compounds that act against the NS1 protein have been studied. In this perspective, peptide-mediated inhibition of NS1 – CPSF30 has been proposed as a strategy for mitigating viral replication [298, 299]. Unfortunately, this virus-specific approach leads to viral mutation and the occurrence of drug resistance.
More recently, Jablonski *et al.* studied a class of molecules derived from the NSC125044 compound, which

displayed NS1 protein inhibition in viral replication assays [300].
Regulated in development and DNA damage responses-1 (REDD1) is a molecule that has recently emerged from comprehensive biochemical screening. Moreover, REDD1 inhibits the mTOR pathway [301].

Other RNA synthesis inhibitors

Cordycepins extracted from *Cordyceps*, a genus of ascomycete fungi, are used for diverse medicinal purposes because of their different pharmacological actions with hypothetical anti-viral activity [302].

Caspase inhibitors

Apoptosis plays a major role in the influenza virus life cycle [303-307]. Indeed, in order to replicate, the virus activates the mechanism of apoptosis through the activation of caspase 3. Cellular inhibitors of apoptosis proteins (cIAPs) are essential regulators of cell death and immunity. Nucleotide-binding oligomerization domain-like receptor type 1 (NLRX1) [308] binds to viral protein PB1-F2, preventing IAV-induced macrophage apoptosis and promoting both macrophage survival and type I IFN signaling. Interestingly, compounds that inhibit this enzymatic activity could be useful as anti-influenza antivirals. Indeed, Wurzer *et al.* have shown that apoptotic activation by caspase 3 is required for efficient virus production [306]. Furman and collaborators have demonstrated that the apoptotic index is a predictive biomarker of influenza vaccine responsiveness [309]. However, the question of whether apoptosis is beneficial to the viral reproductive cycle or to host cells is still under debate. Moreover, Hinshaw *et al.* [307] demonstrated that, on inhibiting apoptosis during viral infection, influenza virus RNP complexes were retained in the nucleus. Therefore, the use of caspase 3 inhibitors could have good potential as anti-influenza drugs [310].

Autophagy

Autophagy (or autophagocytosis) is a catabolic mechanism that involves cellular breakdown of dysfunctional cell components through the involvement of lysosomes. Procyanidin has an anti-IAV activity [311].

Glucosidase, mannosidase and glycosilation inhibitors

L-fructose and L-xylulose can inhibit influenza virus replication [312]. Glucosidase I and glucosidase II inhibitors include iminosugars, which alter glycan processing of influenza HA and NA [313].

Pathway inhibitors

Raf/MEK/ERK pathway inhibitors include compounds, which act as an inhibitor of MEK1 and MEK2 [3]. NFKB inhibitors include Bortezomib [3], among others. These proteasome inhibitors are also effective against paramyxoviruses, HRV, poliovirus, coxsackievirus, HSV and HIV.

Phospholipase inhibitors

Lipid metabolism plays a fundamental role during influenza virus replication: membranes and their components, such as sphingolipids, are crucial to all steps of the viral life cycle, from attachment and membrane fusion, to intracellular transport, replication, protein sorting and budding. Infection by influenza virus stimulates phospholipase D (PLD) activity [314].

Release inhibitors

HDAC6 is an anti-IAV host factor that negatively regulates the trafficking of viral components to the host cell plasma membrane via its substrate, acetylated microtubules [315].
As an anti-influenza chemical, cyclosporin A does not act through its classical targets, namely cyclophilin A (CypA), cyclophilin B (CypB) and P-glycoprotein (Pgp) [316], but by inhibiting influenza virus release. Ching-fang-pai-tu-san (CFPTS) has a similar action [317].

Anti-oxidants, anti-inflammatory compounds and immunomodulators

Oxidation plays a major role in influenza virus life cycle and replication [318]. With regard to anti-influenza drugs that act subsequently to the various stages of viral replication, after the formation of vRNPs, it is worth considering that Resveratrol may be useful as an anti-influenza drug. Indeed, this compound could interfere with the translocation of RNPs from the nucleus to the cytoplasm [319-321]. Dehydroascorbic acid also has antiviral properties [322, 323].
Calcitriol prior to/or post-H1N1 exposure does not affect viral clearance but significantly reduces autophagy and restores the increased apoptosis seen on H1N1 infection to its constitutive level. However, it significantly reduces the levels of H1N1-induced TNF-α (tumor necrosis factor-alpha), RANTES, IL8, IFN-β (interferon-beta) and IFN-stimulated gene-15 (ISG15). 1,25[OH]2 D3 treatment prior to/or post-H1N1 infection significantly downregulates both IL-8 and IL-6 RNA levels [324, 325].
Publications on antiviral drugs are often devoted to the use of statins as anti-flu drugs [326-328]. In particular, Fedson has suggested treating patients affected by H5N1 with statins [326, 327]. Studies *in vitro*, in animals and

in the field seem to support this strategy. Statins are held to act through various mechanisms: through immunomodulatory and anti-inflammatory activity, by interfering with the proteins of the cytoskeleton and the interaction between these and the lipid rafts, and by reducing the availability of intracellular cholesterol. The balanced content of cholesterol in the cell is critical to the replication of IAV. Indeed, a reduction in cholesterol could impair the infectivity of progeny influenza viruses, probably by reducing the cholesterol content of the viral envelope [328]. However, some studies have found statins to be ineffective against influenza viruses [329, 330].

Extracts from *Epimedium koreanum Nakai* have immunomodulatory properties [331], also against HSV, VSV and Newcastle Disease Virus (NDV). Carrageenan [332] extracted from edible red seaweeds can be administered as a nasal spray [333]. In particular, iota-carrageenan appears to be the most effective against influenza.

Cycloferon [334-336], amixin, Larifan, Kagocel and Ragosin stimulate B cells and macrophages to produce IFN-alpha [337]. They are widely used in Russia.

Apocynin, a NADPH oxidase type 2 (NOX2) inhibitor, stimulates cell superoxide production. However, in certain conditions, it can also act as a ROS production stimulator in non-phagocyte cells [338]. By contrast, NADPH oxidase type 1 (NOX1) has anti-inflammatory activity and inhibits ROS production [339, 340].

Rolipram, a selective phosphodiesterase-4 (PDE-4) inhibitor with antidepressant properties, and sertraline, a selective serotonin reuptake inhibitor (SSRI), exhibit strong antiviral activities if combined with oseltamivir [341]. The rationale for using PDE-4 is that it belongs to a family of enzymes that metabolize cyclic adenosin monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are commonly found during inflammatory and immune responses. By reducing bronchospasm and bronchoconstriction, it reduces mortality and morbidity in a mouse model. SSRI downregulates the expression of interferon-alpha, TNF-alpha, IL-6, IL-10 and T helper 1 (Th1) cells, and modulates immune responses from the Th1 toward the Th2 phenotype.

Sphingosine mimetics are able to finely modulate the release of cytokines and chemokines. In one study [342], neutralizing antibody and cytotoxic T cell responses were seen to be reduced, though still protective. As a result, the infiltration of PML and macrophages into the lung was markedly reduced, and thus also pulmonary tissue injury. DC maturation was suppressed, which limited the proliferation of specific antiviral T cells in the lung and draining lymph nodes. Furthermore, they were effective in controlling CD8(+) T cell accumulation in the lungs even when given 4 days after the onset of influenza virus infection.

Leucomycin A3 (LMA3), a macrolide antibiotic, inhibits neutrophil myeloperoxidase (MPO), which contributes to the pathogenesis and progression of severe influenza-induced pneumonia, and mediates the production of hypochlorous acid, a potent tissue injury factor [343].

BG-777, derived from leukotriene B4, exerts both antiviral and stimulatory activities on the host defence system. It is also active against HIV, RSV and Coronaviruses. It recruits leukocytes and fosters the release of chemokines such as MIP1-beta and defensins [344].

QS-21 is a molecule with immunomodulatory properties, and is currently being investigated as an adjuvant for vaccines against influenza [345]. Thymalfasin (Zadaxin), which is derived from thymosin alpha-1, is another powerful adjuvant [346-348]. Canakinumab (Ilaris), an IL1-beta blocking antibody, is also a promising compound in immunotherapy [349].

Some observations should be made on influenza therapy with non-steroidal anti-inflammatory drugs. Seasonal flu is normally treated with over-the-counter (OTC) drugs, which are designed to relieve symptoms. The most common are paracetamol, acetylsalicylic acid (which, however, is contraindicated in individuals under 18 years of age) and ibuprofen or other NSAIDs. Coughing is usually mitigated by means of drugs that use dextromethorphan or acetylcistein as their active ingredient [350-357].

The inflammation driven by innate immunity is usually sufficient to cure the disease. However, especially when the virus is particularly virulent or during pandemics, immunity may be dysregulated (cytokine-storm), which may give rise to very severe forms of influenza. The treatment of both seasonal and pandemic influenza therefore utilises appropriate and timely anti-inflammatory therapy. Some of the above-mentioned drugs, such as statins and naproxen, have anti-inflammatory properties; however, they are probably also able to exert a real antiviral activity.

In the light of the human cases of infection by the H5N1 strain and the lethal cases caused by the H1N1pdm virus, the need for modulators of innate immunity is of particular importance. Indeed, patients with severe or fatal human infections due to the H1N1pdm virus, for instance, have high pro-inflammatory responses early in the illness.

For the above-mentioned reasons, the literature often reports *in vitro* and animals studies which demonstrate the therapeutic utility of anti-inflammatory and immunemodulatory compounds, such as fibrates, against influenza.

Gene therapies

Gene therapy consists of modulating (up-regulating or down-regulating) genes and/or their products involved in the response to influenza [358].

microRNAs (miRNAs) are small non-coding RNA molecules (containing about 22 nucleotides) which function in RNA silencing or RNA interference (RNAi) and in the post-transcriptional regulation of gene expression. Host miRNAs are able to down-regulate the expression of viral genes. Therefore, miRNA modulation could be a promising approach in influenza treatment, despite

the difficulties of delivering miRNAs to cells efficiently [359-363].
Small interfering RNAs (siRNAs) are also mediators of RNAi. They are short (19-26 nucleotides) and induce sequence-specific degradation of homologous mRNA [364-366].
Long non-coding RNAs (lncRNAs) modulate various biological processes [367]. One lncRNA, in particular, plays a major role; it acts as a negative regulator of antiviral response (NRAV) and is down-regulated during influenza infection. NRAV negatively regulates the transcription of multiple critical interferon-stimulated genes (ISGs), by remodeling chromatin [368].

Compounds with unknown mechanisms

In the case of some compounds, the precise nature of their pharmacological activity against influenza is still unknown and requires further research.
Nanoparticles are a promising nanobiotechnological tool that can act as carriers of non-conjugated nanoparticles. Silver nanoparticles [369, 370] modulate SP-A and SP-D [371], and can be used to deliver RNAi [372]. Poly(gamma-glutamic) acid [373], fullerenes [374], chitosan or N-trimethyl chitosan (TMC) [375] and polymeric nanoparticles have also been investigated as vaccine adjuvants [376, 377]. However, single-walled carbon nanotubes (SWCNTs) seem to increase influenza virus pathogenicity and infectivity [378].

Combination therapies

Combination therapies (CTs) can be divided into associations of two or more drugs directly targeting viral components, and associations of a direct-acting viral compound and a molecule targeting host components. CTs may improve clinical outcomes, reduce the risk of respiratory complications, mortality and morbidity, reduce the risks of using single drugs (such as resistance, dose-related toxicity or other side-effects) and may potentiate and enhance antiviral activity [379, 380]. CTs can, in turn, be further divided into early combination chemotherapy (ECC) and sequential multidrug chemotherapy (SMC). Furthermore, many studies have evaluated the efficacy of combining anti-inflammatory drugs with antiviral drugs in comparison with single-drug treatment. However, not all combination therapies, for instance the combination of oseltamivir with zanamivir or simvastatin with oseltamivir, are superior to monotherapy [102, 379, 380].
CTs can also exploit various chimeric monoclonal antibodies [381].

Conclusions

In the last few decades, few antiviral molecules against influenza virus infections have been available. This has conditioned their use during human and animal outbreaks. Indeed, during seasonal and pandemic outbreaks, antiviral drugs have usually been administered in mono-therapy and, sometimes, in an uncontrolled manner to farm animals. This has led to the emergence of viral strains displaying resistance, especially to compounds of the amantadane family. For this reason, it is particularly important to develop new antiviral drugs against influenza viruses. Indeed, although vaccination is the most powerful means of mitigating the effects of influenza epidemics, antiviral drugs can be very useful, particularly in delaying the spread of new pandemic viruses, thereby enabling manufacturers to prepare large quantities of pandemic vaccine. In addition, antiviral drugs are particularly valuable in complicated cases of influenza, especially in hospitalized patients. This latter are individuals at risk, such as the elderly or patients with chronic respiratory diseases. For these subjects, it would be particularly important to have more antivirals to be administered in appropriate manner.
In the light of the extensive experience gained through the use of anti-influenza drugs, and in the light of the considerable advances in the search for new effective molecules against influenza viruses, many important considerations can be made.
Firstly, the study of new compounds should be conducted in a more rational way. Indeed, the models and methods used by various scholars display marked differences. These studies often involve *in vitro* cell cultures and usually use Madin–Darby canine kidney (MDCK) cells and African green monkey kidney Vero cells. However, human tracheal epithelial cell cultures are sometimes used. While some authors have assessed the inhibition of viral growth by applying the haemagglutination test to the supernatant of the cell monolayer, others have used the inhibition of the virus-induced Cytopathic Effect (CPE). Furthermore, more sophisticated tests have been used – for instance, qPCR with the aim of amplifying sequences of viral genes, such as the M2 gene, NP gene, etc., or RT-PCR with the aim of quantifying IAV RNA after *in vitro* antiviral treatment of cell cultures exposed to different influenza virus strains. In addition, the murine model is the most widely used to study influenza compounds, as influenza causes fatal pneumonia in the mouse. Obviously, the human is the best, but results in humans are available only if clinical trials have been performed or if the drug has been licensed. However, as it is very costly to develop a new compound for commercialization, preliminary evaluations *in vitro* and in animal models are very important. In some cases, it is also useful to carry out epidemiological studies on drugs used for other purposes, in order to investigate their possible therapeutic efficacy against influenza.
To optimise the development of influenza antivirals, it is very important to define standardized methods for the evaluation of the molecules that have been hypothesized to have a potential antiviral effect. In *in vitro* studies, for instance, it is important to define the cell line that should be used (MDCK, or VERO, or THE cell line), the standard virus that should be tested (PR8 and/or High

pathogenic virus, such as H5N1) and the antiviral assay that should be performed (Haemagglutination, CPE inhibition, RT-PCR). Likewise, in *in vivo* tests, the choice of which animal to utilize should be established, while in human studies it is important to determine the number and age of the subjects to be studied. Only if standardized methods are defined, will it be possible to correctly evaluate the antiviral potential of the compound under examination. In this perspective, it is also important to compare the antiviral activity of the hypothetical antiviral with that of reference drugs (amantadine, oseltamivir, etc) in order to ascertain the influenza antiviral index of the new molecule. In *in vitro* studies, it is also advisable to evaluate the capacity of the antiviral under study to induce viral resistance.

In the field of medicinal chemistry, the discovery and development of a completely New Molecular Entity (NME) or compound is particularly expensive in terms of time and costs. Research could therefore be carried out along two different lines: designing/optimising new derivatives from an existing lead (such as the second-generation NAI laninamivir and peramivir); and repurposing/repositioning existing drugs for new potential clinical applications [382, 383]. The latter approach, also termed drug retasking or reprofiling, has already yielded promising results. While drug retargeting was initially serendipitous, it was later more systematically developed and exploited, not least by combining advanced biochemical, biophysical and bioinformatics/cheminformatics techniques. Viroinformatics [384] and computational systems biology [385] can suggest rational inhibitors of viral transcription, replication, protein synthesis, nuclear export and assembly/release. Other strategies may emerge from gene data mining. In this regard, Bao and collaborators used a prioritizing gene approach in order to find the most important genes involved in host resistance to influenza virus [386]. They found that the response was controlled by two TNF-mediated pathways: apoptosis and TNF receptor-2 signaling pathways. In addition, systems pharmacometrics and systems pharmacology [387] could identify valuable CTs by studying drug synergy.

Secondly, the available anti-influenza drugs should be used in an appropriate manner, in order to impede or to mitigate the phenomenon of viral resistance. In this regard, the first question is: what anti-inflammatory drug should be chosen? The answer should take into account the age of the patient, the toxicity and tolerability of the drug and its efficacy in alleviating the patient's symptoms. Obviously, therapy should be initiated as soon as possible, and an NSAID (aspirin only for subjects over 18 years, ibuprofen, naproxen or paracetamol [acetaminophen]) should be chosen. These compounds not only relieve the symptoms, but also equilibrate the patient's innate immunity and sometimes have a direct or indirect antiviral effect. For instance, it is interesting that reducing pro-inflammatory cytokines diminishes the activity of proteases involved in HA cleavage. In addition, the administration of acetylcysteine is useful not only because of its mucolytic action, but also on account of its antioxidant activity.

The choice of the antiviral should take into account the broad resistance of influenza viruses to amantadane drugs and also the fact that mono-therapy can easily lead to the emergence of novel viral resistance. In this perspective, topic drugs, such as zanamivir, have proved to generate less resistant viral strains than drugs administered orally. In addition, other antivirals, such as anti-protease drugs, could be useful in influenza therapy. These compounds could have advantages in that, being inhibitors of cellular proteins, they should be less prone to selecting resistant viral strains. However, it should be borne in mind that disturbing the cellular environment in order to disrupt viral functions could have adverse side effects. Furthermore, it has been proposed that therapeutic protocols involving a combination of two or more antivirals should be drawn up in order to reduce the development of drug-resistant viral strains and, at the same time, administer lower drug doses. Another hypothesis could be to administer two or more different antivirals alternately.

Finally, the use of antivirals in the veterinary field (for example, chicken flocks) should be carefully controlled, and in this case the combined or alternated administration of at least two antiviral drugs should be the rule. It is important to realise that this implies a *one world, one health, one medicine, one science* approach [382, 383], in which human and veterinary medicine cooperate in the interest of global health in an increasingly interconnected world.

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Abbreviations

AAT: alpha-1-antitrypsin; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; Asp: aspartic acid; BINASE: Bacillus intermedius Ribonuclease; CAM: Clarihtromycin; cAMP: cyclic adenosin monophosphate; *CAS: Chemical Abstract Service; CBP: CREB binding protein; CCL: CC chemokine ligand; CCL2: CCL type2; CCL5: CCL type 5; CFPTS: Ching-fang-pai-tu-san; cGMP: cyclic guanosine monophosphate*; *CHX: cycloheximide; CI: confidence interval; cIAPs: cellular inhibitors of apoptosis; CL: collectin; CL-43: CL type 43; CL-46: CL type 46; CME: Clathrin-Mediated Endocytosis; COX: cyclooxigenase; COX-2: COX type 2; CPE: cytopathic effect; CRM: chromosomal maintenance; CRM1: CRM type 1; CTs: combination therapies; CVN: Cyanovirin-N; CXCL: chemokine (C-X-C motif) ligand; CXCL10: CXCL type 10; CypA: cyclophilin A; CypB: cyclophilin B; DC: dendritic cell; DNA: deoxyribonucleic acid; DPPC: dipalmitoylphosphatidylcholine; DS: dextran sulphate; EB-peptide: entry block peptide; ECC: early combination chemotherapy; ERK: extracellular signal-regulated kinase; EV: enterovirus; EV71: EV type 71; FGF: fibroblast growth factor; FGF4: FGF type 4; FP: FluPep; FP1: FP type 1, also known as Tkip; GA: glycyrrhizic acid; GR: glycyrrhizin; GTP: guanosine-5′-triphosphate; GTPase: GTP hydrolase; HA: hemagglutinin; HAI-2: Hepatocyte growth factor activator inhibitor 2; HAIs: HA inhibitors; HBV: hepatitis B virus; HCV: hepatitis C virus; HGF: hepatocyte growth factor; HIV: Human Immunodeficiency Virus; HMBL: High mannose-binding lectin; HMG: 3-hydroxy-3-methylglutaryl-coenzyme A; HMGB: high-mobility-group; HMGB1: HMGB type 1; HMPV: Human Metapneumovirus; HPV: Human Papillomavirus; HRV: Human Rhinovirus; HSV: Herpes Simplex Virus; HSV-1: HSV type 1; IAV: influenza A virus; IBV: influenza B virus; IFN: interferon; IFN-α: alpha IFN; IFN-β: beta IFN; IKK: IκB kinase; IL: interleukin; IL6: IL type 6; IL8: IL type 8; IL10: IL type 10; ILI: influenza-like illness; IL1RA: IL type 1 receptor antagonist; IMPDH: Inosine 5'-monoposphate dehydrogenase*; *IRF: interferon-regulatory factor; IRF3: IRF type 3; ISG: interferon-stimulated gene; ISG15: ISG type 15; JNK: c-Jun N-termninal kinase; LMA3: Leucomycin A3; LMB: Leptomycin B; lncRNA: long non-coding RNA; M protein: matrix protein; M1: Matrix type 1 protein; M2 protein: Matrix type 2 protein; MAC: Melaleuca alternifolia concentrate; MAPK: mitogen-activated protein kinase; MBL: mannose-binding lectin; MBP: mannose-binding protein; MD: molecular dynamics; MDCK: Madin Darby Canine Kidney cell line; MIP1-beta: macrophage inflammatory protein type 1 beta; miRNA: microRNA; MPO: myeloperoxidase; mRNA: messenger RNA; MTOC: microtubule organizing center; mTOR: mammalian target of rapamycin; MTP-PE: muramyl tripeptide; MXSGT: Ma-xing-shi-gan-tang; NA: neuraminidase; NAIs: NA inhibitors; NADPH: nicotinamide adenine dinucleotide phosphate reduced; NB-DNJ: N-butyl-deoxynojirimycin*; *NCZ: nucleozin; NDV: Newcastle Disease Virus; NEP: nuclear export protein; NES: nuclear-export signal; Neu5Ac-S-CH2-Lev: α-2-S-[m-(N-levulinyl)aminobenzyl]-5-N-acetylneuraminic acid; NFKB: nuclear factor kappa B; NOX1: NADPH oxidase type 1; NOX2: NADPH oxidase type 2; NLRX1: Nucleotide-binding oligomerization domain-like receptor type 1; NRAV: negative regulator of antiviral response; Nrf2: Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2; NS: Non-Structural protein; NS1: NS type 1; NS1A: NS type 1A; NS1ABP: NS1A binding protein; NSAIDs: non-steroidal anti-inflammatory drugs; OFCs: omeprazole family compounds; OR_{adj}: adjusted odds ratio; OTC: over the counter; PA: polymerase acidic protein; PB: polymerase basic protein; PB1: PB type 1; PB1-F2: PB1 frame 2; PB2: PB type 2; PCR: polymerase chain reaction; PDB: Protein Data Bank; PDTC: pyrrolidine dithiocarbamate; Pet: petasiphenol; PGE2: prostaglandin E2; Pgp: P-glycoprotein; PI3K: phosphatidylinositol 3-kinase; PLD: phospholipase D; PR-3: proteinase 3; qPCR: quantitative PCR; RE: recycling endosome; REDD1: regulated in development and DNA damage responses-1; RIB: ribavirin; RNA: ribonucleic acid; RNAi: RNA interference; RNP: ribonucleoprotein; ROS: reactive oxygen species; RSV: Respiratory Syncytial Virus; RT-PCR; SA: sialic acid; SARS: Severe Acute Respiratory Syndrome; SINE: selective inhibitor of nuclear export; siRNA: short interfering RNA; SMC: sequential multidrug chemotherapy; SOCS: Suppressor of cytokine signaling; SOCS1: SOCS type 1; SP-A: surfactant protein A; SP-D: surfactant protein D; SREBP-1: sterol regulatory element-binding protein 1; SNMC: Stronger Neo-Minophafen C; SWCNTs: single-walled carbon nano-*

tubes; TBHQ: Tert-butyl-hydroquinone; TFs: theaflavins; Th1: T helper 1 cell; THC: tetrahydrocurcumin; TLR: Toll-like receptor; TLR2: TLR type 2; TLR7: TLR type 7; TMC: N-trimethyl chitosan; TNF: tumor necrosis factor; TNF-α: TNF type α; Treg: T regulatory cell; TTO: tea-tree oil; TZV: triazavirine; US: United States of America; USP: ubiquitin-specific peptidase; USP18: USP type 18; Val: valine; vATPase: VEGF: vascular endothelial growth factor; vRNA: viral RNA; vRNP: viral RNP; VZV: Varicella Zoster Virus; XPO-1: exportin-1.

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