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Research paper

Flavaglines as natural products targeting eIF4A and prohibitins: From traditional Chinese medicine to antiviral activity against coronaviruses

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ABSTRACT

Flavaglines are cyclopenta[*b*]benzofurans found in plants of the genus *Aglaia*, several species of which are used in traditional Chinese medicine. These compounds target the initiation factor of translation eIF4A and the scaffold proteins prohibitins-1 and 2 (PHB1/2) to exert various pharmacological activities, including antiviral effects against several types of viruses, including coronaviruses. This review is focused on the antiviral effects of flavaglines and their therapeutic potential against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

1. Introduction

1.1. Overview of the structure and pharmacological properties of flavaglines

Flavaglines, also called rocaglates, represent a distinctive class of cyclopenta[*b*]benzofurans produced in nature by plants of the genus *Aglaia* that grow in Southeast Asia [1]. Some of these plants are used in traditional Chinese medicine to treat contused wounds, cough, diarrhea, fever, and inflammation. Rocaglamide (**1**, Fig. 1) was originally discovered by King and collaborators in 1982. Since then more than one hundred other natural flavaglines, such as silvestrol (**2**) and aglaroxin C (**3**), have been identified. Strikingly, these compounds can selectively kill cancer cells, without being toxic to non-cancer cells. They can even protect neurons and cardiomyocytes against the adverse effect of clinically used cancer chemotherapeutics [2–4]. Flavaglines also possess potent anti-inflammatory effects, in particular in a mouse model of Crohn's disease [5]. These pharmacological effects are mediated by two classes of molecular targets: the translation initiation factor eIF4A and prohibitins-1 and 2 (PHB1/2) (Table 1).

At the current time, no extensive exploration of flavaglines toxicity has been disclosed. Yet, at doses where they exert potent cardioprotectant and anti-inflammatory effects, flavaglines did not exhibit any overt sign of toxicity [2,5]. In addition a synthetic flavagline developed by the eFFECTOR Therapeutics company, Zotatifin (also called eFT226, **4**, Fig. 1) has passed the US regulatory toxicology requirements necessary to enter a phase 1/2 clinical trial

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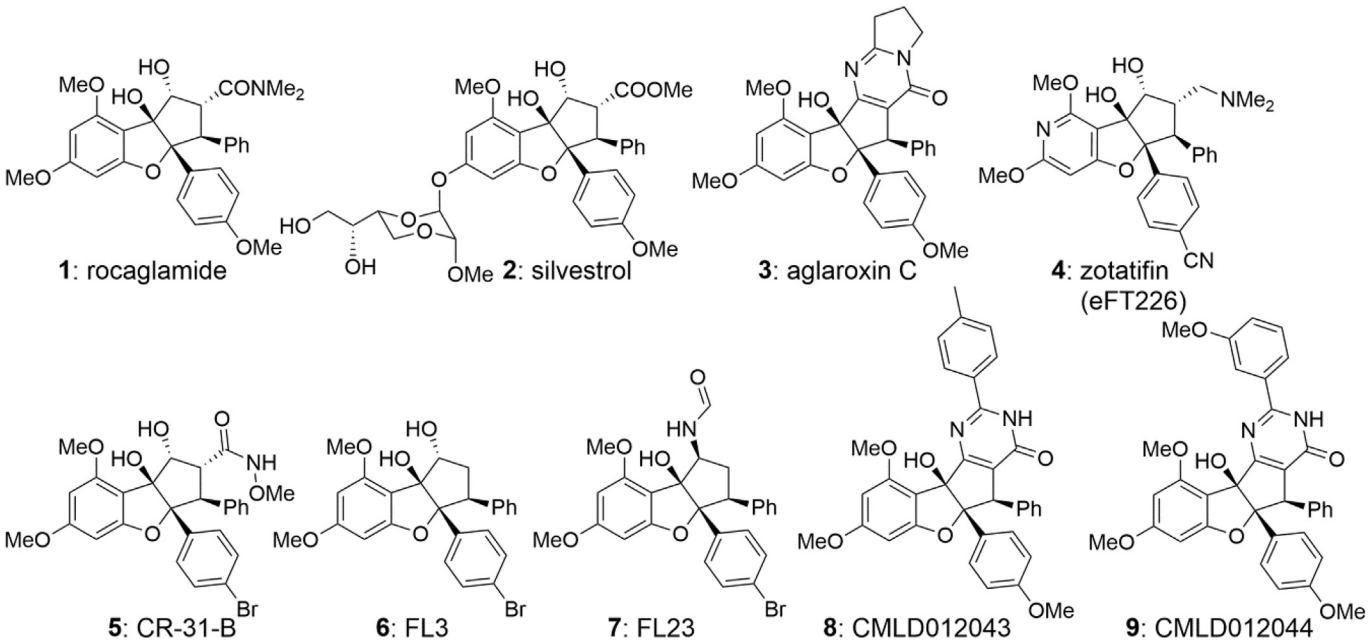

Fig. 1. Natural (**1**–**3**) and synthetic (**4**–**9**) flavaglines with demonstrated antiviral activities.

Table 1
Antiviral activities of flavaglines mediated by their action on eIF4A or PHBs.

Virus	Flavagline	Target	Reference
Ebola virus	Silvestrol (**2**)	eIF4A	[6]
MERS-CoV	Silvestrol (**2**)	eIF4A	[7]
HCoV-229E	Silvestrol (**2**)	eIF4A	[7]
Poliovirus type 1	Silvestrol (**2**)	eIF4A	[7]
Chikungunya virus	Silvestrol (**2**)	eIF4A	[8]
Hepatitis E	Silvestrol (**2**)[a]	eIF4A	[9,10]
Zika virus	Silvestrol (**2**)	eIF4A	[11]
Influenza A virus	Silvestrol (**2**)	eIF4A	[12]
HCoV-229E, MERS-CoV, Zika virus, Lassa virus and Crimean-Congo hemorrhagic fever virus	Silvestrol (**2**) CR-31-B (**5**)	eIF4A	[13]
Chikungunya virus	FL3 (**6**), FL23 (**7**)	PHBs	[14]
Hepatitis C virus	Rocaglamide (**1**) aglaroxin C (**3**)	PHBs	[15]
Hepatitis C virus	CMLD012043 (**8**) CMLD012044 (**9**)	PHBs	[16]
Enterovirus 71	Rocaglamide (**1**)	PHBs	[17]
Zotatifin (**4**)	SARS-CoV-2	eIF4A	[18]

[a] This compound was shown to be active in a mouse model of infection.

against advanced solid tumors refractory or intolerant to standard treatments [19,20]. While it was shown to inhibit eIF4A, its putative effect on PHB signaling has not yet been disclosed.

1.2. Viruses affected by flavaglines

The importance of eIF4A during viral infections tends to be virus specific. In fact, viruses can either use it or not use it at all, or they may alternate between requiring and not requiring the eIF4A protein [21]. Several RNA viruses require eIF4A for the translation of their mRNAs, in particular those that are responsible for Ebola, chikungunya, hepatitis E, poliomyelitis, Zika fever, "hand, foot and mouth" disease, SARS, MERS and COVID-19 (recently reviewed in Ref. [21]). As a consequence, eIF4A has emerged as a promising target to treat these viral infections and the use of compounds that inhibit the activity of eIF4A holds great interest as antiviral agents.

Ebola is a deadly disease manifested by a hemorrhagic fever. It is caused by a negative-stranded RNA virus, and Ebola is currently raging in the Democratic Republic of the Congo in spite of the recent approval of a vaccine [22]. At the current time, no antiviral treatment is available.

Chikungunya virus (CHIKV) is a positive-sense single-stranded RNA *Alphavirus* that induces severe fever and joint pain [23]. Unfortunately, no vaccine or medicine is currently available to prevent and treat this disease.

Flaviviruses are single-stranded, positive-sense RNA viruses that include Zika virus (ZIKV), dengue virus (DENV), yellow fever virus (YFV), and West Nile virus (WNV), which still represent a major public health problem in tropical and sub-tropical (ZIKV, DENV, YFV, WNV) and non-tropical (WNV) areas of the world [24]. Indeed, around 100 million people get symptomatic DENV infection each year, resulting in hundreds of thousands of severe cases and about 10 000 deaths in tropical and sub-tropical countries [25].

Picornaviruses are small non-enveloped RNA viruses responsible for a very wide variety of diseases including the common cold which is caused by rhinoviruses. However, picarnoviruses are also responsible for countless devastating epidemics, such as poliomyelitis caused by polioviruses, and hand, foot and mouth disease

commonly caused by coxsackievirus A16 or enterovirus 71 (EV71) [26,27].

Hepatitis E Virus (HEV) is a positive-sense single-stranded RNA virus member of the *Hepeviridae* family that represents a major cause of acute hepatitis in developing countries, but also in Europe and America [28].

Influenza A viruses (IAV) are negative-sense single-stranded RNA viruses that infect approximately 3–5 million people and kill up to 650 000 people each year [29].

Coronaviruses represent a large family of RNA viruses that usually cause mild respiratory tract infections in animals and humans. However, three new coronaviruses that cause more serious, even lethal, infections have appeared in the last two decades: severe acute respiratory syndrome (SARS) caused by SARS-CoV in 2002, Middle East respiratory syndrome (MERS) caused by MERS-CoV, and COVID-19 caused by SARS-CoV-2. The current absence of an effective treatment for coronavirus infections poses a great public health problem and highlights the urgent need to develop efficient treatment for these diseases.

2. Antiviral activities of flavaglines mediated by eIF4A

2.1. The eukaryotic initiation factor 4A (eIF4A)

Protein synthesis is a complex process tightly regulated by several proteins including eukaryotic initiation factor 4F (eIF4F), a heterotrimeric complex required for ribosome recruitment to capped mRNAs (Fig. 2). The eIF4F complex is composed of the helicase eIF4A, the cap-binding subunit eIF4E and the scaffold protein eIF4G that recruits the 40S ribosomal subunit to mRNA. The helicase eIF4A unwinds a small number of cellular messenger RNAs (mRNAs), for instance those that harbor guanine-rich motifs forming G-quadruplexes in their 5′-untranslated region (5′-UTR) to facilitate binding of the 43S preinitiation complex [30,31]. Importantly, most of these RNAs code for proteins involved in the etiology of cancers, explaining why eIF4A inhibitors exhibit potent anticancer effects without major toxicity to the organism. Flavaglines are the most characterized and potent inhibitors of eIF4A. Their mode action was exemplified with rocaglamide by Iwasaki, Ito, Ingolia and coll [32]. Rocaglamide binds to a bimolecular cavity that is formed between eIF4A and a purine-rich RNA. Uniquely, the binding takes place only following an RNA-induced change in the structure of eIF4A. The stable eIF4A-rocaglamide-RNA complexes block scanning ribosomes and consequently repress translation from the targeted mRNAs. In addition, since eIF4A is trapped to mRNAs, it is no longer available to be included in the eIF4F complex, thereby inhibiting eIF4F-dependent mRNA translation and preventing the recycling of eIF4A. As a consequence, eIF4A is no longer available for other mRNAs.

Recently, a synthetic flavagline developed by the eFFECTOR Therapeutics company, Zotatifin (also called eFT226, **4**, Fig. 1) has entered a phase 1/2 clinical trial against advanced solid tumors refractory or intolerant to standard treatments [19]. While it was shown to inhibit eIF4A, its putative effect on PHB signaling has not yet been disclosed. A first description of the structure-activity relationships of flavaglines for the inhibition of eIF4A was disclosed in 2012 and 2014 [33,34]. This model was more recently refined by Porco, Pelletier and collaborators [35–37] and also by eFFECTOR scientists [20].

2.2. Flavaglines as antiviral eIF4A inhibitors

Many viral mRNAs contain highly structured 5′-UTRs, suggesting that eIF4A inhibitors may block viral replication [21]. Indeed, Grünweller and collaborators found that silvestrol, at low nanomolar concentrations that are not toxic to cells, blocks viral mRNA

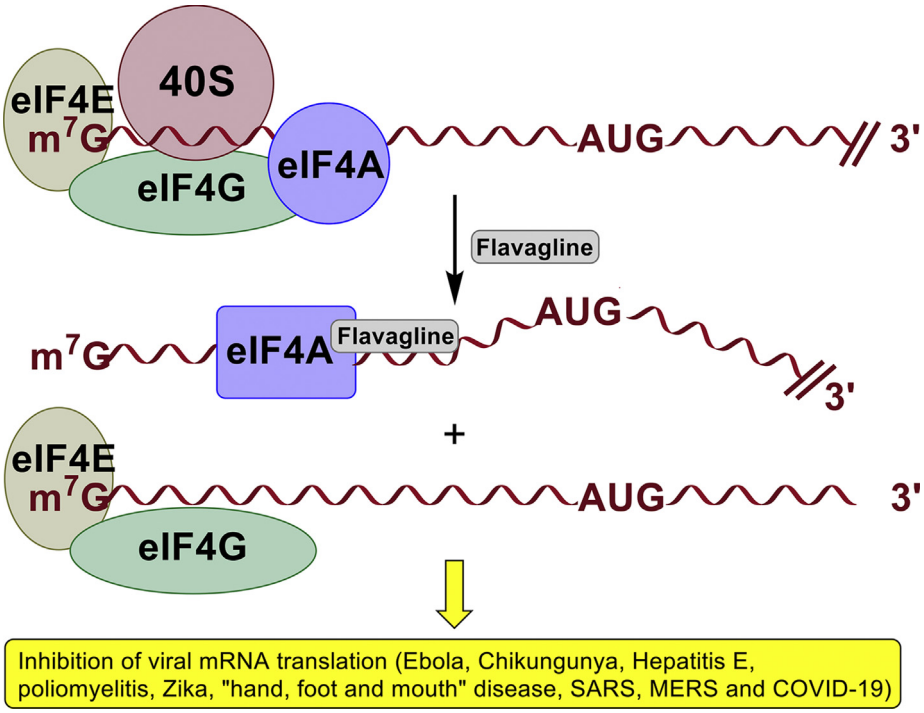

Fig. 2. Structure and role in viral translation of the eIF4F complex. eIF4F includes the helicase eIF4A that unwinds the highly structured 5′ untranslated region (5′-UTR) sequence of some viral RNAs, the cap-binding protein eIF4E, and the scaffold protein eIF4G. Flavaglines stabilize the interaction between eIF4A and the 5′UTR by altering the conformation of both eIF4A and the mRNA. As a consequence, eIF4A recycling is blocked, which leads to an inhibition of cap-dependent translation. AUG, translation initiation codon. 40S, small ribosome subunit, m^7G, 7-methylguanosine located at the 5′ end of the mRNA to which eIF4E binds.

translation and viral replication of Ebola virus and MERS-CoV in cells [6,7]. Silvestrol also blocked the replication of poliovirus type 1, but at higher concentrations with an EC_{50} value of 20 nM [7].

Schnierle and collaborators showed that silvestrol inhibits the production of viral proteins and the replication of CHIKV in infected cells at low nanomolar concentrations [8]. Importantly, silvestrol inhibited the production of the viral nsP2 protein that inhibits STAT1 to evade the innate immune system.

Hepatitis E virus (HEV) has a short 5′-UTR without a complex secondary RNA structure, but it still requires eIF4A for its replication [38]. Accordingly, Hildt and collaborators showed that silvestrol induced a significant reduction in viral particle release and viral protein biosynthesis in infected cells at low nanomolar concentrations [9]. Independently, and at the same time, Steinmann and collaborators also found that silvestrol inhibits the replication of many subgenomic replicons in an additive manner with the clinically used antiviral drug ribavirin [10]. This antiviral activity was also manifested *in vivo*. Indeed, silvestrol (0.3 mg/kg ip.) rapidly and significantly lowered the amount of HEV RNA in the feces of humanized mice, while no effect was observed in control mice. At this stage, this is a unique study that reports an antiviral effect *in vivo* of a flavagline due to an inhibition of eIF4A.

Hildt and collaborators showed that silvestrol inhibits eiF4A dependent Zika virus translation of two strains originating from French Polynesia and Uganda [11]. Silvestrol strongly reduced viral replication after 48 h and 72 h at non-toxic concentrations in primary human hepatocytes.

Influenza A virus (IAV) hijacks the host protein synthesis machinery to express its proteins and prevents this machinery from being blocked by cytoplasmic stress granule formation thanks to the viral nonstructural protein 1 (NS1) [39]. Stress granules are composed of mRNAs, translation initiation complexes and other RNA-binding proteins that can redirect translation following a stress. They can be induced by eIF4A inhibitors such as flavaglines [40]. McCormick and collaborators showed that silvestrol induces the formation of stress granules in several cell lines leading to an inhibition of viral protein accumulation and genome replication [12].

Grünweller and collaborators showed that 10 nM silvestrol significantly inhibits the translation of mRNAs harboring 5′-UTRs derived from the human coronavirus HCoV-229E associated with common cold symptoms and the highly pathogenic MERS-CoV [7]. Silvestrol diminished the viral titer of these two viruses in human fetal lung fibroblast (MRC-5) cells, with EC_{50} values of 1.3 nM and 3 nM respectively (EC_{90}: 27 an 12 nM). The antiviral effect of silvestrol was also found in peripheral blood mononuclear cells (PBMCs) with similar EC_{50} values. At 100 nM, silvestrol abolished the production of double-stranded RNA (dsRNA) and the HCoV-229E nsp8 protein in MRC-5 cells.

Recently, this team compared for the first time the antiviral effects of silvestrol with another flavagline known to inhibit eIF4A, in this case CR-31-B (**5**) [13]. Both compounds were found to display potent *in vitro* antiviral activities at similar non-cytotoxic concentration in the low nanomolar range against HCoV-229E, MERS-CoV, ZIKV, Lassa virus and Crimean-Congo hemorrhagic fever virus.

3. Antiviral activities of flavaglines mediated by prohibitins

3.1. Prohibitin signaling

Prohibitins-1 and -2 (PHB1/2) are evolutionary conserved scaffold proteins that control a myriad of signaling pathways [41]. The multiple functions of PHBs are regulated not only by phosphorylation at different positions by Akt, Cam kinase IV, Aurora A, protein kinase C (PKC), Lyn and insulin receptor, but also by *N*-myristoylation, palmitoylation, tyrosine nitrosylation and sulfatation, transamidation, arginine deamination and *O*-GlcNAc modifications. These post-translational modifications position PHBs in various cellular compartments and also regulate the interaction with their protein partners. PHBs are found in mitochondria, the endoplasmic reticulum, peroxisomes, the cytosol, the nucleus and the plasma membrane [42]. In the plasma membrane, PHBs are involved in cell-cell communication, the immune response, the activation of signaling kinases such as C-RAF or IKK, and also in the viral entry of DENV 2, hepatitis C virus (HCV), CHIKV and EV71.

3.2. Flavaglines as antiviral PHB ligands

In contrast to the role of eIF4A in viral replication [19], the implication of PHBs in viral replication has not yet been reviewed. Several families of small molecules targeting PHBs, including flavaglines, have been shown to display promising activities in some animal models of cancers, osteoporosis, inflammation, cardiac and neurodegenerative diseases [41], and also some viral infections, notably for inhibiting viral entry.

Duncan Smith and collaborators were the first ones, in 2010, to show that a virus, in this case, DENV 2, interacts with PHBs to enter into cells (Fig. 3) [43]. DENV has four serotypes (DENV 1–4) that are transmitted to humans by *Aedes aegypti* and *A. albopictus* mosquitoes [44]. Each of these four serotypes can induce dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Using a combination of separation methodologies, virus overlay protein binding assays and mass spectrometry, they identified PHBs as the first DENV receptor in *Aedes* mosquitoes. Next, the DENV 2 envelope (E) protein was shown to be coimmunoprecipitated and colocalized with PHB1. Recently, using similar approaches, Desai and collaborators showed that DENV 3 also interacts with both PHB1 and PHB2 to enter into neuronal, astroglial and microglial cells [45].

Smith and collaborators also identified PHB1 as the first CHIKV receptor in mammalian cells [46]. Using a combination of different techniques, they demonstrated that PHB1 (but not PHB2) interacts with the CHIKV E2 protein to mediate viral entry into microglial cells. Considering that both DENV and CHIKV, which belong to very different families of RNA viruses use both PHBs as a receptor, it may be possible that PHBs also act as receptors for other human viruses.

Thereafter this team found that two synthetic flavaglines, FL3 (**6**, Fig. 1) and FL23 (**7**), and another PHB ligand structurally unrelated to flavaglines, were all able to inhibit CHIKV infection in mammalian cells and reduce viral production when cells were treated before infection [14]. Pretreatment of cells for only 15 min prior to infection followed by washing out of the compound resulted in significant inhibition of entry and as a consequence virus production, ruling out an involvement of eIF4 in these specific effects. As discussed, silverstol inhibits viral translation [8], indicating that the effects of flavaglines could be dual. On one hand they could inhibit PHB-dependent entry of CHIKV into microglial cells, and on the other hand they could block viral mRNA translation.

Wang and collaborators found that PHBs in lipid rafts interact with viral glycoprotein E2 to promote the entry of chronic hepatitis C virus (HCV) into hepatocytes at a post-binding step through the activation of the kinase C-RAF [15]. Two flavaglines, rocaglamide and aglaroxin C (**1** and **3**, Fig. 1) were found to prevent the localization of PHBs at the cell surface, and consequently to block C-RAF activation and to reduce HCV infection with an EC_{50} of 4 and 0.04 nM (incubation of 48 h in Huh7.5.1 cells) respectively. Thereafter Porco and collaborators synthesized aglaroxin C analogues and showed that two of them, CMLD012043 (**8**) and CMLD012044 (**9**), showed 3-fold greater inhibition of HCV infection in comparison to aglaroxin C and also with very low cytotoxicity [16].

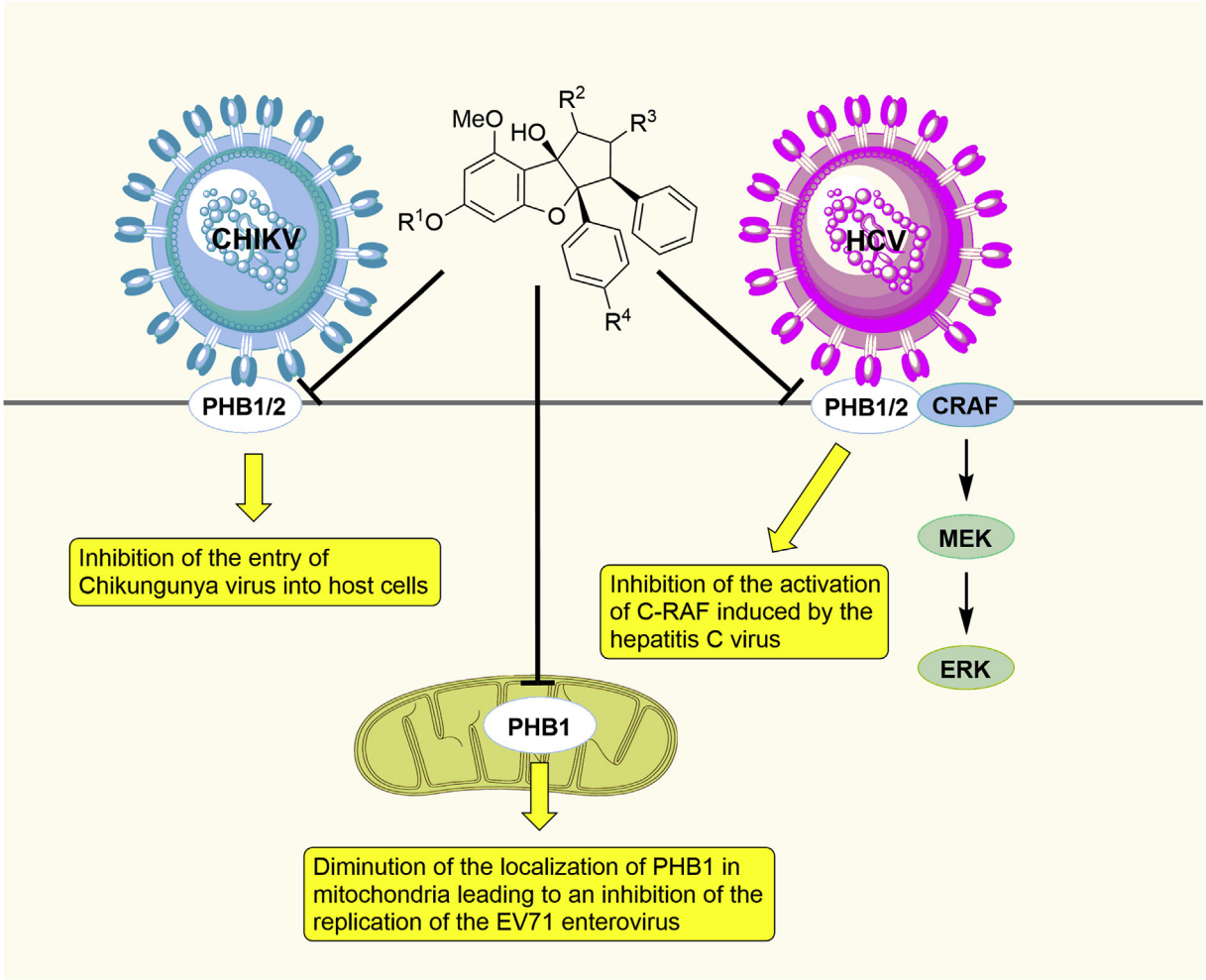

Fig. 3. Antiviral effects of flavaglines mediated by PHBs.

These compounds did not inhibit viral RNA replication or mRNA translation, confirming that the anti-HCV activity of these compounds is mediated through an effect on PHBs and not on eIF4A. Importantly, these two compounds also significantly inhibited the infectivity of DENV and CHIKV, both of which also use PHBs as entry factors.

Enterovirus 71 (EV71), which causes hand, foot and mouth disease, may result in neurological complications in young children. Alonso and collaborators found that EV71 uses cell surface-expressed PHB1 to facilitate its entry into neuronal cells specifically [17]. In addition, mitochondrial membrane-bound PHB1 was shown to facilitate viral replication through association with the replication complex. In line with these findings, rocaglamide was found to reduce the virus load in EV71-infected neuronal cells, due to diminution of the amount of mitochondria-associated PHB, and not through an inhibition of the C-RAF/MEK/ERK pathway. *In vivo*, rocaglamide extended the life of EV71-infected mice and lowered virus loads in the spinal cord and brain, but not in the limb muscles, indicating that flavaglines hold some potential to alleviate the neurological complications of hand, foot and mouth disease in children.

Considering that DENV, CHIKV, EV71 and HCV which belong to very different families of RNA viruses use PHBs as a receptor, it is likely that other viruses also interact with PHBs to infect cells.

4. Flavaglines as drug candidates against COVID-19

4.1. Interaction of the nonstructural protein nsp2 of SARS-CoV to prohibitins and putative implication of nsp2 in the enhanced contagiousness of SARS-CoV-2

The genome of SARS-CoV-2 has about 14 open-reading frames (ORFs) that encode the four structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N), in addition to sixteen nonstructural proteins (nsps) involved in the replication-transcription complex (RTC) [47]. Some ORFs also encode some very poorly characterized accessory proteins with no obvious effect in viral replication or pathogenicity. Indeed, Baric and collaborators showed that the systematic deletion of these accessory proteins does not dramatically alter the replication of SARS-CoV *in vitro* and in a murine model of SARS [48].

At an early stage of virus replication coronaviruses induce the formation of double-membrane vesicles (DMVs) in host cells, which serve as scaffolds for the RTCs and to protect newly synthesized viral RNA (Fig. 4) [49,50].

Buchmeier and collaborators discovered that PHB1 and PHB2 interact with nsp2 of SARS-CoV probably to divert PHB signaling and promote virus replication or to evade the innate immune system [51]. This protein is located in the cytoplasmic side of the DMVs [52]. Although the function of nsp2 remains unknown, nsp2

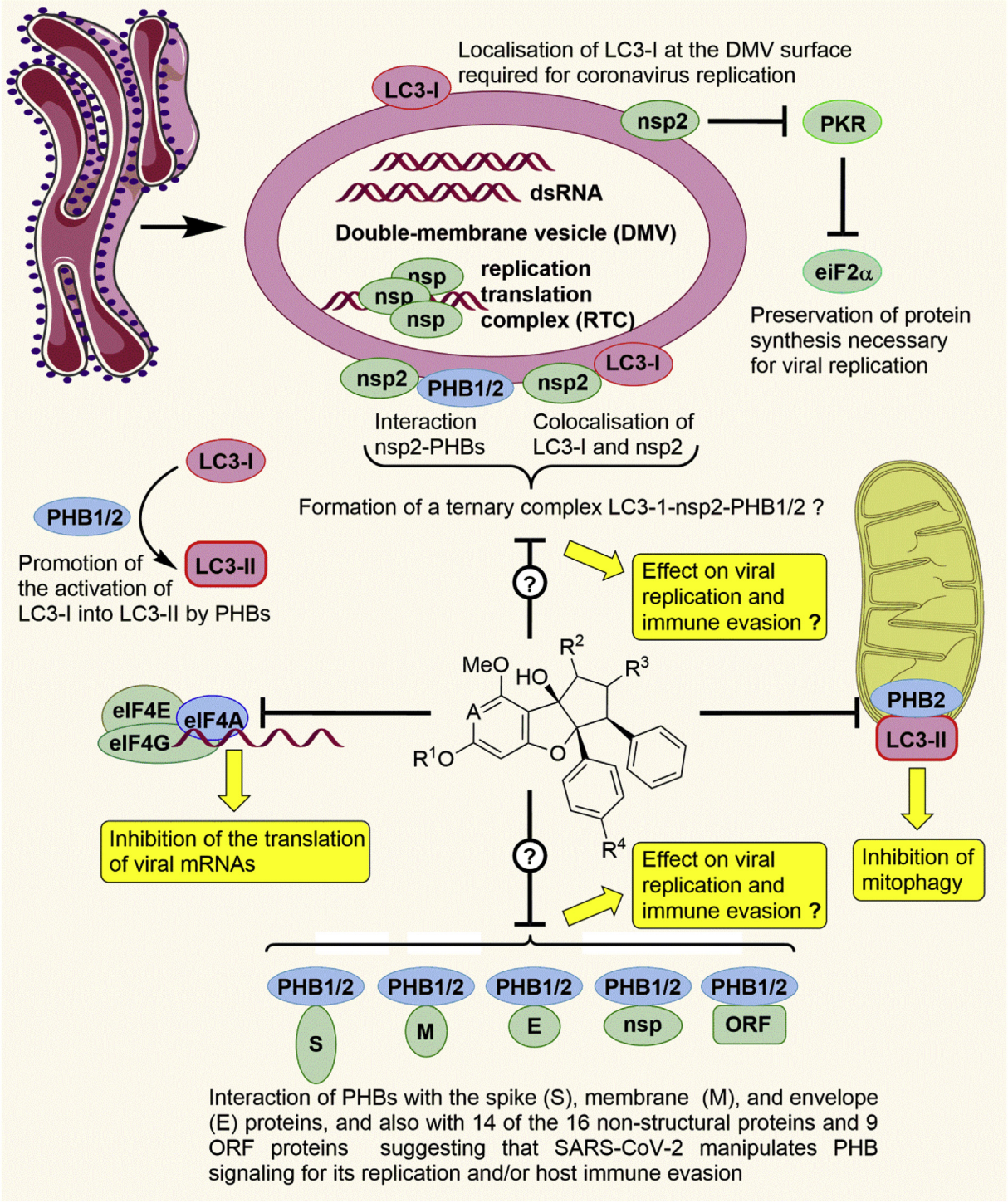

Fig. 4. Putative effects of flavaglines on SARS-Cov2.

is not necessary for replication of SARS-CoV in cell culture and may therefore be involved in the inhibition of the host innate immune response. Indeed, Liu and collaborators found that nsp2 of another coronavirus (infectious bronchitis virus) inhibits protein kinase R (PKR) [53]. PKR is a double-stranded-RNA-dependent kinase that phosphorylates eIF2α to shut-down translation [54]. Whether SARS-CoV-2 also uses nsp2 to preserve protein synthesis and, meanwhile, enhance viral replication, has not been confirmed yet.

A recent analysis of SARS-CoV-2 mutations caused by selective pressure combined with structural modeling indicates that mutations falling in the endosome-associated-protein-like domain of nsp2 stabilize this domain and enhance the contagious character of SARS-CoV-2 [55]. Thus, this study suggests that manipulating the function of nsp2 may represent a therapeutic option to treat COVID-19.

4.2. Involvement of LC3 in coronavirus replication

The microtubule associated protein 1B light chain 3 (LC3) is an important autophagy marker regulated by PHBs, that interacts with PHB2 and is manipulated by coronaviruses to escape antiviral innate immunity. It is thus tempting to hypothesize that coronaviruses control LC3 via PHBs. Indeed, a wide variety of viruses hijack LC3 or other components of the autophagy machinery for their own replication and to escape autophagic degradation [56,57]. LC3-I is a cytosolic protein that, upon autophagy induction, is cleaved and conjugated to phosphatidylethanolamine to form the active, lipidated form LC3-II. LC3-II is then recruited to autophagosomal membranes to promote various forms of autophagy. LC3-II interacts in particular with mitochondrial PHB2 to trigger mitophagy [58]. Recently, flavaglines have been shown to inhibit mitophagy, and a different class of PHB ligands was found to promote the conversion of LC3-I into LC3-II [59,60], suggesting that PHBs regulate the activity of LC3 in different contexts.

LC3-I is also found at the surface of EDEMosomes that transport unfolded proteins from the ER to lysosomes [61]. Reggiori and colleagues showed that coronaviruses misdirect the machinery of EDEMosome formation for the generation of double-membrane vesicles (DMVs) [62]. DMVs are coated with non-lipidated LC3-I that allow them to hijack intracellular membranes for viral replication and escape autophagy, which often mediates the lysosomal degradation of viral elements [62]. Depletion of LC3 by specific RNA interference blocked the formation of double-membrane vesicles, and protected cells from mouse hepatitis virus (*Murine coronavirus*) infection [62]. Back transfection with a plasmid-expressing HA-tagged LC3 restored the infection, confirming that LC3-I is essential to coronavirus replication.

Interestingly, LC3-I colocalizes with nsp2 at the cytosolic side of DMVs of coronaviruses [62]. Considering that both LC3and nsp2 interact with PHBs, one can speculate that PHBs, LC3-I and nsp2 are engaged in a joint complex.

4.3. Interaction of SARS-CoV-2 proteins with prohibitins and eIF4A, and discovery of the strong in vitro antiviral activity of zotatifin

Recently, Krogan and collaborators identified host proteins that physically interact with each protein of SARS-CoV-2 [18]. Surprisingly, they found that most of these viral proteins interact with both PHB1 and PHB2. The viral proteins that interact with PHBs are the following: three of the four structural proteins (spike (S), membrane (M), and envelope (E) proteins,) and 14 of the 16 non-structural proteins (nsp1 and nsp2 (papain-like protease), nsp4, nsp5 (3C-like protease), nsp6, nsp7, nsp8, nsp9, nsp10, nsp11and nsp12 (RNA-dependent RNA polymerase), nsp13 (helicase), nsp14 (3′-to-5′ exoribonuclease), and nsp15 (mRNA cap-1 methyltransferase) and nine accessory proteins with unknown functions (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c and ORF10 proteins).

These data strongly suggest that SARS-CoV-2 manipulates PHB signaling for its replication and/or host immune evasion. Coronavirus accessory proteins locate to many different cellular compartments, as do PHBs, and this may therefore be not entirely coincidental. In addition PHBs have been shown to directly interact with DNA and long noncoding RNAs [42,63–65], raising the possibility that they may also interact with viral RNAs.

Importantly, these authors identified 66 human proteins targeted by 29 FDA-approved drugs, 12 drugs in clinical trials and 28 preclinical compounds. The screening of these compounds revealed 2 families of drugs with extremely promising antiviral activities: the modulators of Sigma1 and Sigma2 receptors and some inhibitors of translation. This latter observation is not surprising, considering the established requirement of eIF4F for the translation of coronaviruses mRNAs. Zotatifin (**4**, Fig. 1) displayed an antiviral activity with a IC_{90} of 37 nM (150 times lower than the IC_{90} of hydroxychloroquine), which confirms the potential of flavaglines to treat Covid-19.

5. Conclusion

Although rare, flavaglines are not the only class of natural products to act on two very different families of proteins [66]. By modulating the activity of PHBs and eIF4A, flavaglines display a wide therapeutic potential, in particular against devastating viral epidemics, including Ebola, dengue, chikungunya and COVID-19. By targeting host proteins these compounds may overcome the problem of resistance that is likely to occur with RNA viruses, which have a high mutation rate. In addition to viruses, PHBs also interact with a wide variety of infectious agents diseases, such as *Salmonella typhi*, the causative agent of typhoid fever [67]. Whether flavaglines could also be useful to eradicate these pathogens is also worthwhile to be explored.

In addition, a large part of the world's population does not have access to modern medicine and relies on traditional medicine. In Southeast Asia, India, South China, Indonesia, Cambodia, Vietnam and Thailand, plants of the genus *Aglaia* synthesizing flavaglines are commonly used for their therapeutic properties. We can therefore wonder whether these plants could not also be effective as herbal therapies against emerging diseases such as COVID-19 by a population that cannot get access to expensive drugs.

Almost 40 years after the first discovery of a natural flavagline in 1982, a synthetic one zotatifin, developed by eFFECTOR, has reached phase 1/2 clinical trial in cancer patients. This company is now exploring with members of the biopharmaceutical and scientific communities, NIAID and funding sources as to how to explore the potential of zotatifin against COVID-19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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