

## Different Aspects of Emetine's Capabilities as a Highly Potent SARS-CoV-2 Inhibitor against COVID-19

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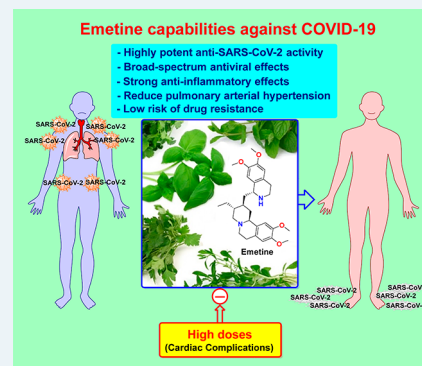
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**ABSTRACT:** In the global movement to find the appropriate agents to fight the coronavirus disease of 2019 (COVID-19), emetine is one of the strongest anti-SARS-CoV-2 compounds with sub-micromolar  $EC_{50}$  values, identified in several studies and high-throughput screening efforts. The reported anti-SARS-CoV-2 mechanisms indicate the effect of this compound on both virus-based and host-based targets. In addition to having excellent antiviral effects, emetine can relieve COVID-19 patients by reducing inflammation through inhibitory activity against  $NF-\kappa B$  by the mechanism of  $I\kappa B\alpha$  phosphorylation inhibition; it can also limit the lipopolysaccharide-induced expression of pro-inflammatory cytokines  $TNF\alpha$ ,  $IL-1\beta$ , and  $IL-6$ . Emetine also can well reduce pulmonary arterial hypertension as an important COVID-19 complication by modulating a variety of cellular processes such as the Rho-kinase/CyPA/Bsg signaling pathway. The therapeutic value of emetine for combating COVID-19 was highlighted when *in vivo* pharmacokinetic studies showed that the concentration of this compound in the lungs increases significantly higher than the  $EC_{50}$  of the drug. Despite its valuable therapeutic effects, emetine has some cardiotoxic effects that limit its use in high doses. However, high therapeutic capabilities make emetine a valuable lead compound that can be used for the design and development of less toxic anti-COVID-19 agents in the future. This Review provides a collection of information on the capabilities of emetine and its potential for the treatment of COVID-19, along with structural analysis which could be used for further research in the future.

**KEYWORDS:** COVID-19, SARS-CoV-2, RdRp, emetine, pulmonary arterial hypertension



Emetine ( $C_{29}H_{40}N_2O_4$ , molecular weight 480.6 g/mol), with the IUPAC name of (2*S*,3*R*,11*bS*)-2-(((*R*)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline, is a well-known isoquinoline-based alkaloid that is mainly extracted from the root of medicinal plants of the Rubiaceae, Alangiaceae, and Icacinaceae families, such as *Carapichea ipecacuanha* and *Psychotria ipecacuanha*.<sup>1</sup> Structurally, emetine is significantly similar to the well-known antiviral alkaloids palmatine and berberine,<sup>2</sup> but it is more flexible than them. As shown in Figure 1, the greater flexibility of emetine is due to the presence of a methylene group ( $-\text{CH}_2-$ ) between the C and D rings, while palmatine and berberine are composed of four interconnected rings, which cause these structures to become dense and rigid.

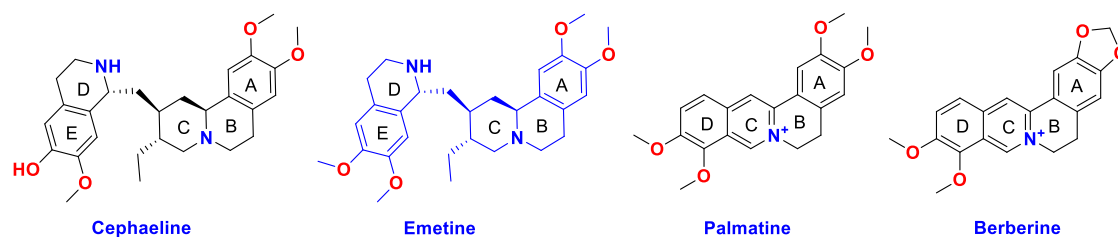
Today, naturally occurring compounds are receiving increasing attention for the treatment of diseases (such as COVID-19) because they offer a diversity of biological activities and low toxicity.<sup>3,4</sup> In structural evaluations to find anti-COVID-19 agents, quinoline and isoquinoline scaffolds are among the most important platforms that have been repeatedly observed in the structure of potent SARS-CoV-2 inhibitors.<sup>5,6</sup> Emetine, which itself has two isoquinoline-like moieties, is the main pharmacologically active alkaloid in ipecac root that was previously used in

traditional medicine and clinics as an expectorant, emetic, and anti-amoebic agent, and it has been approved by competent authorities such as the U.S. Food and Drug Administration (FDA) for clinical usages. In addition to the mentioned drug effects, studies reported some other important biological activities for this compound, such as inhibition of protein synthesis<sup>7,8</sup> and anti-cancer effects.<sup>9–11</sup> This compound also has excellent broad-spectrum antiviral effects against a wide range of RNA and DNA viruses at a non-cytotoxic concentration, without causing drug resistance.<sup>12</sup> Some independent investigations to find severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) inhibitors have identified emetine as one of the most promising compounds in the fight against the coronavirus disease of 2019 (COVID-19). The high potency of emetine in combating COVID-19 is due to it having diverse beneficial pharmacological activities such as anti-inflammatory and anti-

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**Figure 1.** Structural similarity of the emetine and its analogue cephaeline compared to the well-known antiviral alkaloids palmatine and berberine.

pulmonary arterial hypertensive properties, in addition to having highly potent anti-SARS-CoV-2 effects. In addition, having broad-spectrum antiviral effects makes this compound capable of fighting subsequent mutant strains derived from the primary wild-type virus. Despite its valuable therapeutic features, some complications such as cardiotoxicity make emetine unsuitable for some COVID-19 patients, especially those with underlying heart disease. Although this complication can be managed by prescribing low doses as well as a short duration of use, it seems that the effective clinical use of this compound for the treatment of COVID-19 requires higher doses. However, emetine can be used by medicinal chemists and other scientists as a valuable lead compound to achieve less toxic anti-COVID-19 agents. In addition, emetine has many structural analogues whose therapeutic profiles have not yet been investigated for the inhibition of SARS-CoV-2 and the treatment of COVID-19.

Some recent review studies have briefly cited emetine as an important anti-SARS-CoV-2 compound.<sup>13–15</sup> This Review provides a wealth of information on emetine's capabilities and its potential for the treatment of COVID-19, which could be useful for a wide range of researchers pursuing COVID-19-related topics, including clinical practitioners and academic researchers, especially pharmacologists and medicinal chemists. Information on emetine's capabilities against SARS-CoV-2 was collected from credible Internet databases such as Elsevier, PubMed, Web of Science, Wiley Online Library, Europe PMC, etc. All studies published up to January 2022 are included in this Review, but the focus is strongly on studies conducted from the start of the COVID-19 pandemic onward.

## 1. BROAD-SPECTRUM ANTIVIRAL ACTIVITY

Valuable therapeutic effects of emetine and related alkaloids such as cephaeline ( $C_{28}H_{38}N_2O_4$ , molecular weight 466.6 g/mol) in the treatment of viral diseases have been reported for decades. In recent years, many studies have reported the potent antiviral effects of emetine against a broad spectrum of human viruses, such as Dengue viruses,<sup>16</sup> cytomegaloviruses,<sup>17</sup> human immunodeficiency virus type 1 (HIV-1),<sup>18</sup> Hantaan orthohantavirus (HTNV), Andes orthohantavirus (ANDV), Ebola (EBOV), Lassa,<sup>19</sup> rabies (RABV),<sup>20</sup> herpes simplex viruses (HSVs), echovirus-1, human metapneumovirus (HMPV), Rift Valley fever virus (RVFV),<sup>21</sup> etc. Emetine can also potently inhibit the replication of animal viruses such as buffalopoxvirus (BPXV), bovine herpesvirus-1 (BHV-1), peste des petits ruminants virus (PPRV), and Newcastle disease virus (NDV), without producing drug-resistant variants.<sup>12</sup> The *in vitro* antiviral half-maximal effective concentration ( $EC_{50}$ ) values measured for emetine are mostly in the nanomolar range, indicating the high potency of this special compound in inhibiting the replication of viruses. For example, in a recent study, Qi Tang et al. reported that emetine can effectively inhibit enterovirus A71 (EV-A71) in RD cell culture with  $EC_{50}$  = 49 nM

and a 50% cytotoxicity concentration ( $CC_{50}$ ) of 10  $\mu$ M. These researchers also reported that emetine exhibits efficient antiviral activities against other human enteroviruses, including enterovirus D68 ( $EC_{50}$  = 19 nM), echovirus-6 ( $EC_{50}$  = 45 nM), coxsackievirus A16 ( $EC_{50}$  = 83 nM), and coxsackie B ( $EC_{50}$  = 51 nM).<sup>22</sup>

Some research has shown that the antiviral effects of cephaeline (a close structural analogue of emetine having a hydroxyl group at position 6' in the E ring, Figure 1) are also very strong and are comparable to those of emetine. A study conducted in 2018 by Shu Yang et al. showed that both emetine and cephaeline could well suppress Zika (ZIKV) and Ebola viruses *in vitro* and *in vivo*, through molecular mechanisms inhibiting viral replication and disrupting virus entry.<sup>23</sup> The antiviral activity of emetine against ZIKV and EBOV was also confirmed in some other independent studies.<sup>24,25</sup>

Emetine also has strong inhibitory effects against influenza viruses. Because both SARS-CoV-2 and influenza viruses have similar transmission characteristics and common clinical manifestations,<sup>26</sup> and since emetine has reported potent inhibitory effects against both viruses, the usage of emetine can be considered in co-infection situations or situations where it is not possible to diagnose between these infections. In a 2019 study, Petter I. Andersen and co-workers showed that emetine effectively inhibits influenza A virus-mediated green fluorescent protein (GFP) expression *in vitro* in retinal pigment epithelium (RPE) cells, without significant cytotoxicity.<sup>21</sup>

## 2. STRONG ANTI-SARS-CoV-2 EFFECTS

In the pre-COVID-19 period, some studies showed strong antiviral effects of emetine against different strains of coronaviruses. In a high-throughput screening (HTS) effort by Julie Dyal et al., a library of 290 selected FDA-approved compounds was screened for anti-MERS-CoV (Middle East respiratory syndrome coronavirus) and anti-SARS-CoV (severe acute respiratory syndrome coronavirus) activity using virus-infected Vero-E6 cells. Results of evaluations showed that emetine dihydrochloride hydrate has remarkable activity against both MERS-CoV and SARS-CoV, with  $EC_{50}$  = 0.014 and 0.051  $\mu$ M, respectively.<sup>27</sup>

In another HTS study, Liang Shen et al. screened a collection of approximately 2000 drugs and bioactive compounds to find compounds effective against several coronaviruses: human coronavirus-OC43 (HCoV-OC43), human coronavirus-NL63 (HCoV-NL63), MERS-CoV, and mouse hepatitis virus strain A59 (MHV-A59). In this study, once again emetine was identified as one of the most active compounds, with excellent broad-spectrum inhibitory effects against the replication of all tested coronaviruses: HCoV-OC43,  $EC_{50}$  = 0.30  $\mu$ M,  $CC_{50}$  = 2.69  $\mu$ M; HCoV-NL63,  $EC_{50}$  = 1.43  $\mu$ M,  $CC_{50}$  = 3.63  $\mu$ M; MERS-CoV,  $EC_{50}$  = 0.34  $\mu$ M,  $CC_{50}$  = 3.08  $\mu$ M; and MHV-A59,  $EC_{50}$  = 0.12  $\mu$ M,  $CC_{50}$  = 3.51  $\mu$ M.<sup>28</sup>

**Table 1. Summarized Data on the Anti-coronavirus Activity of Emetine Considering the Mechanism of Action, EC<sub>50</sub>, CC<sub>50</sub>, SI, and Cell Lines Used**

virus type	anti-coronavirus activity	EC <sub>50</sub> or IC <sub>50</sub> (μM)	CC <sub>50</sub> (μM)	SI <sup>a</sup>	cell line	ref
SARS-CoV-2	• blocks SARS-CoV-2 entry in a dose-dependent manner	EC <sub>50</sub> = 0.007	1.96	280	Vero E6	31
	• inhibits SARS-CoV-2 replication by reduction in viral RNA copy	EC <sub>50</sub> = 0.46	56.46	122.7	Vero E6	29
	• inhibits SARS-CoV-2 cytopathicity	IC <sub>50</sub> = 0.52	1.13	2	Caco-2	32
	• inhibits interaction of viral mRNA with eIF4E	EC <sub>50</sub> = 0.000147	1.6038	10910.4	Vero E6	34
	• inhibits viral protein synthesis through interaction with the host ribosomes	EC <sub>50</sub> = 0.00771	2.170	281.5	Vero E6	35
	• inhibits SARS-CoV-2 RdRp activity	—	—	—	—	—
	• prevents the SARS-CoV-2 maturation from destroying viral core assembly	—	—	—	—	—
	—	IC <sub>50</sub> = 0.155	—	—	293T	36
	—	IC <sub>50</sub> = 0.273	—	—	293T	36
MERS-CoV	• reduces spike (S) protein expression	IC <sub>50</sub> = 0.08	>25	>312	Vero E6	33
	—	EC <sub>50</sub> = 0.014	—	—	Vero E6	27
	• inhibits MERS-CoV entry with EC <sub>50</sub> = 0.16 μM (using DPP4-expressing Huh7.5 cells)	EC <sub>50</sub> = 0.34	3.08	9.06	Vero E6	28
MHV-A59	—	EC <sub>50</sub> = 0.12	3.51	29.25	DBT	28
HCoV-OC43	—	EC <sub>50</sub> = 0.30	2.69	8.97	BHK-21	28
	• inhibits SARS-CoV-2 nucleocapsid protein expression	EC <sub>50</sub> = 0.21	>25	>238	HCT-8	38
HCoV-NL63	—	EC <sub>50</sub> = 1.43	3.63	2.54	LLC-MK2	28
FIP-CoV <sup>b</sup>	• inhibits SARS-CoV-2 proliferation, assayed by visualization of cytopathic effects on infected Fcwf-4 cells	EC <sub>50</sub> = 0.011	0.03	3	Fcwf-4	38

<sup>a</sup>FIP-CoV: feline infectious peritonitis coronavirus. <sup>b</sup>Selectivity index ratio: SI = CC<sub>50</sub>/IC<sub>50</sub>.

With the spread of COVID-19, some scientists went back to emetine in search of anti-SARS-CoV-2 agents and achieved promising results. Table 1 summarizes the inhibitory effects of emetine on various human coronaviruses, especially SARS-CoV-2. Some of these studies revealed that the *in vitro* antiviral effects of emetine against SARS-CoV-2, with EC<sub>50</sub> = 0.46 μM, were much stronger than those of some of the famous antiviral drugs used in clinical trials for the treatment of COVID-19, such as Remdesivir (EC<sub>50</sub> = 23.15 μM), Lopinavir (EC<sub>50</sub> = 26.63 μM), Homoharringtonine (EC<sub>50</sub> = 2.55 μM), Ribavirin (EC<sub>50</sub> > 500 μM), Galidesivir (EC<sub>50</sub> > 100 μM), Ritonavir (EC<sub>50</sub> > 100 μM), Oseltamivir carboxylate (EC<sub>50</sub> > 100 μM), Baloxivir acid (EC<sub>50</sub> > 100 μM), and Favipiravir (EC<sub>50</sub> > 100 μM). Because of the good synergistic effects between remdesivir and emetine, the researchers suggested that combination therapy with these drugs may offer better clinical benefits in combating COVID-19.<sup>29</sup>

The use of emetine for the treatment of COVID-19 seems more attractive when previous studies reported that the concentration of emetine in the lungs (as the main target organ of SARS-CoV-2) can be approximately 300 times higher than that in the bloodstream.<sup>30</sup> Recent *in vivo* pharmacokinetic studies also displayed that the concentration of this compound in the lung tissue was significantly enhanced 200-fold higher than the EC<sub>50</sub> of the drug and had over 12 h retention time.<sup>31</sup>

Other recent studies have been performed on the inhibitory effects of emetine against SARS-CoV-2 and have shown promising results. Here is a summary of the results of the most important studies.

In a recent study to find active compounds against SARS-CoV-2 cytopathicity, Bernhard Ellinger and co-workers performed a high-content screening on a library of 5632

compounds with special drug effects using microscopy methods in the human epithelial colorectal adenocarcinoma cell line (Caco-2). Among the all tested compounds, emetine as a reference compound was one of the few active compounds having promising anti-SARS-CoV-2 cytopathicity, with IC<sub>50</sub> = 0.52 ± 0.09 μM and CC<sub>50</sub> = 1.13 ± 0.5 μM.<sup>32</sup>

To potentially find anti-COVID-19 drugs, another new HTS was performed by Meehyun Ko et al., in which a collection of 5406 FDA-approved drugs and bioactive compounds were screened for anti-coronavirus activity against a South Korean MERS-CoV clinical isolate using Vero cells. In this study, once again the excellent anti-coronavirus (anti-MERS-CoV) activity of emetine dihydrochloride, as a previously identified anti-coronavirus hit, was confirmed with IC<sub>50</sub> = 0.08 μM, CC<sub>50</sub> > 25 μM, and a favorable therapeutic index ratio (CC<sub>50</sub>/IC<sub>50</sub>) > 312.5.<sup>33</sup>

The efficacy of low doses of emetine as a potential anti-SARS-CoV-2 virus therapy was recently investigated by Aoli Wang et al. The results of this study showed that emetine could effectively suppress SARS-CoV-2 replication in Vero cells, with EC<sub>50</sub> = 0.007 μM (30-fold more effective than Remdesivir, with EC<sub>50</sub> = 0.24 μM), CC<sub>50</sub> = 1.96 μM, and a desirable selectivity index (SI, CC<sub>50</sub>/EC<sub>50</sub>) of 280. Western blot analysis of nucleocapsid levels also showed that the level of SARS-CoV-2-specific nucleocapsid was significantly decreased by emetine (EC<sub>50</sub> = 0.019 μM) in a dose-dependent manner, indicating the effect of this compound on the blockade of SARS-CoV-2 entry in Vero cells. Results from other complementary evaluations also showed that emetine has a significant anti-inflammatory potential, allowing it to significantly decrease the lipopolysaccharide (LPS)-induced interleukin-6 (IL-6) protein level and

moderately decrease the tumor necrosis factor alpha (TNF $\alpha$ ) protein level in the M1 macrophages derived from THP-1 cells.<sup>31</sup>

Ram Kumar et al. also evaluated the *in vitro* anti-SARS-CoV-2 activity of emetine and declared that this compound can potentially suppress SARS-CoV-2 replication in Vero cells ( $EC_{50}$  = 0.147 nM,  $CC_{50}$  = 1603.8 nM, and  $SI$  = 10910.4) by disruption of the SARS-CoV-2 mRNA binding with eukaryotic translation initiation factor 4E (eIF4E), a cell-specific protein used to initiate protein translation. It was also shown that emetine can decrease viral RNA and protein synthesis without affecting other stages of the SARS-CoV-2 life cycle. In addition, the mechanistic evaluations of this study suggested that SARS-CoV-2 modulates the ERK/MNK1/eIF4E signaling pathway for replication in the host cells.<sup>34</sup>

For better analysis of SARS-CoV-2 RNA synthesis and screening of appropriate inhibitors, recently Yuewen Luo et al. engineered an interesting SARS-CoV-2 replicon system consisting of four plasmids expressing the required fragments of SARS-CoV-2. To verify the validity, the researchers evaluated the system with emetine as a positive reference SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) inhibitor and some other drugs such as Remdesivir. In the evaluations of this study, the highly strong anti-SARS-CoV-2 effects of emetine were once again demonstrated in comparison with other commonly used anti-COVID-19 drugs (Table 2).<sup>36</sup>

**Table 2. Inhibitory Activity of Well-Known Anti-COVID-19 Drugs upon Replicon RNA Synthesis Compared to Emetine, Quantified by Detecting Luciferase Activity, and Assessed by the Newly Engineered SARS-CoV-2 Replicon System**

drug	IC <sub>50</sub> ( $\mu$ M)
Remdesivir	12.40
Lopinavir	6.79
Ritonavir	14.77
<b>Emetine</b>	<b>0.27</b>
Disulfiram	9.32

The high potential of emetine to fight SARS-CoV-2, as well as to alleviate some complications of COVID-19 (discussed below), has led some researchers to evaluate the effects of this drug for the treatment of COVID-19 patients. Recently, a clinical trial examined the effects of a low dose of emetine on patients with mild COVID-19 symptoms. The researchers reported that low doses of emetine in combination with conventional antiviral drugs (Emetine 3.6 mg per os, 3 times per day, for 10 days + Arbidol, 200 mg per os, 3 times per day) could improve clinical symptoms compared with the control group. They also suggested that moderate doses of emetine may have a better potential for treating and preventing COVID-19.<sup>39</sup>

### 3. MECHANISMS OF SARS-CoV-2 INHIBITION

Recent studies have well described the mechanism of infection and replication of the SARS-CoV-2 over the past 2 years.<sup>40–42</sup> Generally, SARS-CoV-2 replication involves several steps, starting with the identification of the host cell and attaching to it, and leading to virus assembly and exocytosis. Similar to SARS-CoV, the binding of SARS-CoV-2 to the host cells occurs also through an interaction with the host angiotensin-converting enzyme (ACE2).<sup>40,43,44</sup> In short, after the host cell and the SARS-CoV-2 approach each other, the virus binds to the ACE2 receptor, and then spike (S) glycoprotein is cleaved through

acid-dependent proteolytic cleavage by the host cell transmembrane serine protease 2 (TMPRSS2). After this stage, endocytosis occurs upon fusion of the viral and host cell membranes. Once the virus enters the host cell, it gradually releases its RNA genome in the cytoplasm to be provided to the host cell ribosomes for translation. By translating the viral genome, immature polyproteins pp1a and pp1ab are produced. Under the influence of protease enzymes of the virus (enzymes papain-like protease (PLpro) and main protease (3CLpro)), these polyproteins are transformed into non-structural proteins (NSP1–NSP16). The NSPs along with RNA-dependent RNA polymerase (RdRp, NSP12) as the central enzyme form the replication–transcriptase complex (RTC). This complex is responsible for the synthesis of the viral RNA genome, and RdRp inhibitors such as remdesivir inhibit viral RNA synthesis at this stage.<sup>45,46</sup> Finally, the structural proteins produced by the endoplasmic reticulum, NSPs, and replicated RNA are all assembled by the endoplasmic reticulum–golgi intermediate compartment (ERGIC) to produce the new SARS-CoV-2 virus. After this, exocytosis occurs and the new virus is released from the cell membrane. The RdRp functional complex, which is composed of NSP12 (a catalytic subunit), NSP7, and NSP8 (which can stimulate NSP12 polymerase activity), is a critical enzyme in the SARS-CoV-2 life cycle that mediates the transcription and replication of the RNA genome during the viral replication processes.<sup>47</sup> Since this enzyme is not similar to any other one in humans, so it can be considered a valuable drug target.<sup>46</sup>

Like inhibition of MERS-CoV and Ebola,<sup>48,49</sup> some studies suggests that remdesivir also exerts its anti-SARS-CoV-2 effects through inhibition of RdRp. In addition, recent studies have reported strong effects in inhibiting the RdRp of some viruses for both emetine and cephaline. Recently, Shu Yang et al. examined the inhibitory effect of emetine on Zika RNA-RdRp function to determine the antiviral mechanism of action. The results showed that both compounds strongly inhibited the virus-RdRp activity, with  $IC_{50}$  = 121 and 976 nM, respectively.<sup>23</sup> In addition to *in vitro* assessments, some computational studies have also identified emetine as one of the strongest compounds that can effectively interact with the active site of the SARS-CoV-2 RdRp.<sup>50,51</sup>

Recently, Peng-Xuan Ren and co-workers conducted a multi-targeted antiviral drug design strategy to identify SARS-CoV-2 inhibitors by considering potential antiviral targets, including host-based target ribosome (focus on –1 programmed ribosomal frameshifting region) and virus-based targets RdRp, viral RNA, and nucleocapsid (N) protein. Using this multi-targeted strategy, isoquinoline alkaloids lycorine, emetine, and cephaline were identified as potent anti-SARS-CoV-2 agents with inhibitory effects on viral protein synthesis (occurring through interaction with the host ribosome). In addition, it was shown that emetine can attenuate SARS-CoV-2 propagation, inhibit SARS-CoV-2 RdRp activity, and prevent the virus maturation. The researchers used surface plasmon resonance (SPR) to evaluate how emetine binds to SARS-CoV-2 RdRp and to investigate the binding ability of this compound with the RdRp (NSP-12) catalytic subunit. The results showed that both emetine and cephaline bind with NSP-12 with dissociation constant ( $K_D$ ) values of 25.7 and 19.6  $\mu$ M, respectively. It was also observed that these binding affinities increase sharply (about 10 times more) in the presence of RNA. The researchers also suggested that emetine may play a role in preventing SARS-CoV-2 from maturing by destroying the viral core assembly

through blocking the recognition of the viral genome N protein. The antiviral efficacy and cytotoxicity of these alkaloids were also assessed in this study, and the results showed that lycorine, emetine, and cephaeline have highly potent anti-SARS-CoV-2 activity, with  $IC_{50} = 0.439$ ,  $0.00771$ , and  $0.0123 \mu\text{M}$ , respectively.<sup>35</sup>

Recently, a study revealed some therapy targets and molecular mechanisms that are useful in better understanding the role of SARS-CoV-2 in the modulation of host cell processes by establishing a human cell-culture model for infection with SARS-CoV-2.<sup>37</sup> The results of this study showed that SARS-CoV-2 also modulates some central cellular pathways, such as host translation. Translation machine components translate at higher rates, so SARS-CoV-2 replication is sensitive to host-translation inhibition. In the past, the host-translation inhibition strategy has also been used to inhibit the proliferation of coronaviruses in some studies.<sup>28,52</sup> Using emetine as a well-known host-translation inhibitor in this study showed promising results in the inhibition of SARS-CoV-2 replication, with  $IC_{50} = 0.47 \mu\text{M}$  at non-toxic concentrations in human Caco-2 cells.<sup>37</sup>

In another study, pseudovirus entry assays performed by Liang Shen et al. showed that emetine can effectively block the MERS-CoV S-mediated entry.<sup>28</sup> Given the genetic similarity of MERS-CoV to SARS-CoV-2 and their identical methods of entering the cell, it is likely that emetine could prevent SARS-CoV-2 from entering the host cell by the same mechanism.

#### 4. ANTI-INFLAMMATORY EFFECTS

Sometimes the host's immune response, especially the inflammatory reactions that follow diseases, is more problematic than the diseases themselves. A century ago, emetine was used to treat patients during the Spanish flu pandemic. Based on the therapeutic response of patients with Spanish influenza, some evaluations suggest that the anti-inflammatory effects of emetine may have played a major role in the treatment of these patients.<sup>53</sup> Because the severe inflammatory immune response to SARS-CoV-2 infection is more damaging than viral self-infection, the anti-inflammatory feature of emetine can be useful in treating COVID-19 as it was in treating the Spanish flu. This important therapeutic effect of emetine has been considered and evaluated in some studies. In our previous study, we described the importance of regulating some signaling pathways such as nuclear factor kappa light chain enhancer of activated B-cells (NF- $\kappa$ B) in reducing hyper-inflammatory immune responses in COVID-19.<sup>54</sup> Previous studies indicated that inflammation-related disorders can disrupt and dysregulate the NF- $\kappa$ B signaling pathway.<sup>55,56</sup> Some previous studies indicated that emetine has potent inhibitory activity against the NF- $\kappa$ B signaling pathway. To find small molecules with NF- $\kappa$ B inhibitory activity, Susanne C. Miller et al. performed HTS on a chemical library from the U.S. National Institutes of Health (NIH)'s Chemical Genomics Center Pharmaceutical Collection (NPC) containing about 2800 bioactive compounds and clinically approved drugs, using an NF- $\kappa$ B-mediated  $\beta$ -lactamase reporter gene assay. The results of this study identified emetine as a potent NF- $\kappa$ B inhibitor with  $IC_{50} = 0.31 \mu\text{M}$ , by the mechanism of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha ( $I\kappa B\alpha$ ) phosphorylation inhibition.<sup>57</sup> In another study, by Vallabh Shah, a natural product library containing 480 compounds was screened for their capacity to inhibit the LPS-induced expression of TNF $\alpha$  in whole blood leukocytes, to inhibit NF- $\kappa$ B activation, and to limit the generation of pro-inflammatory signals. According to the

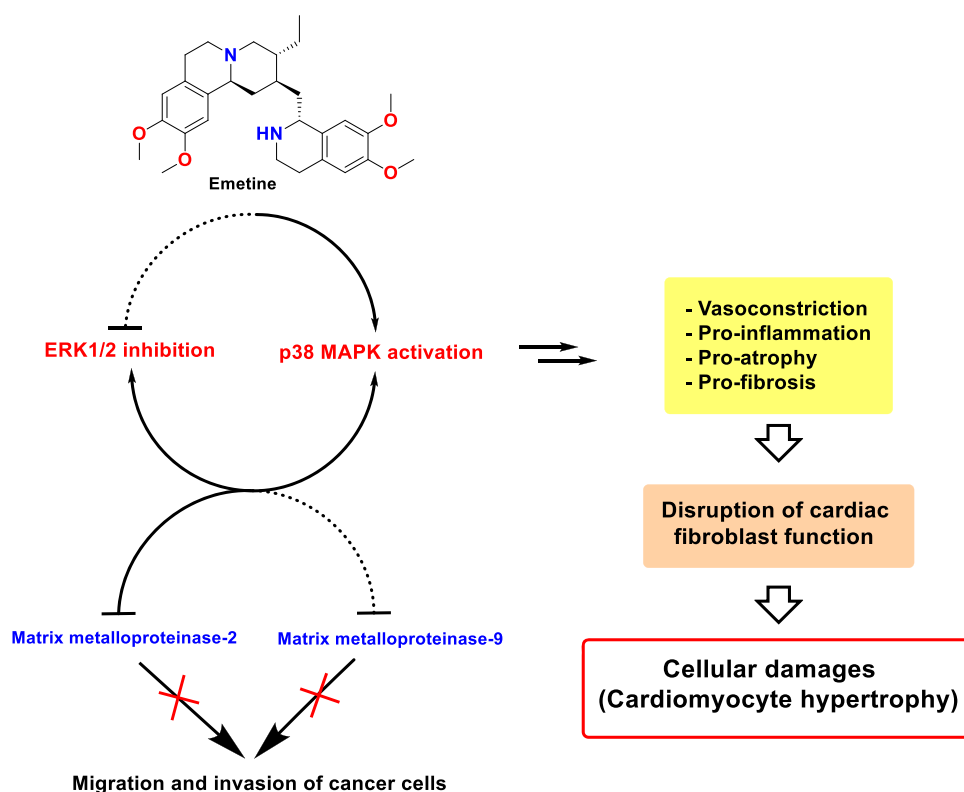
reported results, emetine showed highly potent and broad inhibitory effects on the LPS-induced expression of pro-inflammatory cytokines TNF $\alpha$  ( $IC_{50} = 0.3 \mu\text{M}$ ), interleukin-1 beta (IL-1 $\beta$ ) ( $IC_{50} = 0.3 \mu\text{M}$ ), and IL-6 ( $IC_{50} = 0.4 \mu\text{M}$ ) through an NF- $\kappa$ B-dependent mechanism.<sup>58</sup>

In a recent study, Ming-Cheng Lee claimed to have discovered a new role for NF- $\kappa$ B in the expression of ACE2 (as the major receptor for SARS-CoV-2 infection and negative regulator of the renin-angiotensin system) in human lung cells. In this study, ACE2 expression was assessed in multiple human lung cell lines in the presence of some NF- $\kappa$ B inhibitors such as emetine, using Western blotting and RT-qPCR techniques. The results showed that emetine alone could clearly reduce ACE2 mRNA and protein levels, but in the presence of zinc sulfate supplementation, emetine had more suppressive effects on ACE2 expression in H322M and Calu-3 cells.<sup>59</sup>

#### 5. THERAPEUTIC EFFECTS AGAINST PULMONARY ARTERIAL HYPERTENSION

Patients with COVID-19 who have underlying pulmonary arterial hypertension (PAH) are among the most at-risk COVID-19 patients.<sup>60–63</sup> The release of pro-inflammatory cytokines such as TNF $\alpha$ , IL-1 $\beta$ , and IL-6 in the pulmonary arteries of PAH patients leads to the production of reactive oxygen species (ROS) and ultimately increases oxidative stress.<sup>64</sup> Cyclophilin A (CyPA) is a multifunctional protein belonging to the immunophilin family that is upregulated in inflammatory-related conditions, such as oxidative stress.<sup>65</sup> This chaperone protein increases vascular oxidative stress and angiotensin II-induced aortic aneurysms, affecting the vascular system.<sup>66</sup> In a study, Kimio Satoh et al. reported that oxidative stress induces the release of extracellular CyPA from PAH-PASMCs in pulmonary hypertension. These conditions increase the secretion of cytokines/chemokines and growth factors from PAH-PASMCs by affecting CyPA on its receptor basigin, increasing the migration of inflammatory cells and the proliferation of PASMCs. In fact, basigin promotes pulmonary hypertension by inducing inflammation and proliferation of vascular smooth muscle cells.<sup>67</sup> Other studies showed that Rho-associated coiled-coil-containing protein kinases (ROCK1 and ROCK2) are considerably involved in the pathogenesis of hypoxia-induced pulmonary hypertension,<sup>68</sup> post-capillary pulmonary hypertension, and cardiac dysfunction due to left heart diseases,<sup>69</sup> and activation of them can induce the secretion of CyPA.<sup>70,71</sup> Therefore, proper modulation of the Rho-kinase/CyPA/Bsg signaling pathway can be a rational strategy for the treatment of PAH.

Mitochondrial function is another important concern that is extremely influenced under PAH situations, and pathogenic conditions such as mitochondrial oxidative phosphorylation (MOP) occur, increasing inflammation, proliferation, and apoptosis resistance in pulmonary artery smooth muscle cells.<sup>72</sup> Under mitochondrial dysfunction, PAH-PASMCs perform glycolysis instead of mitochondrial respiration (Warburg effect), and expression of the hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) is enhanced.<sup>73</sup> The disproportionate hyper-activation of HIF-1 $\alpha$  leads to excessive proliferation and apoptosis resistance in PAH-PASMCs. In summary, pulmonary artery smooth muscle cells in PAH conditions acquire certain characteristics such as apoptosis resistance, increased inflammation, and excessive proliferation, and reducing these disturbances can help control and treat the disease.<sup>73,74</sup>



**Figure 2.** Exertion of anti-cancer activity of emetine through the modulation of p38 MAPK and ERK signaling pathways. Activation of the p38 MAPK pathway can lead to pathogenic conditions such as disruption of cardiac fibroblast function, induction of pro-inflammation, vasoconstriction, pro-atrophy, and pro-fibrosis situations that eventually lead to cellular heart damage.

Recently, Mohammad Abdul Hai Siddique et al. tried to identify suitable compounds to modulate the Rho-kinase/CyPA/Bsg signaling pathway, with the aim of treating PAH. For this purpose, these researchers first screened 5562 naturally occurring and synthetic compounds, and after detailed *in vitro* and *in vivo* evaluations, emetine was introduced as an excellent therapeutic agent for the treatment of PAH. Results of the comprehensive *in vitro* assessments showed that emetine, with strong anti-proliferative and apoptotic inducer activity, eliminates well the imbalance between proliferation and apoptosis in pulmonary artery smooth muscle cells. Also, it was been shown that emetine has remarkable inhibitory effects on ERK1/2-Akt activity and the CyPA/Bsg signaling pathway (decrease in the secretion of CyPA). Since CyPA secretion from PSMCs is regulated by Rho-kinase, it was shown that emetine significantly inhibits the expression of Rho-kinase isoforms and reduces ROCK1 and ROCK2 protein levels. The protein levels of bromodomain-containing protein 4 (BRD4) as a key regulatory protein that promotes the PAH,<sup>75</sup> downstream pyruvate dehydrogenase kinase 1 (PDK1), secretion of cytokines/chemokines and growth factors (IL-1 $\beta$ , IL-6, and TNF $\alpha$ ), and protein levels of HIF-1 $\alpha$  and HIF-2 $\alpha$  are other important parameters that were shown to be significantly reduced by emetine *in vitro*. *In vivo* evaluations also showed that emetine could well reduce pulmonary hypertension and inflammation of the lungs in experimental animal models of both sugen/hypoxia-induced and monocrotaline-induced pulmonary hypertension (in a dose-dependent manner) and improve right ventricular function. Effective inhibition of pulmonary arterial hypertension–pulmonary artery smooth muscle cells proliferation without significant toxic effects on normal cells led those

researchers to introduce emetine as a promising drug for the treatment of PAH patients.<sup>76</sup>

## 6. CARDIAC COMPLICATIONS

From the discovery of the anti-amoebiasis effects of emetine by Vedder in 1912 until the advent of metronidazole in 1965, this compound was the drug of choice for the treatment of acute intestinal and extra-intestinal amoebiasis. This long period led to the identification of emetine-related side effects and toxicities in patients. Although emetine showed excellent therapeutic effects during this period, it has generally been reported to have a narrow therapeutic index.<sup>77,78</sup> Some studies have reported that taking therapeutic doses of emetine may cause some cardiovascular complications during or after treatment, including electrocardiogram (ECG) abnormalities, ventricular tachycardia and fibrillation, reversible myopathy, hypotension, and sometimes pericardial pain and tachycardia.<sup>79–81</sup> Some studies have linked emetine-induced cardiac toxicity to calcium channel blockade by this drug.<sup>82</sup> Although some old studies found these side effects to be dangerous,<sup>83</sup> some other reports suggested that these side effects persist for a short time after treatment and then the patient usually improves without any changes in cardiovascular function. The usual therapeutic dose of emetine hydrochloride for the treatment of amoebiasis is 1 mg/kg/day for 10 days or less. One study reported that emetine at an even higher dose (2 mg/kg/day i.p. for 9 days) has no direct adverse effects on cardiac mitochondrial metabolism, and metabolic damage to the myocardium is not considered to be due to the toxicity of emetine.<sup>84</sup>

Since most of these studies were performed decades ago, it seems necessary to evaluate the cardiac toxicity of emetine using

novel facilities to contribute to a better understanding of the advantages/disadvantages of using this compound in current diseases such as COVID-19. However, old studies also provide valuable information about the cardiotoxicity of emetine that can be considered in clinical applications.

Although emetine has valuable therapeutic effects, it appears to be associated with risks for the treatment of COVID-19 patients with underlying heart disease. The results of new evaluations indicate the effect of emetine on some important cellular processes and signaling pathways that can shed light on ambiguities related to its cardiotoxicity. As mentioned earlier, the p38 mitogen-activated protein kinase (p38 MAPK) pathway is one of the critical targets whose disruption following SARS-CoV-2 infection can lead to hyper-inflammatory complications and vasoconstriction.<sup>85</sup> Some previous studies have also well described that an extraordinary increase in p38 MAPK pathway activity eventually leads to damaging conditions such as vasoconstriction, pro-inflammation, pro-atrophy, and pro-fibrosis.<sup>86</sup> Overall, new evaluations suggest that abnormal and severe activation of the p38 MAPK pathway could lead to cellular damage to the heart.<sup>87</sup> Some reputable studies have reported that emetine has significant stimulatory effects on this pathway. A study conducted by Ji Hyun Kim et al. showed that emetine could exert its anti-cancer activity by reducing the degradation of extracellular matrix components via selective down-regulation of matrix metalloproteinases 2 and/or 9, mediated by effects on p38 MAPK and ERK signaling pathways. According to the results of this study, emetine inhibits extracellular signal-regulated kinase (ERK) activation, while stimulating p38 MAPK activation.<sup>88</sup> Another recently published study repeated the findings of stimulatory effects of emetine on the p38 MAPK pathway and its inhibitory effects on the ERK and c-Jun N-terminal kinase (JNK) pathways.<sup>89</sup> The stimulatory effects of emetine on the p38 pathway were also reported in some older studies.<sup>90</sup> Although emetine is an approved drug, its stimulant effects on the p38 MAPK pathway could be one of the possible causes of cardiac side effects (Figure 2).

## 7. DRUG RESISTANCE

The emergence of drug resistance is one of the most important problems that today has challenged the treatment processes in modern medicine by reducing the longevity of drugs and limiting treatment options. This is especially true in viral infectious diseases, as the evolutionary pressure of survival eventually leads to the emergence and strengthening of mechanisms and genetic changes (such as site mutations, deletions, and gene amplification) in these pathogens that ultimately lead to their resistance to drugs.<sup>91</sup> Since the emergence and spread of this phenomenon severely affects public health and creates a heavy financial burden, the development of new strategies to detect and prevent drug resistance is of great interest. Although a structure-based drug design strategy has so far been remarkably successful in the discovery and development of direct-acting antivirals (traditionally developed by directly targeting essential viral components), it seems that this strategy should be further considered for the design and production of host-directed antiviral therapeutics. Some recent reviews have detailed the benefits of developing antiviral drugs that target virus-required host factors but are not mandatory for host cell functions.<sup>92–94</sup> The development of these inhibitors, which block some host cellular receptors/proteins (host-based virus replication regulators), could overshadow the genetic mutations of viruses that

are key to the advent of drug resistance. However, drug resistance against some host-directed agents can also occur under certain conditions, such as the long-term use of host-directed antiviral compounds that may give the virus a chance to adapt to the use of an alternative host agent.

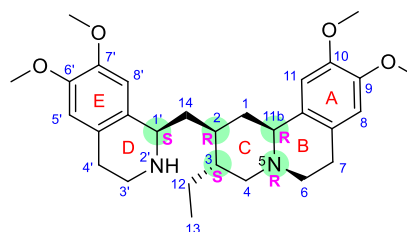
Drug resistance to emetine in the treatment of amoebic diseases has been reported repeatedly in the past. Some of these studies reported that, because emetine is a substrate for p-glycoprotein, these organisms escape the cytotoxicity of emetine through overexpressing p-glycoprotein genes, which results in the reduction of effective cellular concentration.<sup>95–99</sup> In the case of emetine fighting viruses, the situation is different. Emetine is one of nature's interesting products that manifests its antiviral effects by both directly countering virus components and modulating host-based antiviral targets. Because this compound affects host cell function, it is expected that it should not be inclined to produce drug-resistant viruses.

In a study conducted by Khandelwal et al., the potential development of drug-resistant virus variants on long-term passage of some DNA and RNA viruses was studied *in vitro* using Vero cells in the presence of emetine.<sup>12</sup> The results showed that emetine effectively suppresses the replication of both RNA and DNA viruses without generating drug-resistant virus variants. The researchers said that the very low tendency of emetine to generate drug-resistant virus variants was probably due to the effects of this compound on host-based factors, by which altering them indirectly impairs the replication of the virus.

Emetine and its hydroxyl-containing analogue, cephaline (Figure 1), are currently under preclinical development to inhibit PPRV, NDV, BPXV, BHV-1, ZIKV, and EBOV as host-directed antiviral agents by affecting lysosomal function.<sup>12,23,92</sup> Although it is expected that the use of emetine for the treatment of COVID-19 will not lead to significant drug resistance, the accurate acquisition of information requires the design and conduct of independent studies.

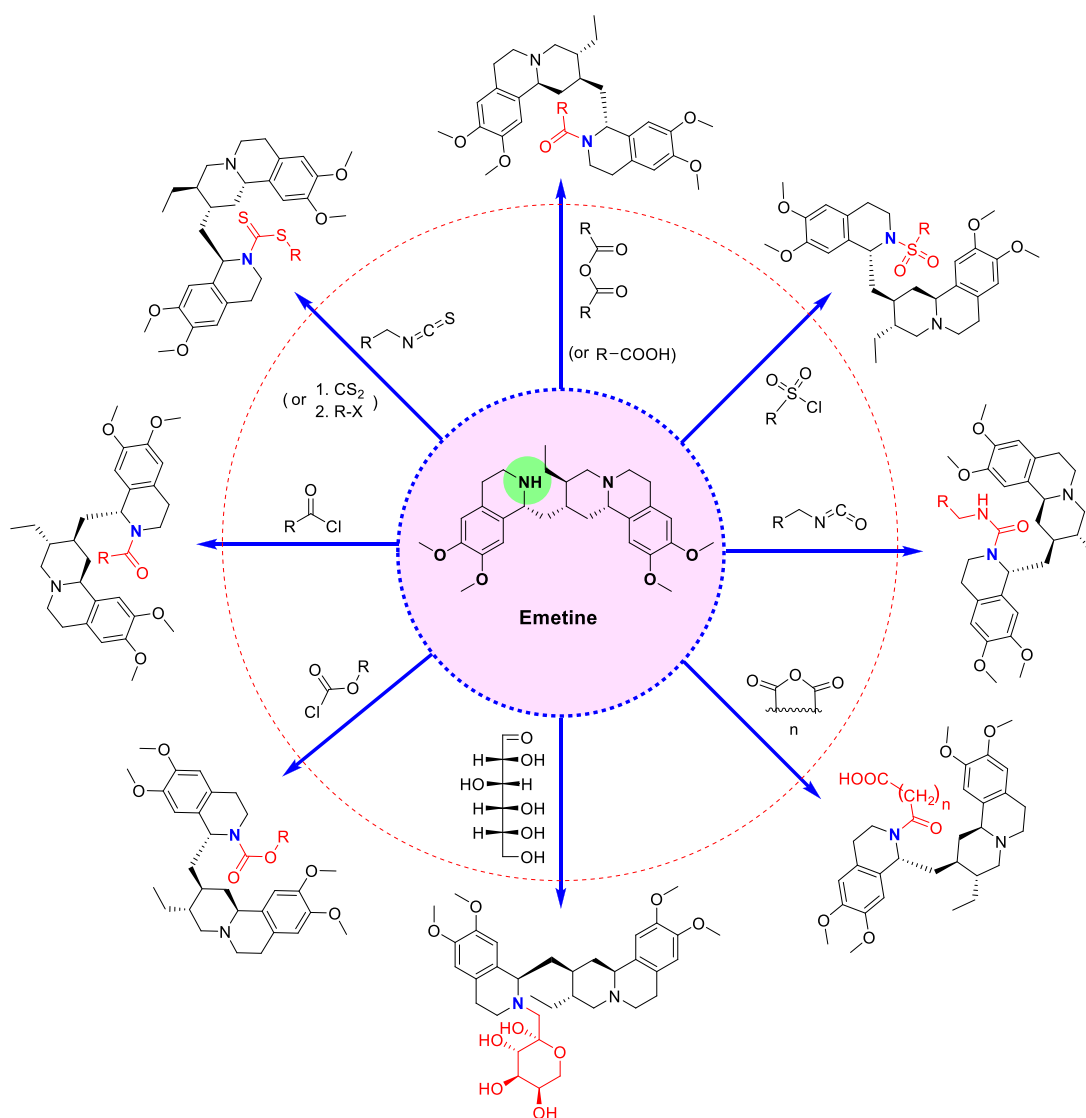
## 8. STRUCTURAL ANALYSIS

Structurally, emetine has a monoterpenoid–tetrahydroisoquinoline skeleton consisting of five rings—A, B, C, D, and E—in which rings D and E are separated by a methylene bridge from interconnected rings A, B, and C (Figure 3). The



**Figure 3.** The chemical structure of emetine contains five chiral centers.

structure–activity relationships (SARs) of emetine and its analogues in the evaluation of some biological activities have been discussed in previous studies.<sup>1,7,100–102</sup> One of the important points mentioned in these studies is that emetine can be biologically active when its C-1' is R-configured. Another important SAR finding is that, in order to have biological activity, the N-2' position must be a secondary amine, which will be discussed below. Because the active sites of the targets are different, the SAR findings for a particular biological activity



**Figure 4.** General structures of various modified emetine derivatives produced by semi-synthetic approaches using emetine along with various electrophiles as starting materials.

cannot be generalized to other biological activities. Since emetine is one of the most potent and promising compounds identified for the treatment of COVID-19, performing SAR studies on its derivatives is an undeniable necessity for achieving the best emetine analogues for inhibiting SARS-CoV-2. However, some past SAR findings related to the cytotoxic effects of these derivatives are still useful for achieving safer emetine derivatives.

In terms of the SAR in medicinal chemistry, the presence or placement of hydroxyl groups in lipophilic bioactive structures often reduces systemic toxicity and increases their solubility in water.<sup>103,104</sup> Cephaeline is one of the analogues of emetine whose antiviral effects have been investigated in some studies. Due to the presence of a hydroxyl group in its structure, cephaeline is expected to be less toxic than emetine and better tolerated in patients. As mentioned above, cephaeline has antiviral effects similar and comparable to those of emetine, and in some cases it shows even stronger effects against viruses.<sup>23</sup> In a HTS effort by Liang Deng et al., in which the inhibitory effects of 2880 known drugs were tested on the replication of vaccinia virus WR in cultured BSC40 cells, cephaeline was identified as

the strongest compound that can inhibit virus replication at non-cytotoxic doses, with  $IC_{99} = 60$  nM. Emetine was also identified as one of the highly potent anti-vaccinia virus compounds in the same study, with  $IC_{99} = 100$  nM.<sup>105</sup> Cytotoxicity evaluations have shown that having a hydroxyl group often causes cephaeline to be less cytotoxic than emetine. For example, in a study by Ren et al., it was found that emetine has remarkable cytotoxicity, with  $CC_{50} = 2.17$   $\mu$ M, while cephaeline has desired cytotoxicity, with  $CC_{50} = 49.05$   $\mu$ M, assessed in Vero E6 cells.<sup>35</sup>

Structurally, the D ring of the emetine is of great importance. Since much higher bioactivity has been observed for emetine in previous studies compared to its analogues containing an unsaturated D ring, it can be concluded that the saturation rate of this ring has a key effect on the bioactivity of these derivatives.<sup>106</sup> The saturation of the D ring in the emetine allows the secondary amine at the 2' position to act as both a hydrogen bond donor and a hydrogen bond acceptor in the physiological environment and in the interactions with the active site of the receptors. In addition to the *in vivo* environment, in synthetic processes the N-2' position of emetine is a proper place for electrophilic attacks, thus allowing the production of new semi-



synthetic modified structures (Figure 4).<sup>106–112</sup> A study by Akinboye et al. reported that the secondary amine at the N-2' position of emetine plays a critical role in its anti-cancer activity, and any structural modification that leads to a change of this amine from the secondary state greatly reduces its cytotoxicity. The study's authors cited the N-2' position as a golden place to design prodrugs with decreased systemic toxicity and enhanced therapeutic usages compared to emetine.<sup>106</sup> This strategy can also be assessed with the aim of achieving emetine prodrugs with anti-SARS-CoV-2 effects but having fewer side effects and lower systemic toxicity. Numerous other studies have also reported that the cytotoxicity of modified emetine derivatives in which substitutions are placed on the nitrogen at the 2' position is significantly reduced compared to that of emetine.<sup>106,108,109,113</sup>

## 9. CONCLUSION

Emetine is one of the few highly potent anti-SARS-CoV-2 agents ever introduced, identified in several studies and HTS efforts. Many studies have reported that this compound has excellent broad-spectrum antiviral effects against a wide range of RNA and DNA viruses at non-cytotoxic concentrations. After the advent of SARS-CoV-2, several independent studies identified emetine as one of the most promising compounds in the fight against COVID-19, and so repurposing it has been suggested.

The high potency of emetine in combating COVID-19 is due to its beneficial pharmacological activities in addition to its anti-SARS-CoV-2 effects. As mentioned in clinical evaluations, proper management of inflammatory complications in COVID-19 is a key point. Emetine has a significant anti-inflammatory capability that could potentially decrease the severity of hyper-inflammatory immune responses induced by SARS-CoV-2 infection through decreasing the level of pro-inflammatory cytokines IL-6, TNF $\alpha$ , and IL-1 $\beta$  and inhibiting the NF- $\kappa$ B signaling pathway. Since the concentration of emetine in the lungs can be much higher than in the bloodstream, these conditions can provide a good ground in the lungs to effectively fight the virus. Pulmonary hypertension is a major problem in some COVID-19 patients. The release of pro-inflammatory cytokines in the pulmonary arteries of PAH patients leads to the production of ROS and increases oxidative stress. When oxidative stress conditions prevail, the body is exposed to a number of secondary injuries, such as brain damage. It has been shown that emetine can effectively combat oxidative stress situations and inhibit pulmonary arterial hypertension and pulmonary artery smooth muscle cells' proliferation without significant toxic effects on normal cells.

Inhibition of SARS-CoV-2 by emetine is accomplished through interactions with both virus-based and host-based targets. Although it is clear that emetine has valuable effects on some host-based antiviral targets, which offers the advantage of not causing drug resistance (in addition to having direct effects on SARS-CoV-2), it can cause resistance if overused or misused. Emetine can disrupt the SARS-CoV-2 mRNA binding with eIF4E and decrease viral RNA production and protein synthesis. Actually, emetine exerts part of its anti-SARS-CoV-2 activity by the modulation of the ERK/MNK1/eIF4E signaling pathway, a critical target applied for viral replication in the host cells. RdRp is a key virus-based target that is critical in the SARS-CoV-2 life cycle; the results of some mechanistic evaluations suggest that the potent inhibitory effects of emetine against SARS-CoV-2 are associated with the inhibition of this enzyme.

Despite the promising antiviral effects of this drug against SARS-CoV-2, its cardiac-related side effects have led to serious

restrictions on its use. Emetine induces some cardiovascular complications, such as heart rate changes and ECG abnormalities, ventricular tachycardia, reversible myopathy, and hypotension, during or after treatment. Some studies suggest that these side effects persist for a short time after treatment and then the patient usually recovers without any changes in cardiovascular function, but these adverse effects undoubtedly limit the use of emetine in high doses. Accordingly, emetine does not appear to be a good candidate for the treatment of COVID-19 patients with underlying cardiovascular diseases. As reported in previous studies, emetine has significant stimulatory effects on the p38 MAPK pathway, which could be one of the possible causes of these side effects.

There is currently very little direct data associated with the clinical effect of emetine against SARS-CoV-2 infection. More validation studies, with high-quality evidence (both *in vitro* and in animal models as well as on humans), are now needed. Overall, it seems that emetine can be used in low doses to treat COVID-19 patients. Some clinical trials showed that low doses of emetine in combination with conventional antiviral drugs such as Arbidol could improve clinical symptoms compared with the control group. Some other assessments have shown a synergistic effect of concomitant use of emetine and remdesivir in effectively inhibiting SARS-CoV-2, which could be evaluated by virologists and clinicians in future clinical trials.

On the topics of drug design and discovery, paying attention to structures similar to emetine is important. Since the N-2' position of emetine is a valuable place to design prodrugs with reduced toxicity, using this atom to produce emetine prodrugs with fewer side effects also could be a logical idea for future research into the discovery of appropriate anti-COVID-19 agents.

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### Notes

The author declares no competing financial interest.

## ABBREVIATIONS

ACE2	angiotensin-converting enzyme
ANDV	Andes orthohantavirus
Bsg	basigin
BHV-1	bovine herpesvirus-1
BPXV	buffalopoxvirus
COVID-19	coronavirus disease of 2019
CC <sub>50</sub>	cytotoxicity concentration 50%
CyPA	cyclophilin A
Caco-2	human epithelial colorectal adenocarcinoma cell line
DNA	deoxyribonucleic acid
EC <sub>50</sub>	half-maximal effective concentration
EBOV	Ebola virus
eIF4E	eukaryotic translation initiation factor 4E
ERK	extracellular signal-regulated kinase
ECG	electrocardiogram

ERGIC	endoplasmic reticulum—golgi intermediate compartment
EV-A71	enterovirus A71
FIP	feline infectious peritonitis
FDA	U.S. Food and Drug Administration
GFP	green fluorescent protein
HTS	high-throughput screening
HIV	human immunodeficiency virus
HTNV	Hantaan orthohantavirus
HSV	herpes simplex viruses
HMPV	human metapneumovirus
HIF-1 $\alpha$	hypoxia-inducible factor-1 $\alpha$
HCoV-NL63	human coronavirus-NL63
HCoV-OC43	human coronavirus-OC43
IL-1 $\beta$	interleukin-1 beta
IL-6	interleukin-6
IC <sub>50</sub>	half-maximal inhibitory concentration
K <sub>D</sub>	dissociation constant
IkB $\alpha$	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
IUPAC	International Union of Pure and Applied Chemistry
JAK3	Janus kinase 3
JNK	c-Jun N-terminal kinase
LPS	lipopolysaccharide
MERS-CoV	Middle East respiratory syndrome coronavirus
MHV-A59	mouse hepatitis virus strain A59
MNK1	MAPK-interacting serine/threonine-protein kinase 1
MOP	mitochondrial oxidative phosphorylation
MAPK	mitogen-activated protein kinase
NF- $\kappa$ B	nuclear factor kappa light chain enhancer of activated B-cells
NDV	Newcastle disease virus
NSP	non-structural protein
NIH	U.S. National Institutes of Health
PDK1	pyruvate dehydrogenase kinase 1
p38-MAPK	p38-mitogen-activated protein kinase
PCR	polymerase chain reaction
PPRV	peste des petits ruminants virus
PAH	pulmonary arterial hypertension
PLpro	papain-like protease
RABV	rabies virus
RNA	ribonucleic acid
ROCK	Rho-associated coiled-coil-containing protein kinase
RPE	retinal pigment epithelium cell line
RdRp	RNA-dependent RNA polymerase
RVVFV	Rift Valley fever virus
RT-qPCR	quantitative reverse transcription PCR
RTC	replication—transcriptase complex
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV	severe acute respiratory syndrome coronavirus
SAR	structure—activity relationship
SI	selectivity index
SPR	surface plasmon resonance
TNF $\alpha$	tumor necrosis factor alpha
THP-1	human monocytic cell line
TMPRSS2	transmembrane serine protease 2
TI	therapeutic index
ZIKV	Zika virus
3CLPro	3-chymotrypsin-like protease

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