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Repurposing cefuroxime for treatment of COVID-19: a scoping review of *in silico* studies

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus disease 19 (COVID-19), is a novel human Coronavirus that is responsible for about 300,000 deaths worldwide. To date, there is no confirmed treatment or vaccine prevention strategy against COVID-19. Due to the urgent need for effective treatment, drug repurposing is regarded as the immediate option. Potential drugs can often be identified via *in silico* drug screening experiments. Consequently, there has been an explosion of *in silico* experiments to find drug candidates or investigate anecdotal claims. One drug with several anecdotal accounts of benefit is Cefuroxime. The aim of this study was to identify and summarize *in silico* evidence for possible activity of Cefuroxime against SARS-CoV-2.To this end, we performed a scoping review of literature of *in silico* drug repurposing experiments for SARS-CoV-2 using PRISMA-ScR. We searched Medline, Embase, Scopus, Web of Knowledge, and Google Scholar for original studies published between 1st Feb, 2020 and 15th May, 2020 that screened drug libraries, and identified Cefuroxime as a top-ranked potential inhibitor drug against SARS-CoV-2 proteins. Six studies were identified. These studies reported Cefuroxime as a potential inhibitor of 3 key SARS-CoV-2 proteins; main protease, RNA dependent RNA polymerase, and ACE2-Spike complex. We provided a summary of the methodology and findings of the identified studies. Our scoping review identified significant *in silico* evidence that Cefuroxime may be a potential multi-target inhibitor of SARS-CoV-2. Further *in vitro* and *in vivo* studies are required to evaluate the potential of Cefuroxime for COVID-19.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), represents a major global public health threat. At the time of writing this report, COVID-19 has been detected in over 200 countries/regions with over 4 million confirmed cases and nearly 300,000 deaths (Johns Hopkins University, 2020). Although, rates of new cases have plateaued in some regions due to social distancing measures, transmission dynamics suggest that, in the absence of a vaccine, a combination of intermittent social distancing, an expanded critical care capacity, and an effective therapeutic treatment will be necessary to facilitate acquisition of sufficient herd immunity to mitigate resurgence of infection in the near future (Kissler et al., 2020).

SARS-CoV-2 is a positive-sense single-stranded RNA virus belonging to the β genus of the *Coronaviridae* family. The SARS-CoV-2 virion consists of at least four (4) structural proteins: Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein (Li et al., 2020). The Spike (S) protein confers the distinguishing "crown" appearance consistent with other coronaviruses and facilitates binding and viral entry with host angiotensin-converting enzyme 2 (ACE2) receptor (Ge et al., 2013). It is also the target for neutralizing antibodies and vaccines (Du et al., 2009). In contrast, some key non-structural proteins include: Papain like protease (PLpro) and Main protease (Mpro), which are responsible for cleavage of viral polypeptide into functional units; and RNA-dependent RNApolymerase (RdRp), which is critical for viral proliferation (Ziebuhr et al., 2000). Expectedly, these proteins have been identified as important drug targets (Dong et al., 2020).

Currently, there is no confirmed treatment or vaccine prevention strategy against COVID-19. Due to the urgency of the situation, drug repurposing is widely accepted as the fastest way to identify possible effective therapeutic options (Ciliberto & Cardone, 2020; Ekins et al., 2020; Parks & Smith, 2020). Clinical trials have investigated the efficacy of various existing drugs for possible repurposing, including Lopinavir/Ritonavir (anti-HIV protease inhibitors), (Cao et al., 2020), hydroxychloroquine (anti-malarial which decreases acidity in endosomes and probably affects the entry of the virus to the cell) and Azithromycin (an antibacterial agent) (Molina et al., 2020; Rosenberg et al., 2020), and Remdesivir (a 1′-cyano-substituted adenosine nucleotide analogue prodrug with established activity against Ebola virus RdRp) (Shah et al., 2020; Tchesnokov et al., 2019). Despite Remdesivir showing

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promising results on preliminary analysis (National Institutes of Health, 2020), the search for additional safe, efficacious, and cost-effective drug candidates for repurposing continues.

A well-established method for identifying drugs for repurposing is via computational means, also termed *in silico*. *In-silico* drug screening techniques and experienced docking experiments allow for the evaluation of available drug candidates against viral protein and host receptor structures (Ekins et al., 2007; Hodos et al., 2016). It is a fast, and cost-effective way of identifying new uses for old drugs and has been successful in identifying drugs for a variety of conditions (Ekins et al., 2007). Since the structures of SARS-CoV-2 viral proteins were characterized and published in early February, 2020, there has been a surge of *in silico* studies seeking potential drugs that could be repurposed to treat COVID-19(Mohamed et al., 2020). One drug that may hold potential is Cefuroxime.

There have been several anecdotal accounts on social media of SARS-CoV-2 positive patients who received oral Cefuroxime experiencing often rapid symptomatic improvement (Aquino, 2020; Barreto, 2020; Sheathomas, 2020; Sur, 2020; Turnipseed, 2020). Cefuroxime is a second generation cephalosporin antibiotic. It has broad spectrum activity and is commonly used for the treatment of both upper and lower respiratory tract infections, Lyme disease, and genitourinary tract infections. It is readily available and affordable, and it exists in both oral and parenteral forms as Cefuroxime Axetil and Cefuroxime Sodium, respectively. It has undergone extensive toxicological investigation and post-marketing surveillance and it is known to have a good safety profile (Emmerson, 1988). The most common adverse events are gastrointestinal disturbances including nausea, vomiting, and diarrhea. (Emmerson, 1988; O'Callaghan et al., 1976; Perry & Brogden, 1996), which is estimated to occur in between 3% to 4% of recipients (Perry & Brogden, 1996). Other less common side effects include headaches, hypersensitivity reactions, hematological derangements, pseudomembranous colitis, vaginitis, and skin rashes, all of which appear to be dose-dependent (Gold & Rodriguez, 1983; Perry & Brogden, 1996). The aim of this paper is to identify and summarize available *in silico* evidence for the molecular basis of possible activity of Cefuroxime against SARS-CoV-2.

Materials and methods

Search strategy

We adopted the Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). Eligible studies were identified through search of articles published in Medline, Embase, Scopus, Web of Science, and Google Scholar from February 1st, 2020 through May 15th. We employed a broad search strategy for peer-reviewed databases by using the following search key; '("*in silico*" or "virtual screening" or "computational") and ("SARS-CoV-2" or "coronavirus" or "COVID 19") and ("drugs" or "drug repurposing")'. Given that Google Scholar allows for searching within full-text, we employed a directed search strategy using the search key: 'Cefuroxime AND ("Coronavirus" or "COVID19" or "SARS-CoV-2") and drug repurposing'.

Study selection

Primary research articles, written in English, that fulfilled the following criteria were included in the analysis: i) described testing of potential inhibitors of any SARS-CoV-2, structural or non-structural proteins, ii) included screening of potential inhibitor drugs from a drug library containing United States Food and Drug Administration (FDA) approved drugs or preselected list that included Cefuroxime, and iii) identified Cefuroxime as a top-ranked (top X drugs, where $X <= 20$) potential inhibitor drug. Studies with any of the following were excluded from analysis: i) articles that did not report results of primary research, ii) articles not written in English, iii) studies that investigated only natural or traditional drugs, iv) studies that described testing of specific drugs or a preselected drugs list that did not include Cefuroxime v) studies that did not identify Cefuroxime as a top-ranked potential inhibitor drug.

Two investigators (AD and CW) independently searched and reviewed the titles and the abstracts of the retrieved studies to identify potentially relevant articles. The full text publications of potentially relevant articles were retrieved and re-screened by the same two investigators. Disagreements were resolved by consensus between the two investigators. The final selected articles were reviewed, data extracted, and the methodology and findings were summarized in this paper.

Outcomes of interest

The primary study outcome was to identify and summarize *in silico* evidence that suggest a molecular basis of possible activity of Cefuroxime against SARS-CoV-2.

Data extraction

Data from each eligible study were extracted by the two investigators. Extracted data included the name of first author, country of origin of corresponding author, peer reviewed status, methodological approach, software tool used, FDA approved drugs or drug library screened, SARS-CoV-2 protein target(s), and Cefuroxime rank.

Results

A total of 165 articles were found after initial search from which 83 unique articles remained after the identification and removal of duplicates. Out of the remaining studies, 59 studies were removed for not being relevant while 27 studies were retained for full-text review. Following full-text review, 21 studies (Beck et al., 2020; Cava et al., 2020; Chen et al., 2020; Elfiky, 2020; Elmezayen et al., 2020; Encinar & Menendez, 2020; Gordon et al., 2020; Hall & Ji, 2020; Hijikata et al., 2020; Kandeel & Al-Nazawi, 2020; Liu et al., 2020;; Mahanta et al., 2020; Mirza & Froeyen, 2020; Mittal et al.,

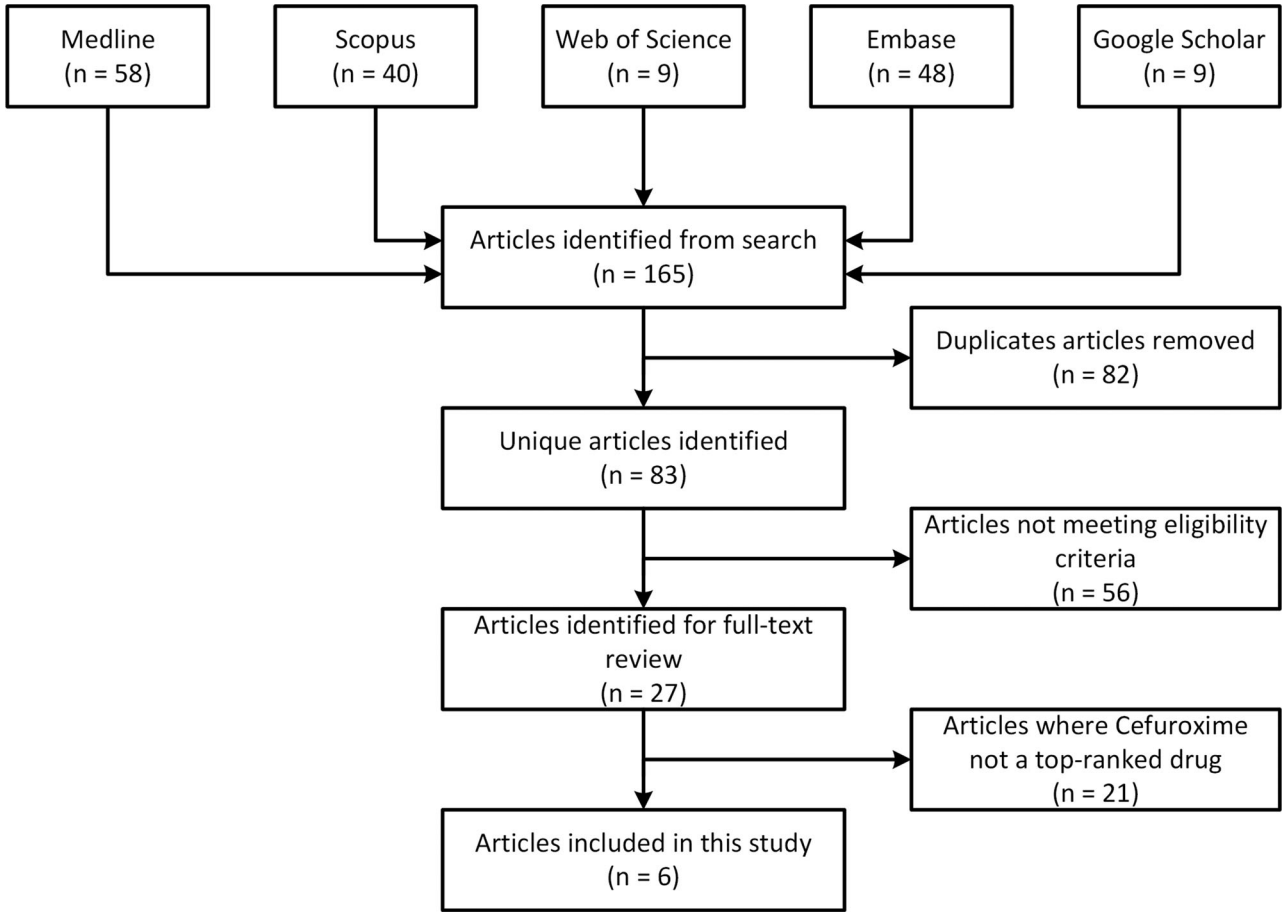

Figure 1. The search flow for the study.

2020; Ortega et al., 2020; Pant et al., 2020; Peele et al., 2020; Sarma et al., 2020; Ton et al., 2020; Tsuji, 2020; Wang, 2020;) were excluded because Cefuroxime was not identified as a top-ranked candidate drug. This included a study (Elfiky, 2020) that investigated the binding affinity of a few selected drugs, including Cefuroxime, to RdRp without explicitly ranking the drugs. Six studies (Al-Khafaji et al., 2020; Alméciga-Díaz et al., 2020; Dar'ya et al., 2020; Galvez et al., 2020; Koulgi et al., 2020; Wu et al., 2020;) reported Cefuroxime as a top-ranked Candidate drug and were included in this study. The study flow is depicted in Figure 1. The characteristics of the 6 studies is presented in Table 1. A target based summary of the identified studies is presented here.

Potential activity against mpro

Four studies (Al-Khafaji et al., 2020; Alméciga-Díaz et al., 2020; Jorge Galvez et al., 2020; Koulgi et al., 2020) reported Cefuroxime as a top-ranked inhibitor drug for Mpro. Galvez and colleagues (Jorge Galvez et al., 2020) employed a Molecular Topology (MT) methodology that has been successful in identifying drugs for cancer, Alzheimer's disease, and Malaria (J. Galvez et al., 2012). The MT approach involves representing the structure, and by extension, the pharmacologic activity of drugs or molecules by a set of numbers called topological indices. Based on topological indices, drugs can be partitioned into groups that have similar mathematical patterns. A mathematical model or topological model is trained to learn a desired mathematical pattern. Once validated, the topological model can be used to search drug libraries to identify other drugs that have the desired mathematical pattern, hence, the desired pharmacologic activity (J. Galvez et al., 2012; Jorge Galvez et al., 2020). Galvez and colleagues took Lopinavir, the HIV-1 protease that was predicted in some studies to have activity against Mpro, as a gold standard drug. Using the MT approach, they screened about 15,000 molecules from 2 drug libraries and identified 22 other drugs, including Cefuroxime, that are predicted to bind tighter than Lopinavir. The predicted inhibitory potency of these drugs was expressed by an arbitrary index. Lopinavir had an index score of 2.9 while Cefuroxime had an index score of 3.9.

Almeciga-Diaz and colleagues (Alméciga-Díaz et al., 2020) used a proprietary algorithm (Alméciga-Diaz et al., 2019) to screen a subset of ZINC library for drugs that could bind to the active cavity of Mpro. Prior to screening, they demonstrated that their algorithm correctly predicted the binding of a number of inhibitor molecules that have been reported for Mpro, including N3 and α-ketonamide-based inhibitors. They observed a very strong correlation ($R^2 = 0.89$) between the binding energy and reported $IC_{50}$of these inhibitors. Consequently, they predicted IC_{50} based on binding energy. From screening of over 11,000 drugs, they identified 10 potential inhibitor drugs, including Cefuroxime, that had smaller binding energy than the previously reported

Table 1. Studies predicting Cefuroxime as a top-ranked potential inhibitor drug for SARS-CoV-2.

First author, country	Peer-review status	Methodological Approach	Software	FDA approved drugs screened	SARS-CoV-2 Target Protein	Cefuroxime Rank
Wu, China	Yes	Homology docking with Internal Coordinate Mechanics	Molsoft 3.7.3	1. ZINC 2. Known anti-virals Database	All	1*
Galvez, Spain	No	Mathematical modeling via Molecular Topology	Not stated	1. Comprehensive Medicinal Chemistry 2. Drug Bank	Mpro	20
Dar'ya, Canada	No	Artificial intelligence via Deep Learning	Ligand Design, a proprietary platform	PolypharmDB, a proprietary resource generated by MatchMaker, a proprietary technology	Mpro, Spike, TMPRSS2, and Cathepsin B	3^
Almeciga-Diaz, Colombia	No	Molecular docking	AutoDock	ZINC	Mpro (PDB:6LU7)	8
Koulgi, India	No	Direct docking and Ensemble approach	DOCK 6	1. Drugs@FDA 2. Sweetlead	Mpro (PDB:6LU7)	2
Al-Khafaji, Iraq	Yes	Covalent docking	CovDock module of Schrodinger 2020-1 Suites	48 pre-screened drugs	Mpro (PDB:6LU7)	5

*Against RdRp ranked via ICM scores provided in supplementary files of the article.
^Against ACE2-Spike complex.

inhibitors. Cefuroxime ranked 8th and was predicted to bind with affinity energy of -9.2 kcal/mol with an IC_{50} of 2.09 μM. The top-ranked drug had an affinity energy of -9.8 kcal/mol and an IC_{50} of 1.84 μM.

Koulgi and colleagues (Koulgi et al., 2020) using both a "direct docking" and an "ensemble docking" approach. The direct docking was a straightforward docking of potential drugs against the crystal structure of Mpro while the ensemble approach involved docking against variations in conformation of the active site of Mpro, which usually leads to better results. To achieve the ensemble approach, they performed molecular dynamic simulation (MDS) via Root mean Square Deviation (RMSD) based clustering and Markov State Modeling analysis to obtain 16 conformations of Mpro. Grid scores for drugs in two drug libraries, one of which was the official FDA approved drug list, were reported for both approaches. Expectedly, the ensemble approach produced better docking scores. Cefuroxime, via trade name of Ceftin, was identified as the second-best drug from the FDA drug library via the ensemble approach with a grid score of -49.33. This score was better than a score of -46.05 for the best ranked drug from the direct docking approach.

Al-Khafaji and colleagues (Al-Khafaji et al., 2020) employed covalent docking screening to identify potential drugs that could bind covalently, hence irreversibly, to Cys145 of the active site of Mpro. Cys145 of Mpro has been identified as a vital residue that can be covalently bound by drugs to inhibit activity of Mpro (Dai et al., 2020; Xue et al., 2008; Zhang et al., 2020). To this end, they obtained the crystal structures of 48 pre-screened FDA-approved drugs and antiviral agents, including Cefuroxime, that are known to bind covalently to targets. The drugs were ranked by their binding energies that was determined using Prime MM-GBSA (Genheden & Ryde, 2015). They concluded that the top 8 drugs showed a higher affinity to form covalent, irreversible bond with Cys145 of the active site of Mpro. Cefuroxime was the 5th highest ranking drug with a binding energy of -54.25 kcal/mol while Remdesivir ranked third with a binding energy of -65.19 kcal/mol.

Potential activity against RdRp

Wu et. al (Wu et al., 2020) was one of the earliest and one of the most cited paper on *in silico* experiments for SARS-CoV-2 as at the time of writing this paper. The authors screened FDA-approved drugs from ZINC database, and a database of known antiviral agents against active sites all SARS-CoV-2 proteins. Drug candidates were scored based on the well established Internal Coordinate Mechanics (ICM) (Abagyan et al., 1994). The binding energies of potential drug candidates were expressed as ICM scores and ICM mfscores (mean force scores). The ICM score is a measure of the overall empirical function of the predicted physical interaction while the ICM mfscore is an independent score of the strength of drug-receptor interaction (Abagyan et al., 2020; Muegge & Martin, 1999; Neves et al., 2012). Per the ICM user guide, the score is considered the best scoring to use for docking result analysis, and ICM scores less than -32 are generally considered to be good scores. (Abagyan et al., 2020). Wu and colleagues considered drug candidates with ICM scores less than -30 or ICM mfscores less than -110 to have potential activity against targeted proteins of SARS-CoV-2. Cefuroxime was among top-ranked drugs was predicted to inhibit RdRp. From the ICM score data provided in supplementary files, against Rdrp, Cefuroxime had an ICM score of -41.30, which was the highest, and mfscore of -63.04. Remdesivir had a score of -27.4 and a mfscore of -113.

Although excluded for not meeting eligibility criteria, we report a study (Elfiky, 2020) that also reported potential binding of Cefuroxime to RdRp. The author conducted MDS with molecular docking to investigate the binding of a handful of pre-selected drugs including antiviral agents and Cefuroxime to RdRp. The average binding energy for Cefuroxime at -6.875 kcal/mol was within the margin of error of Remdesivir at -7.16 kcal/mol.

Potential activity against ACE2-Spike complex

Dar'ya and colleagues (Dar'ya et al., 2020) predicted that Cefuroxime may inhibit the ACE2-Spike complex. First, they

created a resource called PolypharmDB that contained the predicted binding profiles of over 10,000 approved and experimental drugs. The resource was built using a proprietary tool, MatchMaker, that uses artificial intelligence via deep learning to predict the binding of drugs to about 8700 human and viral proteins. PolypharmDB was then queried for potential drugs that could inhibit SARS-CoV-2 proteins of interest, which revealed Cefuroxime as a top 5 drugs that may inhibit ACE2-Spike protein complex.

Discussion

COVID-19 pandemic is a major public health threat that requires immediate action. Despite the intense efforts to develop novel drugs for SARS-CoV2, this process is time consuming with limited progress to date. Therefore, drug repurposing has been identified as the fastest way of realizing therapeutic agents for COVID-19 to meet the urgency of the situation.

There has been anecdotal evidence suggesting various drugs may be effective against SARS-CoV-2. Prospective studies investigating initially touted agents such as Hydroxychloroquine and Azithromycin have failed to show whether Hydroxychloroquine alone or in combination with Azithromycin can effectively alter the disease course in patients with severe COVID-19 (Taccone et al., 2020). However, preliminary data analysis from a National Institutes of Health (NIH) sponsored randomized clinical trial (RCT) for Remdesivir involving patients with advanced COVID-19 suggested that patients who received Remdesivir had a significant 4-day difference in median time to recovery compared to those who received placebo (National Institutes of Health, 2020). Therefore, in-keeping with its commitment to expediting the development and availability of potential COVID-19 treatments, the FDA issued an emergency use authorization on 1st May, 2020 for Remdesivir to be used for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease (U.S. Food & Drug Administration, 2020). The potential mortality benefit of Remdesivir is less clear, with a clinical trial from China showing no mortality benefit (Y. Wang et al., 2020), and conclusive results from the NIH trial being awaited. Nevertheless, the preliminary results of the NIH trial suggest that the virus can be inhibited *in vivo* resulting in clinically meaningful outcomes. Despite this early success, many unanswered questions remain about Remdesivir including its availability, route of administration (exists only in intravenous form), cost, and indication for use in non-severe hospitalized and non-hospitalized patients. For these reasons, additional therapeutic agents are needed in the fight against SARS-CoV-2.

In this study, we set out to determine if there was a molecular basis for possible activity of Cefuroxime against SARS-CoV-2 by conducting a scoping review of literature of *in silico* drug-repurposing experiments against SARS-CoV-2. We identified 6 original articles from 4 continents that, from a large library of existing drugs, reported Cefuroxime as a top-ranked potential inhibitor of 3 key SARS-CoV-2 proteins. Four studies reported that Cefuroxime may inhibit Mpro, one study reported Cefuroxime may inhibit RdRp, while another reported Cefuroxime may inhibit the ACE2-Spike protein binding complex. These findings suggest that there is an *in silico* basis to assume Cefuroxime may be active against SARS-CoV-2. Although not previously known to have antiviral activity (GlaxoSmithKline, 2019), given the reported strong binding to 3 SARS-CoV-2 proteins *in silico*, Cefuroxime may be a multi-target inhibitor of SARS-CoV-2. Multi-target agents carry the prospect of being more robust and more likely to live up to expectations as they tend to be less affected by individual differences in response, modifications in key disease- relevant biological pathways, and the activation of compensatory mechanism (Talevi, 2015; Xie et al., 2012; Zimmermann et al., 2007).

To the best of our knowledge, this is the first review to suggest Cefuroxime as a possible "weapon" in the fight against SARS-CoV-2. However, the clinical usefulness of Cefuroxime for COVID-19 will depend on its clinical efficacy and safety profile. To determine clinical efficacy, phase II/III clinical trials are needed. Regarding safety, Cefuroxime has a good profile. The most common adverse drugs reactions are gastrointestinal effects; nausea, vomiting, and diarrhea, and these effects are dose dependent, occurring with higher doses and longer duration of use (Emmerson, 1988; Henry et al., 1995). In one large study, gastrointestinal adverse effects were seen in less than 5% of patients with only 2.2% discontinuing use predominantly due to gastrointestinal side effects (Perry & Brogden, 1996). Consequently, one concern that may arise with its use for COVID-19 is the possibility of exacerbation of gastrointestinal symptoms of COVID-19. A systematic review/meta-analysis of 60 studies of gastrointestinal symptoms of COVID-19 reported a pooled prevalence of 17.6% with higher prevalence (17.1%) in patients with severe disease than patients with non-severe disease (11.8%). The most commonly reported symptoms were anorexia (26.8%), diarrhea (12.5%), nausea and vomiting (10.2%), and abdominal pain (9.2%). (Cheung et al., 2020). Therefore, if Cefuroxime were prescribed for COVID-19, worsening gastrointestinal symptoms would suggest either disease progression or adverse drug effects, the two of which can be distinguished by presence of symptoms such as dry cough, shortness of breath, loss of smell, loss of taste, which are seen with COVID-19 but not with Cefuroxime. Other adverse effects of Cefuroxime occur less commonly and have been estimated to occur in between 0.1% to 1% of subjects over several multiple-dose trials (GlaxoSmithKline, 2019).

Besides the possibility of being an inhibitor of SARS-CoV-2, there may be additional benefit to using Cefuroxime for COVID-19. Though actual numbers may vary, it is not uncommon for patients with COVID-19 to have suspected or confirmed bacterial super-infection or co-infection requiring antibiotic coverage. A single site study (Zhou et al., 2020) from China reported 15% prevalence of secondary bacterial infection among hospitalized patients while a rapid review of literature of bacterial and fungal co-infection among COVID-19 patients (Rawson et al., 2020) reported 8% bacterial/fungal co-infection. Nevertheless, up to 70% of hospitalized patients received empiric antibiotics for suspected bacterial

infection (Cox et al., 2020; Rawson et al., 2020). Since Cefuroxime is a broad spectrum antibiotic with excellent activity against many respiratory pathogens, it is reasonable to consider it as an option for empiric therapy in suspected cases of bacterial super-infection/co-infection, particularly for patients with mild disease (non-hospitalized patients or hospitalized patients without respiratory compromise), pending the isolation of a specific pathogen. Patients with moderate-to-severe disease with suspicion of bacterial super-infection will likely benefit from broader empiric coverage than offered by Cefuroxime as they are at a higher risk of mortality (Lippi & Plebani, 2020; Zhou et al., 2020).

There are certain limitations in our scoping review that should be acknowledged. First, there was significant heterogeneity among the studies we reviewed, especially with regards the methodology. While this can be regarded as a strength, this also hints at need for reproducibility. Second, only studies that reported Cefuroxime as a top-ranked drug were included in this study. There are many other studies that did not identify Cefuroxime as a top-ranked drug. Consequently, it is unclear if the 6 studies included in this review represent a significant finding in the larger body of literature on *in silico* drug repurposing for COVID-19. An early systematic review of *in silico* drug repurposing for COIVD-19 identified 21 studies (Mohamed et al., 2020), which included one paper in this study. Since then, several studies have been published. Consequently, new systematic reviews are needed to evaluate the significance of our findings. Third, this was a review of *in silico* studies. Further *in vitro* and *in vivo* studies are required to determine the efficacy of Cefuroxime and its potential as a therapeutic agent against SARS-CoV-2.

Conclusion

COVID-19 is a significant public health emergency that carries a pressing demand for an effective therapeutic. Due to the urgency of this health crisis, drug repurposing is the most efficient method of meeting this need. Successful interventions may require action on multiple targets of the SARS-CoV-2 virus. The second-generation cephalosporin Cefuroxime demonstrates potential activity against three SARS-CoV-2 proteins in *in silico* experiments and may be a promising multi-target inhibitor. Cefuroxime's long history of population monitoring makes it a reliable option for further *in vitro* and *in vivo* studies in the fight against COVID-19.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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