

A fuzzy logic-based computational method for the repurposing of drugs against COVID-19

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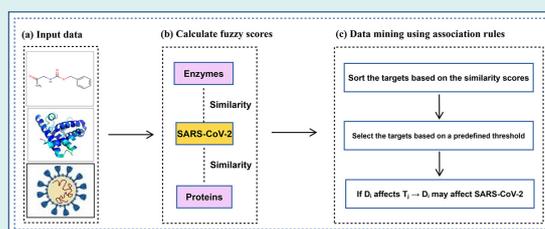
Abstract

Introduction: COVID-19 has spread out all around the world and seriously interrupted human activities. Being a newfound disease, not only many aspects of the disease are unknown, but also there is not an effective medication to cure the disease. Besides, designing a drug is a time-consuming process and needs large investment. Hence, drug repurposing techniques, employed to discover the hidden benefits of the existing drugs, maybe a useful option for treating COVID-19.

Methods: The present study exploits the drug repositioning concepts and introduces some candidate drugs which may be effective in controlling COVID-19. The suggested method consists of three main steps. First, the required data such as the amino acid sequences of targets and drug-target interactions are extracted from the public databases. Second, the similarity score between the targets (protein/enzymes) and genome of SARS-COV-2 is computed using the proposed fuzzy logic-based method. Since the classical approaches yield outcomes which may not be useful for the real-world applications, the fuzzy technique can address the issue. Third, after ranking targets based on the obtained scores, the usefulness of drugs affecting them is examined for managing COVID-19.

Results: The results indicate that antiviral medicines, designed for curing hepatitis C, may also cure COVID-19. According to the findings, ribavirin, simeprevir, danoprevir, and XTL-6865 may be helpful in controlling the disease.

Conclusion: It can be concluded that the similarity-based drug repurposing techniques may be the most suitable option for managing emerging diseases such as COVID-19 and can be applied to a wide range of data. Also, fuzzy logic-based scoring methods can produce outcomes which are more consistent with the real-world biological applications than others.



Introduction

Since the emergence of coronavirus disease 2019 (COVID-19), researchers have tried to discover its biological behavior and its mechanism of action.¹ The disease is caused by the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) which is a new member of the beta coronavirus subfamily.^{2,3} The virus has a single-stranded positive-sense RNA genome that is 79% similar to SARS-CoV and 50% similar to Middle East respiratory syndrome coronavirus (MERS-CoV) in term of genomic sequence.⁴ The virus complete genome was published on

January 12, 2020, in the GISAD database.⁵ Analysis of the virus encoding sequences shows that its 30 kb genome encodes 14 open reading frames (ORFs). ORF1a and ORF1b, on the 5'-end of the genome, encode a polyprotein that converts to 16 nonstructural proteins (NSPs 1-16) by autoproteolytic degradation to form the replicase-transcriptase complex, whose members of this complex are involved in the virus transcription and replication. This complex includes Papain-like protease (NSP3), Main protease (NSP5), and primary RNA-dependent RNA polymerase (RdRp or NSP12), which are considered



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drug targets for inhibiting virus replication activity.⁶ The four main ORFs on the 3'-end of the genome of the virus also encode the structural proteins spike glycoprotein (S), envelope (E), membrane (M), and nucleocapsid (N) proteins.⁷

Currently, countries all around the world are faced with a big challenge and are trying to come up with a suitable treatment plan.⁸ Whereas some aspects of the virus are unknown, producing an efficient medication may require a long time. In addition, the process of developing a drug is a very time-consuming procedure and needs a huge investment.⁹ Therefore, researchers are testing alternative approaches such as drug repositioning, which aims to investigate the effectiveness of the existing drugs on COVID-19.¹⁰ Regardless of cost reduction, the drug repurposing technique trims development time of drug development projects and may play a critical role in curing the disease.¹¹ Moreover, some drug development projects, which have failed due to various reasons such as safety, low performance, side effect issues, bioavailability, etc., may be revived and used for treating COVID-19.¹²

To address the mentioned challenge, this study offers a fuzzy logic-based drug repurposing method which contains two main contributions. First, a fuzzy logic-based alignment technique is proposed to compute the similarity score between the amino acid sequences of the existing protein targets and genome of SARS-CoV-2. Although there is the main challenge for scoring matches, insertions, and deletions between the sequences, the fuzzy logic can address such the limitation. This principle can obtain results which are more consistent with real-world applications than classical methods. Second, potential drugs, which may help treat COVID-19, are detected based on the calculated scores. The medications, which affect the targets sharing a higher value of sequence similarity score with SARS-CoV-2, may have an application in curing the disease. The proposed approach utilizes information existing in the sequences of the targets (proteins or enzymes as well as the genome of SARS-CoV-2). The amino acid sequence of a protein is considered the primary structure of that protein and determines the secondary, tertiary, and quaternary structures of a protein. Proteins can play a structural or functional role through their tertiary or quaternary structures. Each protein can form unique structural and functional motifs due to its specific amino acid sequence. Thus, the amino acid sequences of a protein and being directly involved in its function can also indirectly affect its function through its effect on forming the protein's spatial structure. Hence, proteins with similar amino acid sequences are more likely to have the same structure and function.

Since the COVID-19 outbreak, different efforts have been made to obtain vaccines worldwide to increase the body's immunity to the SARS-CoV-2 and reduce the mortality rate. Fortunately, vaccines for the virus were developed quickly, and according to the World Health

Organization (WHO) reports, up to now (February 12, 2021), 66 vaccines are in clinical trials. Some of these vaccines included in the clinical trials have been approved and licensed for utilization, such as Pfizer-BioNTech, Moderna, Comirnaty, AstraZeneca, and Sputnik V.

The main contributions of this study are listed as follows:

- i) Introducing a novel fuzzy logic-based sequence alignment algorithm
- ii) Proposing some candidate medications for combating COVID-19.

Related works

For the repurposing of drugs, researchers have proposed various approaches such as *in silico*, *in vitro*, and *in vivo* techniques.¹³ Computational methods are at the center of the attention for researchers since they reduce time and produce helpful solutions.^{14,15} In this study, the computational techniques have been divided into several categories as follows:

i) **Molecular docking techniques:** most of the carried out studies fall into this class of computational methods and consider the 3D structure of SARS-CoV-2's proteins and existing drugs.¹⁶ Usually, two classes of docking methods exist. The first class determines whether two biological components complement each other or not in terms of the total number of bonds and their properties such as the length of the bond. The second class calculates the existing energy between elements.¹⁷ The lower the potential energy; the tighter the interaction between two biological components.^{13,18} The two above-mentioned approaches have been frequently used, which each of them face some advantages and disadvantages. The docking methods are very time-consuming processes and are not practical to use on larger scales. For instance, it is not possible to calculate the score between all the existing drugs and components of SARS-CoV-2. In addition, if the 3D structure of a protein is not available, these approaches cannot be employed. Unlike these techniques, our proposed method can be used on a large scale and does not rely on the 3D structure of a protein.

ii) **Machine learning (ML) techniques:** these methods create machines that mine relationships between inputs and outputs.¹⁹ For example, they can be used to discover whether a drug and a target may interact or not.²⁰ In this field, many types of learners, such as support vector machine, decision tree, artificial neural network, and many other approaches are used.^{21,22} Although ML methods can produce a model in an acceptable time and lead to desired results, they face particular challenges in generating a model. There is also another type of artificial neural networks which is known as deep neural networks and has a higher prediction capacity.²³ For example, using deep learning approaches, an attempt to design potential inhibitors of SARS-CoV-2 has been carried out.²⁴ The ML-based approaches face a great challenge in invalidating the predicted outcomes. To this end,

researchers usually compare their outcomes with other experimentally reported data or use docking methods to score the interactions between the predicted drug and target. ML methods also require an adequate volume of data to generate an acceptable model. Although our fuzzy logic-based proposed method needs secondary validation techniques such as molecular docking, it only depends on the amino acid or nucleotide sequence of the targets and viruses and, unlike the ML methods, can be used in the early stage of a disease pandemic.

c) **Network-based techniques:** biological elements are part of a complex system, which can be modeled by the graph theory concepts.²⁵ By doing this, a network of different biological components and their relationships is formed.²⁶ Then, graph analyzing algorithms are applied to discover hidden information and introduce effective therapeutic plans against COVID-19.^{27,28} Drug repurposing using a generative network method, is an approach that researchers have introduced to identify potential drugs for curing COVID-19. For this purpose, associated genes with SARS-CoV-2 have been considered as the seeds of biological communications, and the network has then been extended by them. In other words, the interactions between the elements of SARS-CoV-2 (including genes or proteins) and the host cell are constituted. After analysis, the desired targets have been specified, and some potential drugs have been proposed for controlling them.²⁹ Since some aspects of SARS-CoV-2 are unknown, it is essential to produce data of interest by experimental techniques such as mass spectrometry. Hence, as the ML approaches, this category of the methods cannot be used in the early stages of a pandemic whereas the method proposed in this study can address this limitation.

d) **Hybrid techniques:** the main idea of the hybrid methods is to utilize the advantages of single approaches and obtain an efficient method with higher reliability capabilities.³⁰ For example, researchers have proposed a two-step technique for the repurposing of drugs against COVID-19. To this end, first, the candidate drugs have been chosen using a computer-aided method. Second, the docking techniques have been applied to select drugs that may have a proper functionality in treating COVID-19.^{31,32} Besides, another study has combined the statistical and ML methods and has generated an efficient model for predicting drugs, which may be useful in curing COVID-19.³³ To validate the approach, the researchers have used medications exploited for healing SARS and MERS diseases. Although these techniques utilize the benefits of each of the single methods used in the combined procedure, they may suffer from their synthetic disadvantages.³⁴

The proposed method of this study is a similarity-based technique, which considers the likeness between the amino acid sequence of targets (proteins and enzymes) and the genome of SARS-CoV-2. The approach uses fuzzy logic to score the insertions/deletions and the matches in the sequences and aims to reduce the false-positive rate.

Methods

To discover potential drugs which may be useful in curing COVID-19, the present study suggests a fuzzy-based computational approach. Fig. 1 depicts the framework of the proposed method. Fig. 1 includes three main parts as follows:

a) *Collecting data:* the amino acid and nucleotide sequences of the existing enzymes and proteins have been

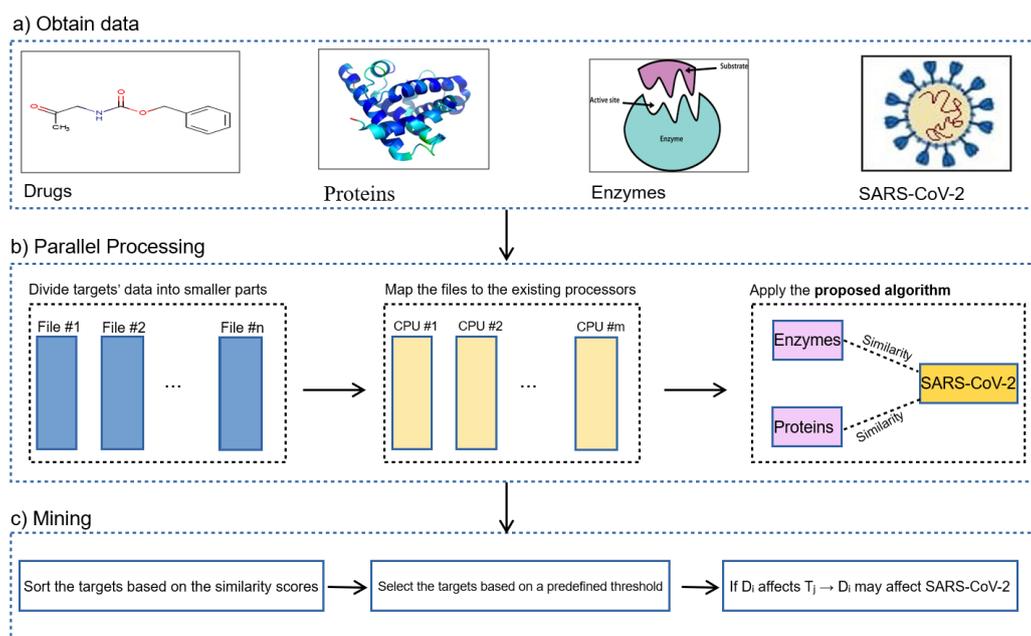


Fig. 1. The framework of the proposed method. First, the data, including proteins and enzymes, are divided into smaller parts, and they are mapped to the existing CPUs. Second, a fuzzy-based similarity algorithm is applied to compute the similarity between the amino acid sequence of targets and SARS-COV-2.

acquired from DrugR+,³⁵ which is a relational version of DrugBank³⁶ and consists of some information about the KEGG³⁷ database. The database also includes drug-targets interaction data and different chemical properties of drugs. Besides, the genome of SARS-CoV-2 has been extracted from PDB.³⁸ The extracted data consist of 4893 drugs and more than 18000 drug-target interactions.

b) *Applying parallel processing techniques*: due to the sheer volume of data, it is essential to utilize parallel processing approaches. For every target, a file, including the profile of the targets (such as the drugs affecting them, their amino acid and nucleotide sequences, the genes coding them, etc.), is generated. Then, they are assigned to the existing CPUs to compute the similarity between the genome of SARS-CoV-2 and the extracted sequences of proteins and enzymes. To this end, different types of algorithms such as Smith-Waterman, longest common substring, and some others can be used as well.³⁹ Since finding a suitable similarity strategy is a challenging problem in computational biology, fuzzy logic, which may produce results consistent with the biological real-world facts, can be a proper option. To implement the fuzzy logic, three steps are considered, as follows:

(1) Fuzzification: the classical inputs are turned into fuzzy data. For this purpose, the inputs are mapped to the membership functions, and it is determined how much a value belongs to a specific group. The inputs incorporate two main components:

First, the total number of matched amino acids between the sequence of a given target and the genome of SARS-CoV-2 is calculated. To this end, an $R \times C$ matrix, named M , is constituted and is completed using Eq. 1. R and C are the length of the first and the second sequences, respectively.

$$M(i, j) = \begin{cases} M(i-1, j-1) + 1 & \text{if a match is occurred} \\ \max(M(i-1, j), M(i, j-1)) & \text{else} \end{cases} \quad (1)$$

The maximum value of M (MAX) shows the total number of the matched amino acids, and MAX divided by the length of the given sequence represents the match percentage between two sequences.

Second, the percentage of insertions and deletions ($INDELS$), which is computed by Eq. 2, is specified. R indicates the length of the sequence.

$$INDELS = \frac{R - Max}{R} \quad (2)$$

Based on the calculated percentage of the matches and $INDELS$, the final similarity score is determined. For the inputs, three fuzzy sets including low, medium, and high sets have been considered. Fig. 2A-C depicts the coverage range of the sets. To determine the ranges of the sets, a phylogenetic tree between different organisms were considered, and, based on the distance among them, the ranges were specified. For instance, for some

entities having the farthest distance, 50% of similarity was observed. Hence, the $[0, 50]$ range was selected for the low setting.

(2) Fuzzy inference step: This process combines the fuzzy membership functions and the defined rules. Given the three fuzzy sets for the inputs, nine rules, shown in Table 1, have been defined.

(3) Defuzzification: many methods have been proposed for concluding the fuzzy output. Mean of maximum, center of gravity (COG), and height methods are commonly used. Because the outputs of this step are continuous values, COG method, considering all areas of the output, has been used in this study. Eq. 3 presents how the defuzzification process is done.

$$COG(S) = \frac{\int \mu_s(x) x dx}{\int \mu_s(x) dx} \quad (3)$$

Where s and x indicate the fuzzy set and the input value of the output membership function, respectively.

c) *Mining*: the targets are ranked based on their calculated fuzzy similarity scores, and, the list is filtered by a prespecified threshold. Next, a defined association rule is applied to discover the drugs that may help treat COVID-19. A drug (D) that affects a target (T) which is similar to the genome of SARS-CoV-2, may inhibit the virus and show therapeutic properties. The mentioned rule has been shown as follows:

If a drug such as D affects a target such as T then D may be useful in curing COVID-19.

Results

The proposed fuzzy-based method was implemented in the python programming language. As mentioned before, the amino acid sequence of protein and enzyme targets, as well as drug-target interactions, were extracted from DrugR+ database. After applying the proposed method to the data, the targets were sorted by the calculated fuzzy similarity scores. The range of the scores fitted between 0 and 93, among which, the score of 10 targets was more than 65. Table 2 explains the mentioned targets and their properties. The listed targets perform several biological functions, including:

- ATP binding activity: adenosine triphosphate (ATP) is an organic compound that is responsible for preparing energy for cell activities. Some proteins interact with ATP and transport different substrates within or outside of a cell.
- Cysteine-type endopeptidase activity: it is an activity in which proteins play the main role in apoptotic cell death.
- Ion-channel activity: ion-channel proteins move across the cell membrane and transport some ions into the cell.
- RNA binding activity: a specific type of proteins, named RNA binding proteins, connect to RNA and

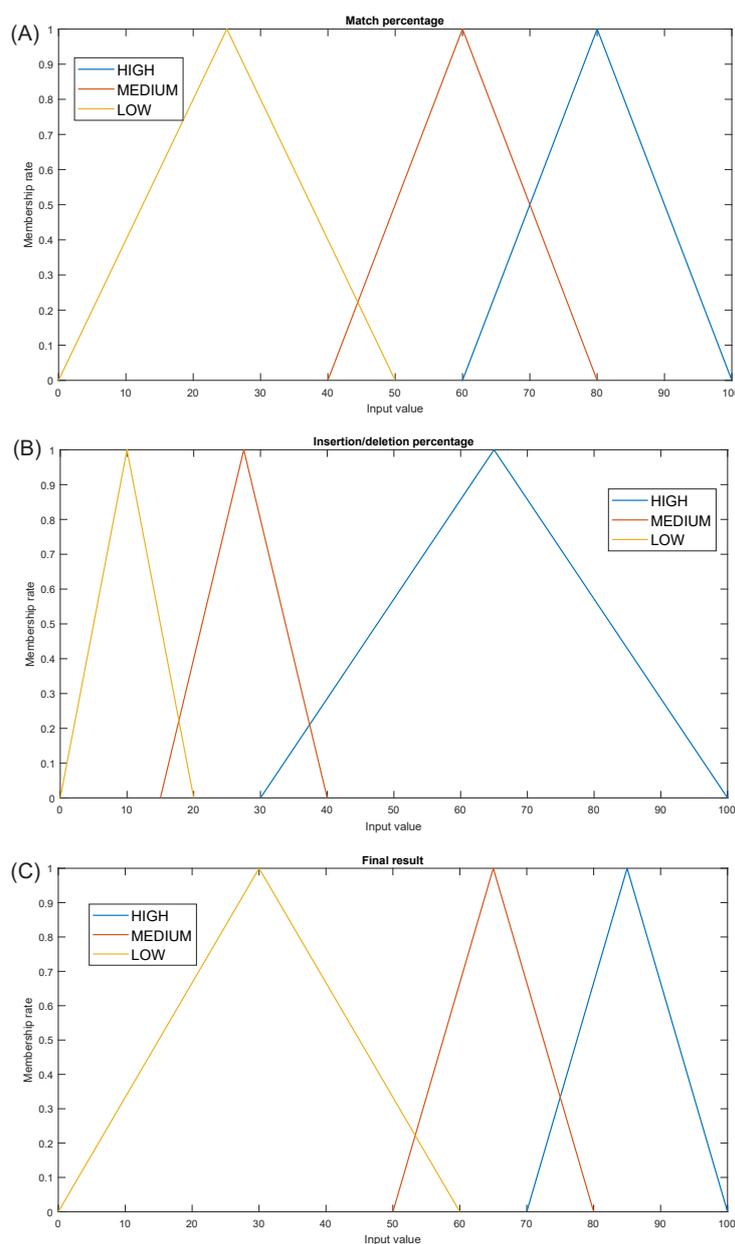


Fig. 2. Fuzzy membership function for the (A) matched elements, (B) unmatched elements and (C) final similarity.

- help to form ribonucleoproteins.
- e. RNA helicase activity: helicase enzymes, also known as motor proteins, unpackaged genes of an organism.
 - f. RNA-directed RNA polymerase activity: this activity is referred to as the specific type of viral enzymes that are responsible for catalyzing RNA replication.
 - g. Structural molecule activity: the activity is the contribution of a protein or enzyme to form complex molecular components.

The discovered targets can be inhibited by 23 drugs which have been listed in Table 3. This Table consists of different medicines from the approved and clinical investigation groups. Two classes of drugs exist in Table 3. The first class is the small molecules group which incorporates chemical compounds having less than 900 Dalton molecular weight.

Small molecules drugs, which have more therapeutic properties than non-small molecule medicines, can be considered as a tool for probing biological functions.⁴⁰ The second category is biotech drugs, which researchers have recently been interested in them. These drugs use biotechnology as a means to manipulate microorganisms such as bacteria. Then, the organisms can perform a specific biological process.

Fig. 3 depicts the relationships between the targets and the drugs affecting them. COVID-19 (the disease induced by SARS-CoV-2) has been shown in the core of communications. The targets, which share an impressive number of sequence individuals with the virus (determined by the proposed fuzzy score), exist in the second level. Also, the drugs, having an interaction with

Table 1. The defined rules

No.	Rule
1	If the similarity percentage is HIGH and the INS is LOW then the similarity is HIGH
2	If the similarity percentage is HIGH and the INS is MEDIUM then the similarity is MEDIUM
3	If the similarity percentage is HIGH and the INS is HIGH then the similarity is LOW
4	If the similarity percentage is MEDIUM and the INS is LOW then the similarity is MEDIUM
5	If the similarity percentage is MEDIUM and the INS is MEDIUM then the similarity is LOW
6	If the similarity percentage is MEDIUM and the INS is HIGH then the similarity is LOW
7	If the similarity percentage is LOW and the INS is LOW then the similarity is LOW
8	If the similarity percentage is LOW and the INS is MEDIUM then the similarity is LOW
9	If the similarity percentage is LOW and the INS is HIGH then the similarity is LOW

Table 2. The protein targets sharing a higher value of similarity with the SARS-CoV-2's genome

Target ID	Description	Length	Score
BE0001031	Basement membrane-specific heparin sulfate proteoglycan core protein	13492	65
BE0001261	Genome polyprotein	10362	93
BE0001283	Apo lipoprotein(a)	13900	73
BE0001478	Genome polyprotein	9208	69
BE0002110	Prolow-density lipoprotein receptor-related protein 1	13940	80
BE0002460	E3 ubiquitin-protein ligase UBR4	15868	78
BE0002813	Genome polyprotein	10368	68
BE0003427	Genome polyprotein	9211	91
BE0003801	Replicase polyprotein 1ab	21624	88
BE0003935	Genome polyprotein	9211	79

Table 3. The detected potential medications and their descriptions

ID	Name	Drug type	Description
DB00031	Tenecteplase	Biotech	Tissue plasminogen activator
DB00039	Palifermin	Biotech	Recombinant human keratinocyte growth factor
DB00513	Aminocaproic acid	Small molecule	This drug inhibits plasminogen activator
DB00811	Ribavirin	Small molecule	The drug interferes with the synthesis of viral mRNA.
DB02331	Phenyl-Propionic acid	Small molecule	It is an experimentally validated drug and its application has not been reported
DB03605	Propionic acid	Small molecule	It is an experimentally validated drug and its application has not been reported
DB04005	Uridine 5-triphosphate	Small molecule	The drug consists of three phosphate groups esterified to the sugar moiety.
DB04298	Dihydro-pyran-2-one	Small molecule	It is an experimentally validated drug and its application has not been reported
DB04473	Alpha-L-fucose	Small molecule	It is an experimentally validated drug and its application has not been reported
DB04959	Verpasep caltespen	Biotech	It is a vaccine and is an immune system booster
DB05868	Ciluprevir	Small molecule	It acts against HCV NS3 protease
DB06058	XTL-6865	Small molecule	The drugs operate against the hepatitis C virus
DB06974	phenylpyridazin	Small molecule	It is an experimentally validated drug and its application has not been reported
DB07062	methanesulfonamide	Small molecule	It is an experimentally validated drug and its application has not been reported
DB07293	benzyl (2-oxopropyl) carbamate	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08578	oxobutanoic acid	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08579	dimethylpiperidin	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08580	(2-chlorobenzyl) pyrrolidin	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08581	dimethylpiperidin-1-y	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08582	Morpholin-4-yl-4-oxobutanamide	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08644	CARBAMIC ACID	Small molecule	It is an experimentally validated drug and its application has not been reported
DB08656	Amino-2-methyl	Small molecule	It is an experimentally validated drug and its application has not been reported
DB11779	Danoprevir	Small molecule	The drug is in the investigation phase and has been developed for treating hepatitis C

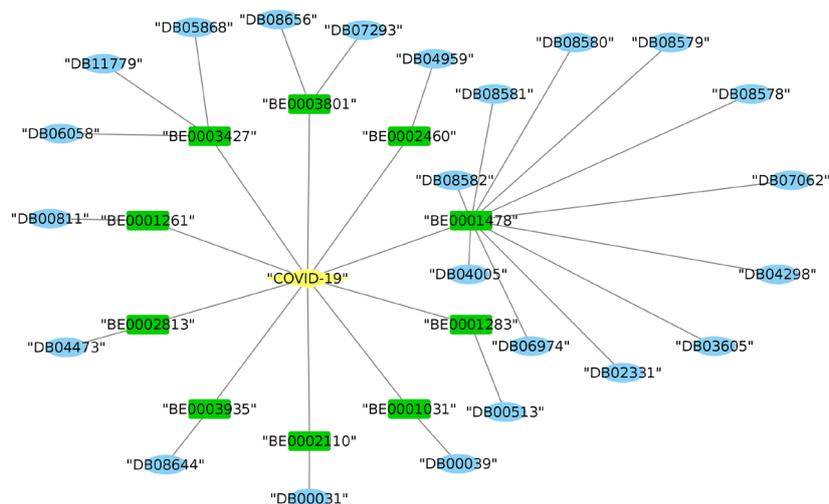


Fig. 3. The drugs and their similar targets to SARS-CoV-2. Yellow, green, and blue colors show the virus related to COVID-19, the targets, and the drugs, respectively.

the identified targets, have been shown in the third layer.

Table 2 consists of 4 medications (ribavirin, ciluprevir, XTL-6865, and danoprevir) whose antiviral applications have been experimentally proved. These medications have been developed for curing hepatitis diseases and maybe a proper plan in treating COVID-19 given their scores. Fig. 4 represents the chemical structures of the drugs except for XTL-6865 whose data was not available in databases.

Discussion

This study proposed a novel fuzzy logic-based method for calculating similarity scores between the amino acid sequence of the existing targets and the genome of SARS-CoV-2, which utilized parallel processing techniques due to the huge volume of the existing data. Although different algorithms have been introduced for computing

the similarity score between sequences,⁴¹ they confront some challenging issues such as scoring matches and gaps of the given sequences and may increase the false-positive rate of the predictions. In other words, they may produce outcomes, which are not consistent with real-world biological applications. The proposed fuzzy logic-based method can address this limitation and can be considered as a straightforward therapeutic plan for curing emerging infectious diseases because of its capabilities in discovering potential medicines based on the rudimentary information on the genome sequence of the virus. Also, in the early stages of an infectious disease in which many aspects of its pathogenesis are unknown (e.g., there is not enough information on the proteins of the virus), the proposed fuzzy logic-based computational method can be helpful and may propose candidate drugs

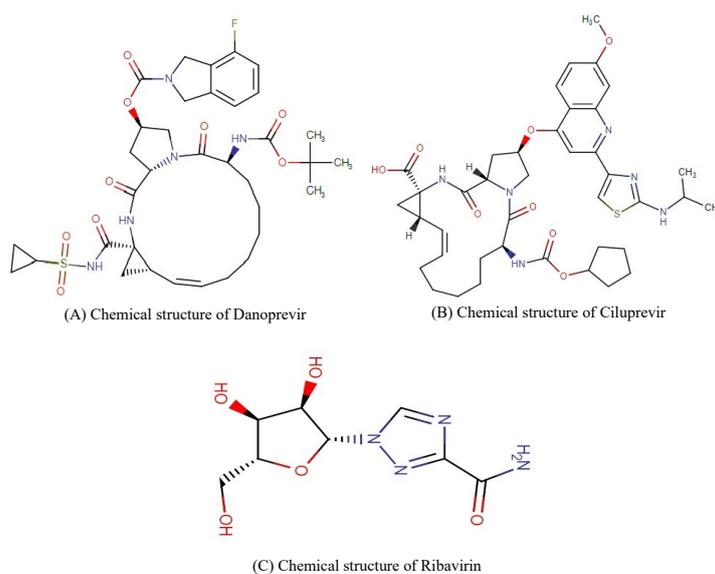


Fig. 4. Except for XTL-6865, the chemical structure of the proposed drugs has been depicted.

for treating the emerged disease.

The final output of the proposed approach is 23 drugs, which have a higher sequence similarity score with the genome of SARS-CoV-2 than the others. Among them, 4 medications (ribavirin, ciluprevir, XTL-6865, and danoprevir) have antiviral traits that have been clinically validated. The drugs have been designed for managing hepatitis patients.⁴² Hepatitis, having several types and be induced by different agents, is an inflammation of an area between the liver tissues. Viruses are one of the most prevalent reasons for hepatitis difficulties and can seriously threaten the life of patients.

The outcomes of the proposed methods consist of three hepatitis medications: Ciluprevir, danoprevir, and ribavirin. Ciluprevir is an antiviral medication that is used for controlling hepatitis type C. The experimental studies have shown that this medicine is an inhibitor of nonstructural protein 4A (NS4A) and nonstructural protein 3 (NSP3). NS4A is a viral protein found in the hepatitis C virus (HCV) and is a cofactor of the NSP3 enzyme. Like NS4A, NSP3 is a viral NSP and plays a role as a serine protease, helicase, or nucleoside triphosphatase. Furthermore, a portion of its amino acids is a cofactor domain for NS2. Ciluprevir has been tested on humans in the clinical phase and has shown a remarkable effect on the patients. However, its development has been halted due to the observation that it has a higher value of toxicity in animals. The ideas obtained from developing ciluprevir led to the development of simeprevir and danoprevir that have shown impressive antiviral activities.⁴³ Simeprevir significantly reduces the viral load when combined with remdesivir. It acts by inhibiting the M^{pro} (or NSP5) and RNA-dependent RNA polymerase (RdRp).⁴⁴ Concomitant use of ribavirin and Simeprevir is likely to reduce the effects of COVID-19. Unlike simeprevir, ciluprevir has higher toxicity, but it may be a suitable option for combination therapy. Using a minimum dosage of medications, combination therapy may enhance the efficacy of drugs and can revive many drugs that halted during different drug development phases.^{45,46}

Danoprevir, inspired by the ciluprevir project, is also a 15-membered macrocyclic peptidomimetic inhibitor of nonstructural proteins (NS4A/NSP3). From a pharmaceutical perspective, the half-maximum inhibitory concentration (IC₅₀) and effective concentration (EC₅₀) of danoprevir are 0.2-0.4 nM and 1.6 nM, respectively. These parameters state that the medication has a very favorable profile and is an interesting option for curing viral diseases such as hepatitis C.⁴⁷ Ribavirin, playing a critical role in blocking viral RNA synthesis, is used for curing hepatitis C patients and is a very helpful agent in managing hemorrhagic fevers and hantavirus infections. This drug, as a guanosine analog, has several effects on the various RNA and DNA viruses and acts as a competitive inhibitor of the inosine monophosphate dehydrogenase enzyme, which is a critical enzyme in the synthesis of de

Research Highlights

What is the current knowledge?

- ✓ A similarity-based method has been introduced for the repurposing of drugs against COVID-19.
- ✓ Fuzzy logic may yield to the outcomes which are more consistent with the real-world biological applications.

What is new here?

- ✓ The proposed fuzzy logic-based method investigates huge volume of the existing data and proposes some medications for curing COVID-19.

novo purine nucleotides.⁴⁸ By inhibiting this enzyme, the amount of intracellular GTP storage is reduced, indirectly reducing the viral polymerase activity. Also, ribavirin is involved in inhibiting viral polymerase's catalytic activity and interfering with the mRNA capping process, thereby preventing virus replication. Clinical trials have also shown that ribavirin inhibits SARS-CoV-2's replication at micromolar concentrations.⁴⁹ Although this medicine has shown a very desired effect on patients, it has several side effects. Hence, ribavirin may be combined with newer antiviral drugs developed for treating hepatitis C.⁵⁰ Besides, a combination of ciluprevir and Ribavirin may show a synergistic effect in curing COVID-19 and reduce the toxicity of ciluprevir and the side effects of ribavirin. In some studies, the helpfulness of ribavirin has been evaluated and discussed. For instance, in a docking-based computational approach, it has been indicated that ribavirin, Sofosbuvir, and Remdesivir can bind to the SARS-CoV-2 RdRp enzyme.⁵¹

Like the above-mentioned drugs, XTL-6865 is an antiviral agent which is used for curing viral diseases.⁵² This drug, which is a combination of two human antibodies ab68 and ab65, is a small molecule, which tries to prevent virus entry into a cell. Researchers have followed two main goals in developing XTL-6865. First, they aim to hinder viral re-infection after doing a liver transplant. Second, they aim to introduce an effective drug for curing chronic HCV. Since the drug is in the investigational group of medications, its different properties have not been reported.

Conclusion

COVID-19 is an emerging disease, and there is an urgent need for detecting a proper treatment plan for inhibiting it. In order to cut down on the time, computational-based drug repurposing approaches may be a helpful plan and can propose potential drugs in a short time. This study introduced a fuzzy logic-based computational method for the repurposing of drugs against COVID-19. The proposed approach calculated the sequence similarity scores in such a way that they are more compatible with real-world biological concepts. The outcomes showed

that hepatitis C antiviral drugs can be useful in treating COVID-19. Although some drugs have a suitable profile in treatment, some others have a higher value of toxicity and a large number of side effects. Therefore, combination therapy can alleviate such limitations and can yield an efficient treatment plan for combating COVID-19.

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Ethical statement

Not applicable.

Competing interests

None.

Authors' contribution

YMS: Conceptualization, data preparing, formal analysis, investigation, writing-manuscript. AMN: Conceptualization, Supervision, project administration, editing the manuscript. Both the authors have read and approved the manuscript.

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