Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A contemporary review on the important role of *in silico* approaches for managing different aspects of COVID-19 crisis

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ABSTRACT

In the last century, the emergence of *in silico* tools has improved the quality of healthcare studies by providing high quality predictions. In the case of COVID-19, these tools have been advantageous for bioinformatics analysis of SARS-CoV-2 structures, studying potential drugs and introducing drug targets, investigating the efficacy of potential natural product components at suppressing COVID-19 infection, designing peptide-mimetic and optimizing their structure to provide a better clinical outcome, and repurposing of the previously known therapeutics. These methods have also helped medical biotechnologists to design various vaccines; such as multi-epitope vaccines using reverse vaccinology and immunoinformatics methods, among which some of them have showed promising results through *in vitro*, *in vivo* and clinical trial studies. Moreover, emergence of artificial intelligence and machine learning algorithms have helped to classify the previously known data and use them to provide precise predictions and make plan for future of the pandemic condition. At this contemporary review, by collecting related information from the collected literature on valuable data sources; such as PubMed, Scopus, and Web of Science, we tried to provide a brief outlook regarding the importance of *in silico* tools in managing different aspects of COVID-19 pandemic infection and how these methods have been helpful to biomedical researchers.

1. Introduction

Bioinformatics is an area of biology that focuses on the use of computer-based methods for studying the biological systems, which could provide some precise predictions that might come true in laboratory studies and clinical trials [1]. The emergence of computer-based biological methods has revolutionized the life science studies, and thanks to the bioinformatics methods, a lot of pressure related to the costs of laboratory works and animal sacrifices has been reduced from medical centers. The *in silico* techniques come useful for categorizing the proteins based on their structure and function, and could be helpful when we need to develop servers for assorting these molecules by using machine learning (ML) methods [2–4].

Moreover, the *in silico* methods of studying molecular interaction; such as molecular docking could be used for analyzing the potential natural therapeutics ligands and receptor complexes [5,6]. These methods could also provide information regarding the unknown molecular structures, including enzymes and their potential ligands [7–9], which could be important in future genetic engineering studies in different area of biotechnology. These *in silico* methods could also be used for optimizing the structure of biotherapy agents, like decoy ODNs, that their efficacy has been reported to suppress cancer cells in various malignancies, such as breast and colorectal cancer [10,11]. These advents come really useful for developing modern therapeutics, for example designing the multi-epitope vaccine constructs that are a new type of vaccines, with more benefits than the previous ones [12].

One of the critical conditions in which bioinformatics and *in silico* methods proved their importance was during the COVID-19 outbreak [13]. The universal crisis of COVID-19 is caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started at 2019 in Wuhan (China) [14]. Since the beginning of this life threatening crisis, many attempts have been devoted to study the different structures of this

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virus, providing molecular modeling of the viral structures, and to develop preventive and therapeutic agents against SARS-CoV-2 [15].

Since the beginning of the COVID-19 pandemic, the experts in the field of *in silico* studies have devoted an enormous contribution to the healthcare providers by classification of COVID-19 related data through ML methods [16], presenting precise predictions regarding the new molecular structures in SARS-CoV-2, investigating the efficacy of potential drugs against different targets in COVID-19 virus [17], developing preventive agents such as vaccines, and analyzing the potential therapeutic efficacy of the natural products and improving the efficiency of the synthesized therapeutics; such as antimicrobial peptides and even designing novel agents, like peptidomimetics, to overcome this universal human life threatening condition [18].

The use of previously designed webservers such as I-TASSER [19] and Phyre2 [20] came really helpful for molecular modeling of protein structures prior to crystallography analysis, virtual screening of potential inhibitors for different viral targets, studying SARS-CoV-2 related molecular interactions via special molecular docking tools [21], dynamics simulations [22], and the immunoinformatics tools such as VaxiJen, T-cell and B-cell epitope prediction tools for investigating the potential target sequences for vaccine development. Moreover, the availability of immune response simulation tools has come helpful for COVID-19 vaccine design. Also, the application of ML algorithms has proved useful to assort the COVID-19 related information and helped to provide timely diagnosis [23] and even designing many useful special servers for future analysis of SARS-CoV-2 [24].

Overall, this review aims to provide a quick glance of how *in silico* methods have come useful for managing the different aspects of COVID-19 and their potential for application in future crisis conditions. Fig. 1 presents a schematic view of how *in silico* methods were useful at assisting life science experts to improve the quality of the researches at the time of COVID-19.

Through this manuscript, we tried to provide a concise review of the previous literatures of using *in silico* methods to battle COVID-19. The main topics are dealing with SARS-CoV-2 structure predictions and phylogenetic analysis, drug's virtual screening, natural source-derived chemicals, Anti-microbial peptides and peptidomimetics, SARS-CoV-2 vaccine design, and ML and Artificial Intelligence (AI). The last section of the article offers the potential of using some updated *in slico* tools to fight COVID-19, and explains how these techniques could be used against the possible future pandemics.

2. Evidence acquisition

At this study, it was aimed to provide a contemporary review of 132 related papers from the acquired published reports via searching the key words such as *in silico*, bioinformatics, immunoinformatics, SARS-CoV-2, Machine learning, Drug design, Vaccine design, and virtual screening, from valuable data centers including Web of Science, PubMed, and Scopus, Google scholar and the other valid data bases like preprint servers (bioRxiv, medRxiv, arXiv) to find out in what extent the *in silico* methods have helped researchers to handle this universal issue and to provide a perspective of possible future application of these computer-based methods.

3. Results

This section of the current review is composed of six subsections; including prediction of SARS-CoV2 structures using *in silico* method, virtual screening of potential drugs against this pathogen, prediction of potential natural compounds to suppress SARS-CoV2, application of anti-microbial peptides and peptidomimetics against COVID-19, designing vaccines, and artificial intelligence (AI) and different ML methods.

3.1. SARS-CoV-2 structure predictions and phylogenetic analysis

At the beginning of COVID-19 pandemic, there was not enough information regarding the structures of SARS-CoV-2 and its relation to the other viruses was not completely clear. At this condition, application of *in silico* methods came to assist the researchers by enriching their knowledge about this virus via providing valuable predictions such as homology modelings of this virus's structures [25]. Since the process to identify all components of SARS-CoV-2 virus by laboratory methods were time consuming, application of *in silico* methods helped the computer-aided researchers to be one stay ahead of those who only waited for the results of laboratory studies.

In an early study, Li et al. used in *silico* approaches like multiple sequence alignment, homology modeling, sequence analysis, virtual screening, reverse mutation, protein structure overlap and surface property analysis. Their study indicated that there is no significant difference in envelope protein, membrane protein, nucleocapsid protein and the key proteases in the open reading frame (ORF) 1 ab [26]. Another study by Baruah et al., used sequence analysis and structure prediction methods about SARS-CoV-2 accessory proteins 9b and ORF14. Their study suggested that there is a close relationship with bat

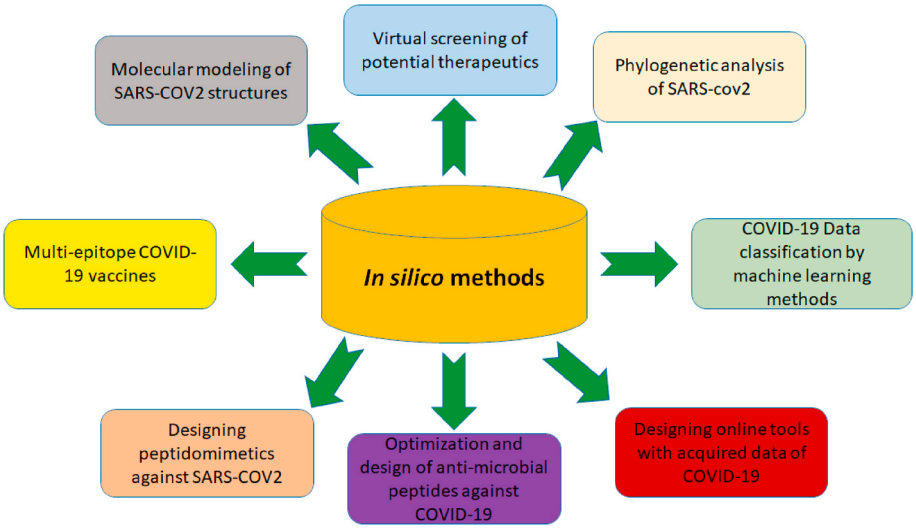

Fig. 1. The critical role of *in silico* assays in universal battle against COVID-19 and some of their application in medicine and biology.

coronavirus [27]. Another study by Vandelli et al., applied genome analysis approach on SARS-CoV-2, which provided a prediction of human interactome. For this aim, they calculated the secondary structure of >2000 coronaviruses and computed >100 000 human protein interactions with this virus [28].

In silico methods have also provided phylogenetic analysis of the SARS-CoV-2, which is an important technique for realizing the relationship of various structures with peer ones in the other viruses. A phylogenetic supertree investigation by Li et al. reported that matrix representation with parsimony (MRP) pseudo-sequence supertree could provide more information regarding the SARS-CoV-2 evolution inference compared to the normal phylogenetic tree analysis based on full-length genomic sequences [29]. Table 1 provides some examples of *in silico* structural predictions and phylogenetic studies regarding COVID-19.

3.2. Drug's virtual screening

One of the area in which *in silico* methods came helpful is virtual screening of potential anti-viral drugs for SARS-CoV-2. These *in silico* techniques have prevented a considerable time and expenses by removing the less likely effective drugs from considerations. Without application of these *in silico* methods, one should have tried all of the potential drugs in lab, that could be time consuming and very expensive. In this regard, so many studies have been carried out; such as an investigation by Pundir et al. who used the famous 5-steps rules of Chou for virtual screening of SARS-CoV-2 Mpro inhibitors. In that study, they used molecular docking, toxicity, pharmacophore analysis, and MD simulation which showed that two potent inhibitors of the Mpro (PubChem3408741 and PubChem4167619) act as anti-viral candidates against COVID-19 [35].

Repurposing of a previously known and safe drug against new target could help the researchers to use a previously known agent against a new target and avoid all of the unnecessary researches required for introducing a new drug which also faces a delay for medical application prior to all of the safety studies and approvals from medical resources. In this regard, a recent study by Mahdian et al. reported that application of *in silico* methods could be helpful for targeting SARS-CoV-2 RdRp enzyme and host cell receptors (ACE2, CD147) [36].

Another *in silico* study by Marinho et al. evaluated the molecular interactions of various drugs for treatment of COVID-19 (Azithromycin, Baricitinib and Hydroxychloroquine) and drugs with similar structures (Chloroquine, Quinacrine and Ruxolitinib) via molecular docking with SARS-CoV-2 main protease (Mpro) protein. Their study shed light of the fact that all of the inhibitors bind to the same enzyme site, among which domain III of the SARS-CoV-2 main protease was a more specific target [37]. Moreover, a study by Hu et al. claimed that virtual screening for human host cell transmembrane protease serine 2 (TMPRSS2) could provide a potential treatment through *in silico* step [38].

Application of QSAR modeling for drugs screening is another area that has considerably helped scientists to develop therapeutics, such as the study by Ishula et al. who used QSAR modeling and pharmacoinformatics of SARS coronavirus to investigate the 3C-like protease inhibitors [39]. Table 2 provides five more examples of using *in silico* methods for COVID-19 drugs screening.

3.3. Natural source-derived chemicals

In silico methods provide a platform for screening the activity of potential therapeutics against the molecular targets, which helps to select the ones with the highest potential activity for further *in vitro* and *in vivo* experiments. Focusing on only selected targets will reduce the cost for laboratory trial that requires financial and human resources [45]. One of the fields in which *in silico* methods have proved to be useful is investigating the efficacy of natural products-derived compounds against COVID-19 [46]. Regarding this area of biomedicine, *in silico* assays have come very helpful by providing simple and effective assays, such as molecular docking. From this perspective, a novel study by Xu et al., investigated the efficiency of flavonoid inhibitors against COVID-19 3CL protein by screening 2030 natural compounds via six ML algorithms. Their study indicated that compound Rutin presents the most satisfactory results compared to the other candidates [47].

Another study by Majumder et al. used molecular docking and dynamics assay to screen plan-based natural compounds against COVID-19. Their study showed that Peonidin 3-O-glucoside, Kaempferol 3-O-β–rutinoside, 4-(3,4-Dihydroxyphenyl)-7-methoxy-5-[(6-O-β-D-xylopyranosyl-β-D-glucopyranosyl)oxy]-2H-1-benzopyran-2-one, Quercetin-3-D-xyloside, and Quercetin 3-O-α-L-arabinopyranoside present high molecular docking scores, along with providing high stability and flexibility, therefore they could be regarded as suitable candidates for future COVID-19 studies [48]. A more recent study by Moradi et al. investigated the activity of plant-derived protease inhibitors to suppress the activity of Papain-like protease of SARS-CoV-2. That study was performed by using molecular docking for selecting the potential agents for suppressing the target enzyme and the results were confirmed through molecular dynamics assay which indicated that VcTI from Veronica

Table 1
Examples of *in silico* structural predictions and phylogenetic studies regarding COVID-19.

Author and Reference	Aim of study	Results
Tabibzadeh et al. [30]	Study and tracking SARS-CoV-2 in Iranian COVID-19 sufferers by molecular and phylogenetic methods	Isolates showed to be closely related with Chinese and reference sequences. No considerable differences were detected between Iranian isolates and those of other countries.
Zhang et al. [31]	Reanalysis of protein structure and sequence of COVID-19 genome	Suggesting that snakes are the intermediate hosts of SARS-CoV-2 and spike protein insertions share a high similarity with HIV-1
Zhang et al. [32]	Genomic characterization and phylogenetic evolution of SARS-CoV-2	SARS-CoV-2 is closely related (88% identity) to bat-SARS-like coronavirus
Sacco et al. [33]	Developing dual inhibitors against Mpro and cathepsin L	The structure of Mpro with calpain inhibitor II proved that S1 pocket could accommodate a hydrophobic methionine side chain
Sakkiah et al. [34]	Using homology modeling to construct a trimeric form of the spike protein complexed with h. ACE2	Interactions between ACE2 and the tertiary structure of the full-length S protein trimer are different from those of ACE2-truncated monomer of RBD

Table 2
Examples of *in silico* virtual drugs screening against COVID-19.

Author and Reference	Molecular target	Potential drugs
Chen et al. [40]	C-like protease (3CL pro)	Yelpatasvir, and ledipasvir
Rahman et al. [41]	Main protease (Mpro)	Simeprevir, Ergotamine, Bromocriptine and Tadalafil,
Hosseini et al. [42]	Mpro, PLpro, and RdRp	Antiemetics rolapitant and ondansetron, labetalol and levomefolic acid, leucal and antifungal natamycin
Senathilake et al. [43]	Spike Glycoprotein	Dgitoxin, zorubicin and aclarubicin, rolitetracycline, cefoperazone and E−155
Alibakhshi et al. [44]	Envelope (E) and Membrane (M) Proteins	Conivaptan, Ecamsule, Conivaptan, etc.

hederifolia provides a suppressive activity against both Zn-site and the classic active site of this enzyme [49]. Table 3 presents some of the other studies that used *in silico* approaches for analysis of natural compounds against COVID-19.

3.4. Anti-microbial peptides and peptidomimetics

Anti-microbial peptides (AMPs) are by nature a part from the innate immune response of various organisms that provide immunity toward a wide variety of infectious agents; such as viruses, bacteria and fungi. These agents prevent the infection via different patterns, such as membrane disruption or physical blocking of the molecular receptors. In the case of COVI-19, one of the initial therapeutics candidates were these peptides that provide a precise viral life cycle inhibition and the virus could not easily develop resistance toward these agents [55,56]. Application of the natural existing AMPs without any information regarding their influence on a specific target requires to use all of these components, hoping that maybe one provides a good response against a target, but application of *in silico* methods not only helps to screen these components prior to laboratory application, but also provides a platform to make desired modifications in their construct.

Considering the therapeutics limitation for remedy of COVID-19 sufferers, application of AMPs, anti-viral peptides (AVPs), and the other peptide-like compounds such as peptidomimetics, that are more tolerant toward digestion, are justified to battle SARS-CoV2 pandemic conditions [57]. So far, many different AMPs have been used against COVID-19, and the future studies on some of these natural peptides; such as Lactoferrin (LF) has been recommended [58].

In silico studies have been helpful in respect of repurposing and designing and optimizing of the AMPs. Another example is a study by Ahmadi et al. has reported the efficacy of Enfuvirtide (an effective inhibitor against HIV-1) to be useful against SARS-CoV-2 [59]. Another *in silico* study by Al-Rabia the repurposing of sitagliptin-melittin optimized nanoformula against SARS-CoV-2 via anti-viral screening and molecular docking assays [60].

In the case of designing peptidomimetics, a study by Alagumuthu et al. reported the structure-based design of novel peptidomimetics for targeting spike protein of SARS-CoV-2 which were bound at the ACE2 binding site of the receptor-binding domain (RBD), effectively [61]. Table 4 shows more examples of *in silico* studies at developing peptide-based therapeutics against COVID-19.

Table 3
Examples of studies that used *in silico* approaches against COVID-19.

Author and Reference	Source of compound	Results
Nouadi et al. [50]	Moroccan Plants	Taxol, Rutin, Genkwanine, and Luteolin-glucoside showed to a high affinity with ACE2 and 3CLpro
Nikunj et al. [51]	Red Algae	n-Decanoic acid and 9-dodecenoic acid, methyl ester,(E) showed 81.90% and 81.81% affinity on RBD, respectively
Joseph et al. [52]	Green tea and Spirulina extracts	Blocking the cell entry of SARS-CoV-2
Marwal et al. [53]	Piperine (Black Pepper), Eugenol (Clove), Alliin (Garlic), Gingerol (Ginger) and Curcumin (Turmeric	All compounds showed good docking scores with their respective receptor, ranging from −8.195 to −5.263 via DockThor
Beirami et al. [54]	6570 molecules from different herbal plants	Sodwanone B, Cyclomulberrin, and a glycosylated derivative of kaempferol were chosen for future studies based on their docking score

Table 4
Some *in silico* studies for developing peptide-based therapeutics against SARS-CoV2.

Authors and Reference	Name of peptide	Viral target	Results
Ling et al. [62]	HR1-P and HR2-P	Spike	Binding energy of HR2-based antiviral peptide to HR1 was−43.0 kcal/mol, stronger than the natural fusion compound
Baig et al. [63]	Two novel 23aa and 18aa peptides	Spike	18aa peptide showed a stable and effective blocking of SARS-CoV-2 cell entry
Barh et al. [64]	cnCoVP-3, cnCoVP-4, and cnCoVP-7 chimeric peptides	Spike	Optimal blockade of the Spike RBD and hACE2 interaction which potentially leads to preventing the cell entry
Balmeh et al. [65]	glycocin F from Lactococcus lactis and lactococcine G from Lactobacillus plantarum	Spike, RdRp, 3CL, and N protein	Efficient structural suppression of the viral structures by peptides derived from probiotic bacteria
Mohammadi et al. [66]	Pacific oyster Antiviral Polypeptides	Main Protease	HIV–1PIP-1 (Leu-Leu-Glu-Tyr-Ser-Leu) polypeptide could be a potential inhibitory compound for Mpro

3.5. SARS-CoV-2 vaccine design

Designing an inclusive vaccine that could cover more subtypes of SARS-CoV-2 is a serious issue at the time of this universal crisis, when we see new subtypes are coming from each corner of the world [67]. In the past, vaccine design studies were only based on laboratory and dead pathogens or weakened ones were injected to the subjects, that was along with a life treating hazards such as acute immune response and being time consuming and expensive were among the disadvantages of those vaccines. Although, the previous methods of vaccine design; such as virus inactivations are still used and present some good results, the modern generation of vaccines such as multi-epitope ones, DNA, and RNA vaccines have emerged that show promising results.

Application of *in silico* methods help the scientists to present a more potent vaccine with adjusted components that does not pose hazards such as those of earlier ones. *In silico* approaches have shown to be useful for designing various multi-epitope vaccines for viruses such as influenza A [12]. In this regard, application of reverse vaccinology (RV) which is a common approach for identifying potential vaccine constructs via screening of the proteome of the target pathogen by *in silico* analysis [68], has been the subject of many SARS-CoV-2 vaccine studies. For example, a study by Qamar et al. used the reverse vaccinology technique to design a multiepitope-based subunit vaccine (MESV) against SARS-CoV-2. They investigated the presence of the epitopes suitable for potential vaccine candidate design using AllerTOP and VaxiJen to selected their epitopes, and made a construct that could provide B-cell and T-cell esponse.

There are many online *in silico* tools that come helpful for designing multi-epitope peptide vaccines; such as IEDB MHC-I prediction tool (http://tools.immuneepitope.org/analyze/html/mhc_binding.html) [69], IEDB MHC-II prediction online server (http://tools.immuneepitope.org/mhcii) [70], VaxiJen RV tool (http://ww.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html) [71], ElliPro (http://crdd.osdd.net/raghava/bcepred) [72], and IEDB population coverage tool (http://tools.iedb.org/population) [73] that are used or screening the potential epitopes from protein sequences.

For predicting the antigenicity, there are various program such as Predicting Antigenic Peptides (http://imed.med.ucm.es/Tools/antigenic.Pl) [74], and AlgPred (http://crdd.osdd.net/ragha va/algpred/) [75]. In the case of toxicity, ToxinPred (http://crdd.osdd.net/raghava/toxinpred/) [76] is one of the common tools, and C-IMMSIM tool was helpful for simulating the immune responses (http://www.cbs.dtu.dk/services/C-ImmSim-10.1/) [77].

Fig. 2 presents a simple schematic workflow of the multi-epitope vaccine design, and one should consider that there are always new steps could be added to improve the novelty of study and increase the potential efficacy of the designed vaccine. In the case of COVID-19, attempts for designing multi-epitope peptide vaccines were initiated at the beginning of the crisis, and since then, many studies have been performed regarding such a vaccine design [78].

A study by Pourseif et al. reported designing of two domain-based vaccine constructs against SARS-CoV-2 on the basis of two different vaccine production and delivery systems; including an adjuvanted domain-based protein vaccine construct (DPVC), and a self-amplifying mRNA vaccine (SAMV) by using the target of spike glycoprotein, which require future *in vivo* and *in vitro* investigations [79]. Another study by Kar et al. also designed a multi-epitope vaccine candidate based on the structure of spike glycoprotein of SARS-CoV-2 and verified the quality of the designed vaccine candidate based on *in silico* assays; such as molecular docking, molecular dynamics (using the steepest descent algorithm of GROMACS) and *in silico* immune response simulation. They further optimized the vaccine candidate structure for expression by *E. coli* expression system [80].

Moreover, application of ML and deep learning algorithms has also come useful for multi-epitope vaccine design against SARS-CoV-2. In this regard, a study by Yang et al. used an *in silico* deep learning method to predict and design of a multi-epitope vaccine candidate (DeepVacPred). Their study predicted 26 potential vaccine subunits from the available SARS-CoV-2 spike protein sequence, which could be used in a multi-epitope vaccine. They used the best 11 of the epitopes (694 amino acids) to construct a multi-epitope peptide as a potential vaccine candidate for SARS-CoV-2 virus [81]. Another study by Behmard et al., provided a multi epitope vaccine constructed by epitopes from whole set of viral structural proteins which proved its safety and efficacy at *in vivo* level, too [82]. It also has been proven that application of reverse vaccinology could provide a better outcome, when it is accompanied with ML method, such as VaxiJen-ML application by Ong et al. [83]. Table 5 presents more examples of *in silico* designing of multi-epitope SARS-CoV-2 vaccine.

Another type of vaccines that were provided by the help of *in silico* methods are nucleic acid base vaccines. In this regard, designing a SARS-CoV-2 spike-based DNA vaccine by Alamri et al. could be noted, who used these computational methods for designing the codon-optimized synthetic consensus S protein [89]. A similar study by Prompetchara et al. reported a DNA vaccine that showed strong humoral and T helper type 1 (Th1) cell-mediated immune responses in mice [90]. Regarding the potential of RNA vaccines against COVID-19 and how *in silico* methods could be helpful, the readers are suggested to refer the study by Borah et al. [91]. Moreover, the *in silico* methods were also have been used for designing an RNA-Peptide fusion vaccine candidate against COVID-19 [92].

Table 5
In silico studies of vaccine design against COVID-19.

Authors and Reference	Viral antigens	Results of study
Enayatkhani et al. [84]	Nucleocapsid, ORF3a, and Membrane protein	Designed chimeric protein showed to elicit humoral and cell-mediated immune responses
Dong et al. [85]	ORF7a protein, ORF8 protein, nsp9, nsp6, nsp3, endoRNAse, ORF3a protein, membrane glycoprotein, and nucleocapsid phosphoprotein	*In silico* assays validated the efficacy of the designed multi-epitope vaccine
Rahman et al. [86]	S, M, and E proteins	Vaccine candidate showed a significant potential *in silico*
Arshad Dar et al. [87]	Spike	Proposed multiepitope vaccine could provide protective immunity against COVID-19
Kumar et al. [88]	Spike	Eliciting a strong immune response for vaccine *in silico*

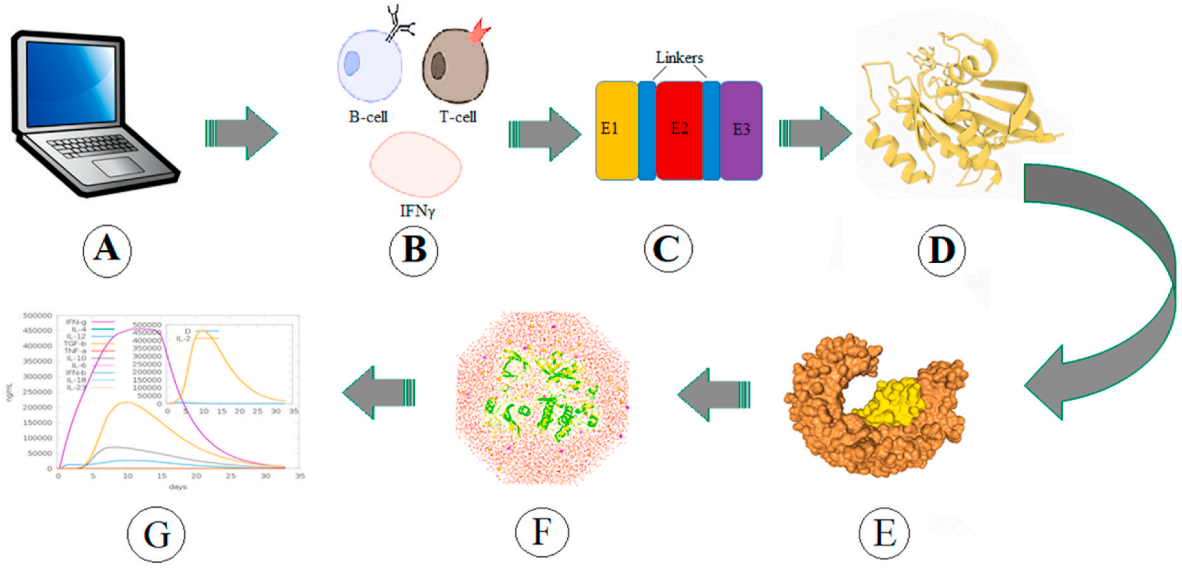

Fig. 2. Schematic workflow of *in silico* designing a multi-epitope vaccine. **A.** Collecting the required information regarding the potential vaccine target structures **B.** Predicting the potential T-cell and B-cell and IFN-γ epitopes in the structure of the molecular target, such as spike protein **C.** Joining the selected epitopes, and peptide adjuvants by using suitable linkers **D.** structure prediction and analyzing the modeled multi-epitope peptide **E.** Molecular docking with potential immune receptors, such as TLRs **F.** Molecular dynamics simulation to investigate the stability of the complex **G.** *In silico* simulation of immune response toward the designed multi-epitope construct.

3.6. Machine learning (ML) and artificial intelligence (AI)

ML is a novel technology that has been provided by advancements of *in silico* approaches. ML methods are useful for classification of data and help to provide an accurate prediction of the unknown queries using different algorithms [2]. These methods could be useful for identifying patients at high risk, analyzing the death rate, and the other abnormalities. These technologies use different algorithms, which could help to learn more about the nature of this virus. Moreover, ML also could help to analyze the risk factors as per age, social habits, location, and climate [93]. Some of ML methods such as Support Vector Machine (SVM), Convolutional Neural Network (CNN), and Generative Adversarial Network (GAN), are among the broadly used ones for diagnosis of SARS-CoV-2. AI methods have helped to provide high quality studies on drug repurposing, analysis of dissemination patterns, and clinical diagnosis this virus [94].

Regarding COVID-19 pandemic condition, AI methods have showed efficiency to predict specific properties, potential risks, and results of a pandemic condition of COVID-19. Application of deep learning has provided opportunities to detect various aspect of this pandemic situation. In this regard, the use of deep learning and reinforcement learning showed useful to predict some of the COVID-19 related problems [95].

Due to the advances in the field of AI and emergence of valuable *in silico* assays, it is possible to provide an accurate diagnosis model of COVID-19 based on patient symptoms and routine test results via application of ML and reanalysis of collected COVID-19 related data, such the study by Li et al. who trained an XGBoost model to provide a sensitivity of 92.5% and a specificity of 97.9% for discrimination of COVID-19 patients from influenza patients [96].

Various ML algorithms; such as SVM, RF, Covariance Discrimination (CD) and Optimized Evidence-Theoretic K-nearest Neighbor (OET-KNN) have shown to be useful for assorting the data provided by pseudo amino acid composition, which is really helpful to provide high accuracy predictions about the protein structures of different enzymes [2,3], and such predictions are very important for the designing online tools for future analysis of similar proteins [21].

One of the most critical points while using modern ML algorithms is to define the right question about how these algorithms could be helpful to provide an optimum clinical outcome. An issue that must be considered in this regard is acting without expert clinical oversight. The wrong used AI research could end up in solutions' looking for problems: a form of supply that tries to find a demand, instead of the pre-thought application [97].

A previous meta-analysis by Khalid Raza demonstrated that state-of-the-art AI applications against COVID-19 could be useful at four major areas of applications; including diagnosis and prediction of infection, epidemiology of viral infection namely viral forecasting, control, and spread dynamics, molecular studies such as categorizing the viral structures, designing drugs and remedy for sufferers and social aspects such as commerce, business, governance, and education and training [98]. Table 6 presents a list of highlighted ML studies for battling COVID-19.

Table 6
Some of the highlighted studies that used ML.

Authors and year	Aim of study	The algorithms used	The outcome of study
Ong et al. [83]	COVID-19 Vaccine Design	Five supervised classification algorithms, including logistic regression, SVM, k-nearest neighbor, RF, and extreme gradient boosting (XGB)	The designed construct showed to trigger immune response, and the Sp/Nsp cocktail vaccine could stimulate effective complementary immune responses
Magar et al. [99]	Discovering Potential neutralizing antibodies	XGBoost, Random Forest, Multilayer perceptron, SVM, and Logistic Regression	Screening of thousands antibody sequences and finding nine stable ones that potentially inhibit SARS-CoV-2
Khalifa et al. [100]	Classification of potential coronavirus treatments on a single human cell	SVM, decision trees, ensemble and DCNN (Deep convolutional neural networks)	DCNN provided 98.05% testing accuracy, and was more effective than classical ML methods
Wu et al. [101]	Rapid and accurate identification of COVID-19 infection based on clinical available blood test results	RF	Developing a tool for preliminary assessment of suspected patients and help them to get timely treatment and quarantine suggestion
Mohapatra et al. [102]	Predicting the efficacy of commercially available drugs against COVID-19	Naive Bayes	Amprenavir (DrugBank ID–DB00701) could probably be an effective drug for COVID-19

4. Future perspective

Since the beginning of COVID-19, experts in the field of bioinformatics have been dedicated to find a solution for SARS-CoV-2 pandemics and have made a considerable contribution by reducing the workload of laboratorians, diminishing the costs and preventing the unnecessary animal sacrifices. In this regard, application of drug screening tools such as QSAR, molecular docking methods, molecular dynamics simulation tools; such as GROMACS came helpful to discriminate the potential drug candidates [103,104].

In the case of COVID-19, many innovations at the field of bioinformatics came out; such as the study by Russo et al. who used Universal Immune System Simulator (UISS) *in silico* platform for trial investigation of the COVID-19 candidate vaccines, and such a platform showed to be an effective way for discovery pipeline of vaccine against SARS-CoV-2 [105]. These innovative *in silico* platform applications could come very helpful in the face of possible pandemics in future and will assist to provide a timely, and cost effective therapeutics design.

Some of the bioinformatics assays could be really useful for prediction of the possible dangers that are invisible to the naked eyes, for example to investigate the potential long term effects of viruses on the nervous system due to the prion-like domains in the viruses that show their effect years after infection. In this regard, bioinformatics methods could be applied for analysis of these structures [106]. Regarding these concerns, there are some reports that predict the potential presence of these structures at the spike protein of SARS-CoV-2 at the site of interaction with human ACE2, which might be a reason for higher virulence of this pathogen, and be a sign of caution for those who study in this field for drug and vaccine design against COVID-19 [107]. Another study by Mohabatkar et al. reported the prediction of a potential prion-like domain in SARS-CoV2 polyprotein at the nonstructural protein 3 (Nsp3) site, by using *in silico* tools [108].

Considering the importance of early patient's diagnosis, which helps to the better outcome for provided therapy, ML methods have been a blessing to the medical experts. In this regard, modified Manta-Ray Foraging Optimization used by Elaziz et al. showed to be effective for image-based diagnosis of COVID-19 [109]. Moreover, the model provided by Goodman-Meza et al. showed to provide sensitivity of 0.93 (95% CI 0.85–0.98), and specificity of 0.64 (95% CI 0.58–0.69) for inpatient diagnosis [110]. Furthermore, emergence of neural networking showed promising results regarding COVID-19, such as the study by Hartono who used pairwise predictions and similarity maps for analyzing the transmission dynamics of COVID-19 [111].

In silico tools have also been used for designing and optimization of the molecular constructs that could be used for early diagnosis of the

COVID-19 viruses. An example in this regard is the *in silico* study of designing quadruplex aptamers against the spike protein of SARS-CoV-2 [112]. These agents are really useful for molecular detection of SARS-CoV-2, and could be used in immediate responding tools such as biosensors. Regarding the importance of designing aptamers, its necessary to note that ML tools, and genetic algorithms could come helpful to discriminate the optimum structures [113].

In silico methods could be used for diagnosis of possible other viral epidemics, since they have shown their effectiveness in the case COVID-19 [114]. In this regard, many studies have emphasized the importance of these tools; such as the *in silico* detection of SARS-CoV-2 specific B-cell epitopes by Phan et al. [115] or *in silico* discovery of antigenic proteins and epitopes COVID-19 for diagnostic purpose by Can et al. [116]. These computational methods have also aided researchers to present diagnostic devices such as nanocarbon biosensors for accelerated diagnosis of COVID-19 [117], and still there are much more potential for developing other tools by the use of bioinformatics.

Application of computer methods have also come very useful in managing other aspects of COVID-19 crisis, for example helping the healthcare providers to design and develop web-based registry systems for suffers, which help to better handle the condition and plan for patients [118]. *In silico* methods have also been used for programming the diet for COVID-19 patients, and to provide an optimum diet, which could act as both preventive and even co-therapeutics agents. Considering this issue, a study by Matteo et al. has provided useful insights regarding the importance of *in silico* methods for programing of foods that help individuals for battling COVID-19 pandemic condition [119].

These ML methods have also shown to be useful for psychological distress during COVID-19, which is an important area of managing the health of people [120]. Also, there is a high potential for application of these *in silico* methods for personalized medicine in the case of COVID-19, which could be an area of study for future researches, that could revolutionize the healthcare system [121]. Regarding the importance of such an issue, a study by Voutouri et al. reported a comprehensive mathematical model that considers factors such as innate and adaptive immune responses, rates of viral replication, and inflammatory cytokines. This model indicated divergent treatment responses and clinical outcomes by accounting the dynamics of COVID-19 phenotypes, which helps to improve the clinical management and provide a framework to understand trajectories for individual patients [122].

Moreover, application of ML has proved its efficiency to predict the severity of disease and its outcome in COVID-19 suffers [123], which could be used against the future possible tragic crisis similar to that of SARS-CoV-2 or perhaps controlling the new strains of COVID-19 that are being reported from different corners of the world due to mutations [124,125]. Such predictions about these health crisis's could be really helpful, especially when it comes to planning for the health of these sufferers by governments [126].

Another area in which the *in silico* methods have shown their efficiency against COVID-19 was single-cell transcriptomics. These assays investigate the levels of gene expression at individual cells in a specified population via simultaneous measuring of the messenger RNA (mRNA) concentration of many genes. The discovery of heterogenous cell populations, reconstruction of cellular developmental trajectories, and transcriptional dynamics modeling are possible via studying these data [127–129]. Regarding COVID-19 condition, so many studies were performed in this area, such as the study by Wang et al. who investigated the single-cell transcriptomic of COVID-19 patients' lungs, which provided an extensive cellular and molecular atlas that could facilitate the identification of biomarkers and developing the symptomatic treatments [130].

A study by Shi et al. revealed that Mucosal-associated invariant T (MAIT) cells could be involved in the host immune response against this virus and their transcriptomic data presented a better knowledge of the immune pathogenesis of SARS-CoV-2 [131]. Moreover, it has been suggested that considering the high similarity between the transcriptome of SARS-CoV and SARS-CoV-2, the data of immunological regulations, signaling pathways, and proinflammatory cytokines in SARS-CoV infection could be expanded to COVID-19 to provide a better platform for future medical investigations [132]. This field of study showed to be useful to battle COVID-19, and perhaps could be used against the other potential pandemics in future.

5. Conclusion

From reviewing of contemporary publications regarding the applications of *in silico* methods and managing different aspects of COVID-19 infection, it could be concluded that *in silico* methods have been very helpful for studying unrecognized molecular structures, classification of the COVID-19 related data via AI and deep learning methods, analyzing the interaction of potential inhibitors and their viral targets, and designing novel preventive and therapeutic agents. The *in silico* platform also showed to assist the experts in the bioinformatics field to develop novel and specific web servers for various scientific applications for SARS-CoV-2 management.

Research involving human participants and/or animals

No human or animal was involved in this study.

Informed consent

There was no human participant and consent was not required.

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Data availability statement

The data supporting this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

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

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