



The Role of Machine Learning and Artificial Intelligence in Clinical Decisions and the Herbal Formulations Against COVID-19

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ABSTRACT

COVID-19 causes global health problems, and new technologies have to be established to detect, anticipate, diagnose, screen, and even trace COVID-19 by all healthcare experts. Several database searches are carried out in this literature-based study on machine learning (ML), artificial intelligence, computer-based molecular docking analysis (CBMDA), COVID-19, and herbal docking analysis. In the battle against different infectious diseases, ML, AI, and CBMDA's past supporting data are involved. These devices have now been updated with advanced features and are part of the SARS-CoV-2 screening, prediction, diagnosis, contact tracing, and drug/vaccine production healthcare industries. This article aims to comprehensively analyse the essential role of ML and AI and CBMDA in the screening, prediction, contact tracing, and production of herbal drugs for this virus and its associated epidemic.

KEYWORDS

Artificial Intelligence, Computational Molecular Docking Analysis, Coronavirus, Herbal Compounds, Ligand, Machine Learning, S-Protein

INTRODUCTION

Several viral diseases that have been documented throughout history have become pandemic or infectious diseases. In the current situation, novel coronavirus disease 2019 (COVID-19) is also a viral infectious disease, and that is associated with many other health issues, including cancer, neurodegenerative diseases, and diabetes (Vehik et al., 2011; Sohrabi et al., 2017). To manage and prevent this disease, clinicians, scientists, national healthcare systems of different countries, and members of the World Health Organization (WHO) are continually searching for tools to solve this problem and fight against this disease (Sohrabi et al., 2017).

COVID-19 is a highly contagious viral disease and has now caused a pandemic since it was discovered in 2019. The first confirmed case of COVID-19 was identified in Wuhan, Hubei Province

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(China), in December 2019 with a respiratory problem. In India, the first COVID-19 case was registered in Kerala when the patient arrived from Wuhan, China. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its symptoms include coughing/sneezing, fever, difficulty in breathing, chest pain, sore throat, gastrointestinal problems, and loss of sense of smell and taste, and it can also lead to brain and kidney dysfunction (Sohrabi et al., 2017). COVID-19 is a helical single-stranded, positive-sense RNA, and its genome size is 29,891 kb, enclosed by a 5'-cap and 3'-poly (A) tail. Its genome contains 38% G + C. COVID-19 has four main structural glycoproteins in its nucleocapsid: spike (S), membrane (M), envelope (E), and nucleocapsid (N) (Vehik et al., 2011; Sohrabi et al., 2017).

COVID-19 is spread mainly by droplets of an infected person through coughing or sneezing and this can happen in two ways: direct close contact and indirect contact to an infected person (Sohrabi et al., 2017). According to a WHO study, COVID-19 patients may be asymptomatic or symptomatic and associated with other symptoms such as “strange symptoms” or skin rashes and “COVID tongue” or mouth ulcer or white patches on the tongue. These new symptoms are related to previous symptoms. Due to the rapid increase of COVID-19 cases (Boukhatem et al., 2020; Roosa et al., 2020), the WHO declared COVID-19 as a pandemic on January 30, 2020. Besides China, COVID-19 has affected all countries worldwide within a brief period; therefore, it has become a human health crisis of international concern (Vehik et al., 2011; Sohrabi et al., 2017).

Pathogenic COVID was identified from poultry in 1937, causing colds and mild digestive infections in humans (Vehik et al., 2011; Boukhatem et al., 2020; Roosa et al., 2020). Another new human coronavirus strain was identified in Southeast Asia and Canada in 2003 (Wang et al., 2005). According to a recent report by the WHO, around 90,054,813 cases of COVID-19 were confirmed, and more than 1,945,610 deaths were recorded until January 13, 2021 (Wang et al., 2005). New York City was the epicenter (Center for Systems Science and Engineering at Johns Hopkins University 2020) of COVID-19 with over 200,000 positive cases and more than 17,400 deaths. During the disease outbreak, available clinical facilities were overwhelmed by an emergency health crisis, forcing healthcare professionals, COVID-19 patients, and their families to make critical, time-sensitive decisions based on inadequate information (Evans et al., 2020).

Other members of the coronavirus family (Figure 1), including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), have been reported to infect humans and animals such as cattle and pets; these viruses also cause breathing issues and affect the gastrointestinal tract (Drosten et al., 2003; Vehik et al., 2011; WHO, 2020; JHU, 2020; Guo et al., 2020).

At present, given that there is no approved medicine available for COVID-19, scientists and research communities around the world are continuously developing antiviral or anti-COVID-19 drugs and are involved in the preparation of vaccines to protect and save human life (Vehik et al., 2011; Hu et al., 2015; Yang et al., 2020). Thus, we should take some precautionary measures to prevent COVID-19 infection, including avoiding social gatherings and physical contact, maintaining social distancing (2 feet), staying at home, and practicing good hygiene (regular handwashing with soap, alcohol-based handwash, or sanitizer). The lack of standard treatment drives physicians and medical caretakers' exceptional work process, even though the trajectory for patients most likely to decompensate is being studied but remains elusive. Given the severity of these conditions and the rise in the number of cases, there is a need for additional medical equipment (Zhou et al., 2020; Debnath et al., 2020).

Moreover, the current healthcare resources and tools should be augmented. Scientists need innovative computerized clinical tools or technology to monitor infected patients in various phases of COVID-19 infection to find a way to prevent the spread of the disease, contribute to the development of vaccines, and develop an antiviral drug. These computerized clinical tools can track infected patients and make clinical decisions regarding their infection (Zhou et al., 2020; Debnath et al., 2020).

Considering the increasing number of COVID-19 cases and the growing shortage of pathologists globally, automated computer-based, machine learning (ML), and artificial intelligence (AI)-based tools should be developed to support pathologists. COVID-19 diagnosis and this communicable disease prediction spectrum are crucial in the clinical management of afflicted men. ML and AI are computer-based methods. Both techniques can be applied to understand the subgroups of COVID-19 patients, guide timely clinical decision-making, and improve patient-centered outcomes and maneuverability. However, accurately diagnosing COVID-19 is difficult because its possible number grows as new strains are discovered. As a result, for an automated method to be used in medicine, it must have clinical range accuracy. ML and AI offer multiple clinical applications to healthcare professionals, including risk recognition, identifying patients, producing medications more quickly, identifying drugs that can assist in treatment, predicting disease spread, a better understanding of viruses, mapping where viruses come from, and predicting the next pandemic.

We have been attempting to focus on the novel's relationship with one another. Through this study, COVID-19 will be curtailed, as well as the most up-to-date ML and AI technologies. It aims to clear up the pandemic assignment and increase herbal-based antiviral or anti-covid tablets or vaccines. As a result, we have attempted to include such concise statistics to overcome the global pandemic burden. This viewpoint emphasizes the advantages of computer-based equipment in a variety of clinical environments. It explains how carefully constructed machine learning and artificial intelligence algorithms could be augmented for the duration of the COVID-19 pandemic.

This review's primary goal was to determine how ML–AI techniques and molecular–computational docking work with the novel COVID-19 curtail. What role does this technology play in screening, traction, and treatment? The application of molecular docking techniques to herbal drugs is a relatively new phenomenon that has received much attention recently.

Second, herbal medicines that are anti-SARS-CoV-2 should be repurposed for Covid-19 therapy. It aims to simplify the pandemic assignment and increase herbal-based antiviral or anti-covid tablets or vaccines.

With the help of ML and molecular docking, the current research has contributed a great combination of biological science, therapeutic prospect, and ancient-science-based herbal treatment for the current pandemic.

It also deals with potential research directions, remote screen identification, diagnosis, consultations, impact assessment and evaluation, unreliable and disruptive data and unawareness among the masses, data privacy and protection, and the inconsistency of data collection.

The first part discusses preparing the entire paper and its various sources for article content, such as SpringerLink, ResearchGate, Wiley Online Library, and Google Scholar databases.

The second part discusses algorithm creation and AI, with various models for contact, screening, diagnosis, and herbal immune booster drugs.

The last part mentions the future aspects of the research paper.

MATERIALS AND METHODS

Search engines such as ScienceDirect, Scopus, PubMed, SpringerLink, ResearchGate, Wiley Online Library, Google Scholar, and Elsevier databases were used to find comprehensive information on ML, AI, computer-based molecular docking analysis and its mechanism, pandemic, mobile app, computer app, software, SARS-CoV-2, COVID-19, and herbal antiviral or anti-COVID medication. The literature from SCI and Scopus index journals was screened during the quest, which took place between October and December 2020. The COVID-19 was further screened and tested with automated tools in the current analysis, which met the review's goal.

ML (ALGORITHM DEVELOPMENT) AND AI

In the past, clinical and scientific research have relied on machine learning (ML) and artificial intelligence (AI) to increase forecast accuracy for both infectious and non-infectious disease screening

(Samuel et al., 2020). ML is a computer-based software function of AI, which coordinates how to learn and improve from experience without being programmed mechanically. It also focuses on developing computer-based programs that can access data and learn for themselves and help the clinician screen for diseases for better therapeutic drug development. ML and AI are excellent clinical technologies that a healthcare organization or investigators operate. They are used to develop better screening techniques that result in better scale-up and speed-up processing power. They are also consistent and perform better clinical data analysis in specific healthcare applications (Samuel et al., 2020).

Some recent studies have determined ML and AI's potential for various pandemic outbreaks, supporting healthcare experts in treating variously communicable (SARS, Ebola, HIV, COVID-19) and non-communicable diseases (cancer, diabetes, heart disease, and stroke). ML and AI are used with radio imaging technology such as computed tomography (CT), X-ray, and clinical blood sample data to complement the identified patient's diagnosis and screening process. In this context, detailed information on coronavirus disease detection and screening has been recommended. Radiology images, such as X-rays and CT scans, can be used as standard instruments to complement traditional diagnosis and screening (Davenport and Kalakota, 2019).

ML and AI can be used in multiple applications, such as (1) exchanging de-anonymized raw data from each clinical trial and (2) encouraging the creation of large cohorts. The International Severe Acute Respiratory and Emerging Infection Consortium initiative aims to create a broad, shared clinical database on COVID-19 patients. To ensure that data are exchanged freely and quickly, other organizations have signed a data-sharing agreement (SHR-2020; NIH, 2020).

ML and AI tools are being used by scientists, researchers, representatives of various healthcare organizations, and clinicians worldwide to find the COVID-19 and cure the issue. Both methods are critical in determining a better way to treat diseases (Davenport and Kalakota, 2019). These technologies will aid in the monitoring of COVID-19 and the creation of a model to combat COVID-19. They may also determine the actual number of cases and assist in developing methodologies to combat COVID-19.

ML AND AI – DIFFERENT MODELS FOR IDENTIFICATION, SCREENING, AND DIAGNOSIS: SPECIAL LINK TO SARS-COV-2

DETECTION, SCREENING, AND DIAGNOSIS OF COVID-19

In 1976, the first expert system MYCIN (which used AI to identify bacteria causing severe infections (bacteremia and meningitis) (Phillips-Wren et al., 2008) and discover antibiotics and their dosage) was developed with 450 rules to treat bacterial infection by suggesting antibiotics to an infected person (Phillips-Wren et al., 2008; Peiffer-Smadja et al., 2019; Agrebi and Larbi, 2020). This technology serves as clinical decision support for scientists, medical or clinical experts, and healthcare experts in several types of disease, either infectious (SARS, HIV, COVID-19) or non-infectious (cancer, obesity, neurodegenerative diseases, and diabetes) (Kavakiotis et al., 2017; Barbat et al., 2019; Liu et al., 2019; Karen et al., 2020). Consequently, the early and accurate detection of any disease (whether infectious or non-infectious) plays a significant role in early and better treatment to save more lives (Phillips-Wren et al., 2008).

Improved diagnosis is essential for better treating and detecting any disease at the initial phase, resulting in saving more lives (Dourado et al., 2019; Ozturk et al., 2020). Other studies have supported that for pandemic or infectious diseases such as COVID-19, rapid screening and diagnosis play a significant role in better treatment and preventing the spread of these diseases through precaution and management (Ozturk et al., 2020).

According to Prof. Sectors and his team, the Zoe COVID Symptom app described many "abnormal symptoms". As per the recent reports by system experts, several new computer-based clinical tools and techniques are involved and help the modern medical system to handle this pandemic period (Ozturk et al., 2020).

ML and AI are also used with radio imaging technology (CT), X-ray, and blood sample data as rapid diagnosis and screening tools to identify COVID-19 patients. However, reports have shown that such techniques are not very useful to all patients (Ozturk et al., 2020). As a result, updated models of ML and AI, including deep convolutional network (ResNet-101), are helpful clinical disease diagnosis tools with high accuracy (83.33%–86.27%) and are approved by various healthcare experts and radiologists (Ozturk et al., 2020).

Various expert systems have discovered several other types of rapid diagnosis and screening tools with high accuracy and low cost (Table 1) and need approval based on evidence. These tools can reduce the spread of SARS-CoV-2 and provide more time to scientists and healthcare specialists to find a new way to cure the disease. Different studies have used single or multiple data classification algorithms. However, a hybrid classification method should be applied to potential multi-database algorithms or multiple reports (from clinical trials, mammographic and environmental demographic information or data) and data to help identify patients or infected persons. An alternative method with high diagnostic accuracy was developed using a new model, Automated COVID-19 detection, based on a deep learning algorithm (Dourado et al., 2019). To support the screening prediction of COVID-19, this model uses a bare chest X-ray film of 127 confirmed cases with 500 findings and 500 cases of pneumonia. This model has excellent performance accuracy: 98.08% for binary class and 87.02% for multi-class. It demonstrated the expert system's utility in radiology by validating rapid screening or prediction processes with high accuracy (Dourado et al., 2019; Ozturk et al., 2020). Recently, hospitals in Florida used these screening tools to detect patient's temperature upon entering the hospital. These tools help respond to COVID-19; moreover, some tools automatically scan patients' face at the hospital's entry point and detect whether they have a fever (Ozturk et al., 2020).

Using the clustering algorithm as the primary characteristic classification model, healthcare experts discovered four required medical characteristics configurations of clinical, laboratory, and demographic statistics, using GHS, CD3 percentage, total protein, and affected subject age (Dourado et al., 2019; Ozturk et al., 2020). This new model is more effective in screening and predicting COVID-19 patients in critical or severe conditions. The results show that a four-feature clinical combination has an AUROC of 0.9996 in training and 0.9757 in research datasets. The change or new model's importance can be determined using survival and cox-multivariate regression analysis, valuable resources for healthcare professionals (Dourado et al., 2019; Ozturk et al., 2020). Some wearable technologies or models (based on ML and AI) to screen heart rate can be used to help identify COVID-19 patients (Ozturk et al., 2020). In a recent study of 253 clinical blood samples evaluated by automated tools, 11 essential parameters (including total bilirubin, creatine kinase isoenzymes, GLU, creatinine, potassium, lactate dehydrogenase, platelet distribution distance, calcium, basophil, total protein, and magnesium) could be used to distinguish and verify COVID-19 cases. After employing the random forest algorithm, these parameters were extracted with an overall accuracy of 95.95% and specificity of 96.97%. This tool is available on the web server at http://lishuyan.lzu.edu.cn/COVID2019_2/ to assist healthcare experts (Phillips-Wren et al., 2008; Dourado et al., 2019; Ozturk et al., 2020). The majority of this research encourages early identification and detection to limit disease spread. It gives the clinician more time to correspond to the subsequent diagnosis, allowing them to save more lives for less money. As a result, ML and AI are critical in the battle against COVID-19.

CONTACT TRACING APPLICATION

Detecting an infected individual or a COVID-19-infected zone has also been the subject of many studies. It also includes contact tracing (infect person) and acts as a contact tracing tool (CTT). COVID-19 is an infectious disease transmitted by saliva, droplets, or nasal discharges (coughing/sneezing) of infected patients. According to the WHO, if the spread is not stopped, further infections will occur (Sun et al., 2020).

Recently, Indian experts have developed a different type of CTT for Android phones (CTT linked with Bluetooth and Global Positioning System to perform virtually). Modern or updated machine

learning and artificial intelligence (AI) are used in disease detection, assisted decision-making, risk analysis, and case triage assistants; COVID-19 trackings (COVID-19 touch tracking) are also used (merge with Apple and Google- Aarogay Setu-AS). AS is available in 12 languages, and various platforms have more than 114 million users, which is greater than any other contact tracing app in the world (WHO, 2020; Sun et al., 2020; Wu et al., 2020). Other contact tracing applications, such as Go Corona Go and Sampar-k-O-meter, have also been developed by the Indian Institute of Technology to track infected zones or individuals (Vehik et al., 2011; Wu et al., 2020).

AI and ML have also been used to develop tools to identify mask violators. These tools are connected to CCTV cameras to capture or identify the image of mask violators. After that, a notification will be sent to police headquarters to update the patrolling police team to take more action against mask violators (Vehik et al., 2011; Wu et al., 2020; Vaishya et al., 2020; Ai et al., 2020).

Thirty-six other countries have developed computer-based tools for contact tracing (Australia, COVID Safe; Austria, Stopp Corona; Bahrain, BeAware Bahrain; Bulgaria, ViruSafe; China, Conjunction with Alipay; Cyprus, CovTracer; Colombia, CoronApp; New Zealand, NZ COVID Tracer; UAE, TraceCovid; UK, NHS Covid-11) to help alleviate the spread of COVID-19 (WCA, 2020; MIT, 2020). However, the use of machine learning and artificial intelligence (ML and AI) is an extension of the CTT paradigm in the fight against infectious diseases, and it generates knowledge or data in graphic form (Graph Theory) (between applied CTT model and several infected people) (Ardakani et al., 2020; WCA, 2020; MIT, 2020; BBC, 2020). Simultaneously, these apps have some limitations like data security. So, we need to address and overcome the challenge (BBC, 2020).

As a result, these potential challenges with current COVID-19 necessitate the development of a highly accurate, automated data analyzer, as well as updated algorithms to update ML and AI-based tools or pipelines that can produce reliable data. Based on the output, healthcare experts or clinicians can decide on COVID-19 treatment and save the patient's life. ML and AI technologies can help diagnose COVID-19 patients (Vaishya et al., 2020; Ai et al., 2020). They can assist clinical decision-making for proper management and treatment of COVID-19 patients and improve clinical facilities to fight against the pandemic. ML and AI are innovative automated computer approach with extensive clinical applications in prediction, screening, and diagnosis. Both techniques need to be applied to identify COVID-19 patients at high risk, especially those with comorbidities. They can be used to understand SARS-CoV-2 or the virus's nature and further predict upcoming challenges. Therefore, the benefits of ML and AI tools in COVID-19 treatment are significant.

ML AND AI COMBINED WITH COMPUTATIONAL/MOLECULAR DOCKING TO REPURPOSE ANTI-SARS-COV-2 HERBAL MEDICINES

COVID-19 has infected 219 nations, and researchers are actively attempting to combat the pandemic disease. Currently, no effective vaccines or anti-SARS-CoV-2 medicines are available to treat COVID-19. However, ML and AI can help healthcare experts prioritize herbal medicines much faster by automatically building knowledge graphs and predicting interactions between drugs and viral proteins. ML and AI technologies constitute an attractive way to develop a possible cure or vaccine against COVID-19 through computational molecular docking analysis – in silico methodology (CMDA). Few approved CMDA applications, such as 1-Click Docking, AADS, ADAM, and AutoDock (most famous for COVID-19), are applicable for herbal antiviral medicine drug discovery (Vehik et al., 2011; Sohrabi et al., 2017; Rorres et al., 2018).

Kuntz et al. (1982) created the first molecular docking algorithm in the 1980s, which consisted of two sets: one for the receptor (composed of a series of spheres filling its surface clefts) and another for the ligand (consisting of another set of spheres describing its length). The most substantial steric overlap between the binding site and receptor spheres was found by ignoring any conformational movement. According to the classification, which distinguishes docking methods according to the degrees of flexibility of the molecules involved in the measurement, this method belongs to fully rigid docking techniques (Halperin et al. 2002) (Figure 2).

The potential development of a drug to treat infected patients necessitates research on existing conventional drugs for novel COVID-19, needed for human safety before human consumption. CMDA (computational molecular docking analysis) is integrated with digital drug or medicine discovery component (known as evidence-based digital clinical products or tools) measures and interventions to promote health and prevent disease spread (Pagadala et al., 2017; Rorres et al., 2018). The first algorithm developed in 1980 is an essential drug development tool known as CMDA. It plays a vital role in analyzing ligand binding modes, intermolecular interactions, and ligand-receptor complexes and performing quantitative predictions of binding energy, providing stability of the binding affinity complex (ligand-receptor complexes) (Meng et al., 2011; Pagadala et al., 2017; Coravos et al., 2019).

A few antiviral drugs are currently being used to treat COVID-19. Scientists and researchers from various countries find a complementary or alternative (natural source – plant-based molecules) bioactive compound. This part of the study discusses or tries to repurpose several possible target active molecules for the treatment of SARS-CoV-2 with the help of CMDA (through ML and AI). Computational simulation (which acts as a bridge between theory and experiment) and high-throughput screening are needed before drug production. These tools are victorious against the target site (protein), which is crucial in treating any disease (Pagadala et al., 2017; Coravos et al., 2019).

Chemical molecule libraries have records of millions of biologically active molecules. These molecules interact or docks with several biological target proteins that help cure the disease. However, the development of any drug or pharmaceutical products depends on medicinal chemistry (nature of molecules, design, determination of structure, synthesis of chemical compounds, or isolation of molecules from plants), computational molecular docking analysis, and pharmacodynamic and kinetic data analysis, including molecule potency, affinity, efficacy, selectivity, absorption, distribution, metabolism, excretion, and toxicity (Meng et al., 2011; Pagadala et al., 2017; Coravos et al., 2019).

More than 80% of people in the world rely on conventional or natural medicine (NM; part of herbs (ginger, garlic, lemon) or whole herbs or plants (Tulshi) to treat their diseases with limited side effects. NM entailed ensuring human and animal well-being and preventing and diagnosing disease (Pagadala et al., 2017; Coravos et al., 2019; Kumari et al., 2021).

Plant active components have uncountable health benefits or biological activities such as anticancer, anti-inflammatory, antioxidant, and immunomodulatory effects (response to the immune system) and have been shown to have low toxicity or allergenicity when compared to other synthetic medicines, according to OECD (Organisation for Economic Co-operation and Development) guidelines (Huang et al., 2010; Hughes et al., 2011; Lipinski et al., 2012).

Since ancient times, different herbal antiviral medicines have been used to prevent viral infection by affecting the viral transmission chain. Some plants such as *Azadirachta indica*, *Carica papaya*, *Bupleurum* spp., *Heteromorpha* spp., *Hippophae rhamnoides*, and *Scrophularia scorodonia*, are helpful for the treatment of Covid-19 (Lipinski et al., 2012; Chintamunnee et al., 2012). The active molecules of plants that help prevent and treat infectious diseases must be identified and documented to control future infectious diseases (Huang et al., 2010; Hughes et al., 2011; Lipinski et al., 2012).

The S-protein of coronavirus (structural protein, similar to SARS-CoV-2 and MERS-CoV) interacts with host angiotensin-converting enzyme two cellular receptors and membrane fusion, causing antigen response and inducing the host's immune reaction. During the reaction, neutralizing antibodies block viruses from binding to the host cells and prevent viral infection (Gurib-Fakim et al., 2006; Lin et al., 2016).

Molecule (ligands) docks are part of molecular docking experiments, in which two or more molecules interact and attempt to modify the configuration and fit the best orientation site. Ligands bind to the target protein, shape a complex structure, and are significantly relevant to drug production. Therefore, computational and molecular docking analysis can analyze the orientation site and determine how ligands and targets interact based on their binding energy. Then, the suitable ligands can be predicted to develop antiviral drugs (Lin et al., 2014; Dhama et al., 2018). Generally, computational

and molecular docking analysis or programs perform through a cyclic route, including scoring and evaluating ligand conformation using minimum energy. Furthermore, identifying binding confirmation is dependent on two steps: first, exploring an ample conformational space; and second, determining binding confirmation (potential binding modes). The correct prediction of the interaction energy associated with each predicted binding conformation is the second step (Mehmood et al., 2014; Ferreira et al., 2015).

Researchers recently used computational and molecular docking analysis to establish COVID-19 drugs, in which herbal constituents (bioactive molecules) serve as ligands interacting with the SARS-CoV-2 target S protein. This type of research often describes the essence of hydrogen bonding or binding energy, necessitating the interaction of ligands with receptors and creating novel ethnomedicine herbal formulations to treat this pandemic disease (Kapetanovic et al., 2008).

Several steps are carried out in computational and molecular docking analysis (Figure 3). To understand viral pathogenesis, it is essential to pick viral target proteins. The best target -S-glyco-structural protein and its (PDB ID: 6VYB) three-dimensional (3D) structure can be predicted using the protein data bank. The program RasMol 2.7.3 was used to image protein structures and their docking (Yuriev et al., 2011; Anbazhagan et al., 2020).

Next, *in silico* docking, screening, and post-docking analyses are performed for the selection and preparation of ligands (amino acid residues) and determination and confirmation of their 3D structures confirmed by available data in the PubChem and Generic Evolutionary Method (iGEMDOCKv2.1) analyses (Sayle et al., 1995; Yuriev et al., 2011; Anbazhagan et al., 2020). Target -S-glyco-structural protein and ligands, both uploaded to various “By Current File” and “Prepare Compounds” electrical options, respectively, and analyzed by accessible software, have two computational tools, AutoDock Tool 1.5.6 and AutoDockVina 1.1.2, which are based on the Lamarckian genetic algorithm, and are used to compare and validate item dock data results for the development of a Dr. Dock (O Trott et al., 2010; Yuriev et al., 2011; Hsu et al., 2011; Anbazhagan et al., 2020). As a result, *in silico* analysis or studies of antiviral drug production using phyto-constitute from plants, it is critical to predicting both possible ligand binding efficiency among the phyto-constitute and elucidating the target protein of SARS-CoV-2 S during ligand binding and interaction between ligands and target receptors. Most researchers and experts concentrate on repurposing (Table 2) antiviral molecules from plants and developing compounds that upregulate the immune system based on providing the lowest ligand binding energy (negative energy from a stable complex and strong binding interaction) and a variety of health benefits such as modulating both immune systems, acting as Immunomodulators, and curing diseases (DeLano et al., 2002; Min et al., 2015; Saeed et al., 2017; Calligari et al., 2020; Ayres, 2020).

Recently, Vincent et al. (2020) developed a polyherbal formulation containing 145 plant compounds for COVID-19 treatment. This formulation can be used to treat fever, cough, sore throat, and shortness of breath (symptoms of SARS-CoV-2) [AYUSH Ministry of Health Corona Advisory—DO. No. S. 16030/18/2019—NAM; March 06, 2020]. It can also use structure-based *in silico* molecular docking against the structure of SARS-CoV-2 3CLpro to identify potent anti-COVID-19 natural compounds.

CONCLUSION AND FUTURE SCOPE

The current COVID-19 pandemic is a serious threat. Moreover, it will not be the last. Every clinician, expert, scientist, and research community continuously searches for methods to treat COVID-19 rapidly and help in the screening, prediction, and tracing with high accuracy.

ML and AI are approved and promising computation-based techniques with high effectiveness. This study presents the importance of ML and AI and computational-based molecular docking programs. During this pandemic period, improved modern ML and AI algorithms have played a significant role in the screening, prediction, diagnosis, and prevention of COVID-19 through the development of innovative apps. ML and AI are also an essential part of drug development. Lastly, they are significantly involved in developing improved treatment, medicines/vaccines, and clinical

therapy. However, most of the apps presented did not work accurately, and a modern advanced app with high accuracy should be developed to address the pandemic. The computational molecular docking program accurately identifies ligand binding sites and confirms the orientation and interaction with the SARS-CoV-2 target S-protein. It also helps determine the binding affinity energy between herbal compounds and S-protein. However, in vivo experiments and clinical studies need to be performed to identify herbal blends and develop potent antiviral drugs to prevent and treat COVID-19.

Improved ML and AI models are widely applicable techniques and can be used in variable diagnostic domains to identify, predict, and screen COVID-19. They also recognize existing antiviral or anti-COVID herbal medicines, which can help treat and manage COVID-19 patients. ML and AI algorithms create interferences out of unlabeled input datasets, which can be applied to analyze the unlabeled data as an input resource for the COVID-19 pandemic. Both techniques provide accurate and valuable information compared with traditional calculation-based methods.

Both are equally beneficial to predicting healthcare risk during the current pandemic crisis and analyze the risk factors through demographic factors such as age, social habits, location, and climate. We can save many lives now and in the future if we use this opportunity to gather data, pool our expertise, and combine our skills. Create a machine learning program in a medical setting if you have an immediate need for assistance (e.g., working toward FDA approval).

CHALLENGES AND FUTURE DIRECTIONS TO IMPLEMENT CHANGE SUCCESSFULLY

After seeing the effect of technology and disturbances like AI and ML in managing the voluminous data of COVID-19 patients, it is undeniably a sustainable way of dealing with such unpredictable crises in the future so that processes are organized, linked, knowledge flows seamlessly, and interdependent functionalities are independent so that control and cure are immediate.

The Challenges of AI-based ML and DL Applications in COVID-19 Research are as Follows:

- **Legislation.** Scarcity of proper resources, unawareness of masses, unavailability of large-scale training data and experts to handle voluminous database, vast, noisy data, limited awareness of the intersection between computer science and medicine, data privacy, data integrity, data availability, unreliable text data, violations of consistency, and integrity of records are issues that need to be addressed using IoT and blockchain to make data consistent and seamless and maintain transparency. At the same time, data security challenges will be handled if appropriately implemented.
- **Regulation.** As the pandemic spreads and the number of confirmed infected and deceased cases rises, various measures to contain the outbreak have been considered, including lockdown and social distancing. Authorities play a critical role during a pandemic in identifying laws and policies that can encourage residents, researchers, scientists, business owners, medical facilities, technology giants, and major businesses to participate in COVID-19 prevention. However, due to the rapid spread of COVID-19, there are insufficient databases available for AI. In practice, interpreting training samples takes time and can require the assistance of qualified medical personnel.
- **Inconsistent and noisy data and unawareness among masses:** The challenges emerge from social media; without any significant changes, considerable audio information and false reports about COVID-19 have been reported in different online outlets. However, AI-based ML and DL algorithms appear to be slow in judging and filtering audio and error data. Additionally, with

noisy data usage, the results of AI-based ML and DL algorithms become biased. This issue reduces the use, functionality, and performance of AI-based methods, particularly in pandemic predictions and spread analysis.

- **Data privacy and protection.** The cost of collecting personal privacy data in the age of big data and AI is very weak. Many governments aim to collect a range of personal information, including an ID number, contact number, personal data, and medical data, in the face of public health issues, such as COVID-19. A problem worth addressing is how to efficiently preserve your privacy and human rights throughout AI-based discovery and processing.
- **Problem with data collection's inconsistency (e.g., image, text, and numerical data).** Having a piece of ambiguous and incorrect information in text descriptions is still a big challenge. Vast quantities of information from different sources can be inaccurate. Additionally, excess data make it impossible for valuable pieces of information to be extracted simultaneously.
- AI-based ML and DL systems are surely going to be future tools for detecting and diagnosing COVID-19. They will help prevent this deadly disease, give accurate data to detect the symptoms, and take corrective measures to overcome the crisis. They can help in the identification and screening of fake information. AI-based ML and DL systems can be applied to minimize and delete false news and audio data on Internet forums to provide credible, factual, and scientific information about the COVID-19 outbreak.
- **Detection of non-contact disease and disseminating information to approved individuals:** During the COVID-19 epidemic, automated image classification in X-ray and CT imaging can effectively prevent disease transmission from patients among radiologists. AI-based ML and DL systems can detect patient posture, X-ray and CT image recognition, and camera facilities. It will not only detect but also assist in the seamless maintenance of data.
- **Remote video detection, diagnosis, and consultations.** Combining AI and natural language processing techniques can build remote video diagnostic programs and robot systems to provide COVID-19 patient visits, first group diagnoses, and biological research. AI-based ML and DL systems can be used in the context of biological research to identify protein composition and viral factors via accurate biomedical knowledge analysis, such as significant protein structures, genetic sequences, and viral trajectories. These systems can not only be applied to identify possible drugs and vaccines. They can also be used to mimic drug-protein and vaccine–receptor interactions, thus predicting future drug and vaccine reactions for COVID-19 patients.
- **Impact assessment and evaluation.** Contactless prevention, identification, and response mechanisms can benefit from AI-based machine learning. The effect of various social control modes on disease transmission can be studied using AI-based ML and DL systems in multiple simulations. They will then evaluate scientific and reliable approaches to disease control and prevention in the general population. AI-based ML and DL systems can monitor and track the

characteristics of people living close to COVID-19 patients by creating social networks and knowledge graphs, thereby accurately predicting and monitoring the potential spread of the disease. Intelligent robots can be used in sanitation programs in public areas, product delivery, and patient treatment without human resources. That will stop the spread of COVID-19.

In short, the efficacy of deep learning models and graphical characteristics that lead to the differences between COVID-19 and other forms of pneumonia needs to be clarified. That will help radiologists and practitioners to gain an awareness of the virus and accurately analyze the possible X-ray and CT scans of COVID-19 patients. Future research directions should be focused on molecular-based computational docking, including molecular features of various types (geometrical, energy terms, pharmacophore), advanced ML techniques (e.g., deep learning), and the combination of multiple ML models. Furthermore, some improved sampling methods are no longer just a methodological exercise but are now available to a wide variety of research groups, with practical applications in herbal drugs' production to suppress COVID-19 symptoms.

What is the most significant aspect of COVID-19 diagnosis and treatment? Both are important, but finding a cure for COVID-19 is even more so. We discovered that most current AI-based ML and DL strategies focus on detecting COVID-19 from the literature. More studies based on ML and DL are required to improve treatment methods for COVID-19. AI, ML will significantly enhance the COVID-19 pandemic, medication, screening and prediction, forecasting, contact tracing, and drug/vaccine production while reducing human medical practice involvement. However, most models have not been deployed sufficiently to demonstrate their real-world functionality, but they are still capable of combating the pandemic.

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