Chapter

Immunoinformatics and Computer-Aided Drug Design as New Approaches against Emerging and Re-Emerging Infectious Diseases

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Abstract

Infectious diseases are initiated by small pathogenic living germs that are transferred from person to person by direct or indirect contact. Recently, different newly emerging and reemerging infectious viral diseases have become greater threats to human health and global stability. Investigators can anticipate epidemics through the advent of numerous mathematical tools that can predict specific pathogens and identify potential targets for vaccine and drug design and will help to fight against these challenges. Currently, computational approaches that include mathematical and essential tools have unfolded the way for a better understanding of newly originated emerging and re-emerging infectious disease, pathogenesis, diagnosis, and treatment option of specific diseases more easily, where immunoinformatics plays a crucial role in the discovery of novel peptides and vaccine candidates against the different viruses within a short time. Computational approaches include immunoinformatics, and computer-aided drug design (CADD)-based model trained biomolecules that offered reasonable and quick implementation approaches for the modern discovery of effective viral therapies. The essence of this review is to give insight into the multiple approaches not only for the detection of infectious diseases but also profound how people can pick appropriate models for the detection of viral therapeutics through computational approaches.

Keywords: immunoinformatic, pharmacophore modeling, molecular docking, quantum mechanism, peptide and vaccine design

1. Introduction

Infectious diseases are types of transmissible or communicable diseases mainly caused by pathogenic living microorganisms. The disease not only can transmit from animal to animal but also transfer from animal to human through the parasite, virus,

and bacteria [1]. The sudden invasion of infectious disease is a critical objective for the quietly alive of people in the ground [2]. However, it is not always an easy task to identify and anticipate the small pathogenic like small particles that are responsible for sudden chronic situations increasing incidence in geographic range [3]. Therefore, the situation demands to identify the unpredictable appearance of new infectious diseases as soon as possible that can utilize for further development of new therapeutic agents. Before identifying the causal infectious agents, the inevitable, but unpredictable, the appearance of newly emerging and re-emerging infectious diseases should be understood. The term emerging infectious diseases (EID) refers to infections that are newly arrived or evolved in a certain population, whose incidence can rapidly increase worldwide and threaten for future. On the other hand, infectious diseases that were previously appeared in the population and gradually decrease the incident but currently expanding into new geographical, host, or vector immensely that called re-emerging viral disease [4]. The virus disease has been recognized mostly from zoonotic by infecting a human. The primary source of zoonotic virus from farm and wild animal causes disease in human. Approximately 60 to 75% of known human pathogens ascend from animals [5]. Animal reservoirs have been involved in numerous virus families such as Filoviridae, Arenaviridae, Flaviviridae, and Bunyaviridae that were responsible to transmitted virus animals to humans *vice versa*. Most of the viruses abovementioned can be occurred emerging or re-emerging diseases, which do not have any specific therapeutic agents. Therefore, the development of vaccines and antimicrobial drugs candidates is an urgent issue that can control or prevent emerging or re-emerging diseases as soon as possible.

With the advancement of computational biology and immunoinformatics, rapid detection of pathogens and related proteins responsible for the disease has been developed. The technology helps to determine pathogen types within a short time and is utilized for therapeutic development. For example, immunoinformatic approaches can predict epitopes and their target protein is the recent advancement in vaccine design and development process that controlled the uses of antigen variation as well as hitting conserved epitopes [6]. It mainly designs immunogens by the protective responses of the target-specific receptor [7]. In the consequences of DNA virus infection and replication, it first attaches to the outer cell of the host through the protein receptor and replicates DNA by using host cell enzymes [8]. Finally, DNA goes to messenger RNA and translates it into a viral protein. Complete viral particles have converted by the replicate DNA and viral protein when new viruses were released from the host cell [9]. Additionally, RNA viruses are operated precisely as messenger RNA to make viral proteins. This mechanism of viral infections can be predicted through computational tools and immunoinformatics can identify desired epitopes for designing vaccines against the infections. On the other hand, computer-aided drug design (CADD) consists of a computer-assisted *de novo* design that can predict several models based on drug-target interaction network and help to early stage of drug design through molecular docking, similarity search methods, and deep learning-based model. The confirmation of ligand and the target protein can be initially predicted through molecular docking [10]. However, the performance of docking is quietly dependent on various types of receptors as well as acting best for the hydrophobic vs. hydrophilic pockets, which can also be determined by the CADD approaches.

Furthermore, consistent advancement of medical and pharmaceutical research has been playing an important role in the proper solution of several diseases but remained some problems with viral disease that may suffer or burden to public and

animal health [11]. Therefore, computational techniques have opened a new avenue for minimizing the problems of drug discovery. The pharmaceutical industry has been starting to take up help from computational methods for drug design and development, drug repurposing, enlightening medicinal efficiency, and clinical trial [12]. The increasing data digitalization in a pharmaceutical company can be solved clinical problems that can also be done through computational methods. They have maintained a large volume of data for solving infectious diseases by their automation. The extremely widespread diseases remain virus diseases that cause infection by a type of microorganisms [13]. The most prominent type of virus diseases is common cold, while another one is an infection of virus that affected the upper respiratory tract such as nose and throat [14]. Furthermore, antibiotics have a magical role in preventing bacterial disease and infections but have no effects on viral disease. The most significant challenge to the researcher is finding out the epidemiology, vaccine design, and eradication in a worthwhile manner [15].

2. Infectious disease

Infectious disease is a kind of disorder that is caused by one or more organisms. Many organisms consist of our body where some are normally helpful or infectious with parasites and viruses as well as bacteria and fungi [16]. SARS, recently emerged SARS-CoV-2, tuberculosis (TB), HIV/AIDS, influenza, Chickenpox, the common cold, and Hepatitis A and B are some examples of infectious diseases that can easily transmit from human to human or animal to human under adverse conditions and help to cause diseases. However, the animals or insects are directly or indirectly responsible for transmission to these organisms. Contaminated food items have exposed some infectious to the new environment and move apart from diseases [17]. There are various signs and symptoms of infectious diseases such as fever, fatigue, coughing, muscle aches, and diarrhea, and so on. Infectious diseases can be remedied or controlled by vaccines, but it takes a long time for application. Most infectious diseases controlled by consciousness of diseases such as handwashing can help to protect from many infectious diseases [18].

2.1 Global burden of infectious diseases

Over the last few centuries, millions of people have lost their lives to infectious diseases throughout the world. The risk of public health has been reduced and controlled through the improvement of the sanitation system, the progress of antibiotics and vaccines, living condition, and food quality, which is linked to the socioeconomic modernization of these societies [16]. Despite the improvement of health care facilities and surveillance systems, there have been some uncertainties that still now lead to an increase the human mortality from infectious diseases. The current threat to global human health is zoonoses [19]. The mutually transmitted 200 diseases occurred between humans and animals. The zoonotic disease has been increasing due to the overpopulation, wars, and food scarcity that are associated with humans who contract face to face [20]. However, the global death increased in 2010 due to infectious disease from HIV/AIDS that constitutes 1.5 million, and hereby malaria raised to 1.17 million [21]. At the same time, about 152,000 people died by the neglected tropical disease, and 1.2 million people died of tuberculosis [22]. Long-term illness, disability, and social stigma are occurring from poverty

and are renamed by infectious diseases of poverty (IDoP). Moreover, coronavirus disease 2019 (COVID-19) has the main worldwide burden in this era expressing itself as a pandemic and killed almost 4,825,433 people from the beginning and has been infecting till now [23]. The global health system has been affected by the pandemic due to the unintentional interruption of service delivery. Until now, a total of 369 infectious diseases have been identified based-on mortality and the estimation of life expectancy according to global burden diseases in 2020. There are several factors responsible for diseases that have compiled during the COVID-19 pandemic by analyzing 286 causes of death, about 369 injuries and infections, and 87 threat issues from the 204 nations [24].

2.2 Emerging and re-emerging infectious disease

Several infectious pathogens have been halting their activities from the initial discovery and reappearance after a long and short period in several places [25]. Among them are Emerging and Re-Emerging Infectious Diseases (EIDs). They are types of infections that have newly originated or previously existed in a population that is rapidly increasing in incidence or geographic range. The newly emerging and re-emerging viral disease has threatened public and animal health, which is increasing due to human activities [26]. There are many associated factors related to the spread of infectious viral disease from one place to another place such as population migration, urbanization, public gathering, poverty, malnutrition, increased domestic and global connectivity and environmental changes, and so on [4]. The alteration of genetic phenomena has also been responsible for to spread of disease to a greater extent. Most of the infectious diseases have been estimated in zoonotic that constituted 60 to 70% of total diseases [27]. Hence, the animal virus also mutated with a human virus that accelerates infectious viral disease and generates the chronic problem. As a result, thousands of people die without medicine or even without knowing about the threat [28]. Novel pathogens have occurred due to unplanned urbanization of habitat destruction that enhances the contact or susceptibility to infections between human and animal vectors of viral diseases herewith the lack of immunity of these communities [29]. However, many pathogens re-emerging again after many years such as Chikungunya and Zika virus.

2.3 History of emerging and re-emerging virus

Initially, there was an outbreak of chikungunya between 1963 and 1973 with serious arboviral illness and it re-emerged in 2006, which firstly was observed in the East African strain of chikungunya [30]. Similarly, the Zika virus was initially associated with a serious illness that has conducted by serological studies in 1960 and after a long time, it has identified and reported from Brazil in 2015 [31]. The discovery of novel pathogens in the world has not been clogged and they are associated with economic cost reflect the burden for many developed and underdeveloped countries (**Table 1**). The high cost of medical and intensive care has been banned for all kinds of work from the affected region.

2.4 Factor influences emerging and re-emerging viral bond diseases

Viral diseases have chorionic effects on public health worldwide. The annual death has been attributed to about 20 million by infectious diseases [34]. Most of the death

Family	Pandemic Year	Viruses	Probable/mode of transmission	Outbreak potential
Bunyaviridae	1917	Ganjam virus or Nairobi sheep disease virus (NSDV)	Tick-borne	Yes*
	1954	Bhanja virus	Tick-borne	Yes*
	2009	SFTS virus	Tick-borne	Yes
	1719	Chobar Gorge virus	Tick-borne	No
	2008	EEV	Arthropod-borne	No
	2004	Cat Que. virus	Arthropod-borne	Yes*
	1957	Kaisodi virus	Tick-borne	Yes*
	1955	Umbre virus	Arthropod-borne	Yes*
	1965	Ingwavuma virus	Arthropod-borne	No
	1957	Chittoor virus	Tick-borne	Yes*
	1964	Thottapalayam virus	Rodent-borne	No
Nairoviridae	1944	CCHFs virus	Tick-borne, human to human	Yes
Flaviviridae	1955	Yellow fever	Arthropod-borne	Yes
	1947	Zika virus	Arthropod-borne, mother to child, sexual route	Yes
	1957	KFD	Tick-borne	Yes
	1952	JE	Arthropod-borne	Yes
	1992	Dengue	Arthropod-borne	Yes
	1966	Bagaza virus	Arthropod-borne	Yes*
Paramyxoviridae	1968	Influenza - (H3N2) v alias	Air-borne	Yes
	2004	Avian Influenza	Air-borne	Yes
	2006	Influenza -Avian (H5N1)	Air-borne	
	1956	RSV	Air-borne	Yes
	1953	Quaranfil virus	Tick-borne	Yes*
	late 1950s	Parainfluenza 1–4	Air-borne	Yes*
	2009	Influenza H1N1	Air-borne	
	1962	Enterovirus-D68	Air-borne	Yes
Paramyxoviridae	2001	Nipah virus	Human to human	Yes
			Direct contact/consumption of infected bat/fruit infected with bat	
Picornaviridae	1953	Human rhinovirus A, B and C	Air-borne	Yes
	1957	Hand, foot and mouth disease	Direct contact, feco-oral route	Yes
	1948–49	Coxsackie-A21 virus	Feco-oral route	Yes
	1948–1949	Coxsackie-A10 virus	Feco-oral route	Yes
	1977	Sapoviruses	Feco-oral route	Yes
	1973	Rota	Feco-oral route	Yes
	1997	Polio and non-polio flaccid paralysis	Feco-oral route	Yes

Family	Pandemic Year	Viruses	Probable/mode of transmission	Outbreak potential
Caliciviridae	1936	Noroviruses	Feco-oral route	Yes
Hepadnaviridae	2007	Hepatitis KIs virus new and vaccine escape mutants of HBV	Blood-borne	Yes
Togaviridae	1740	Rubella virus	Air-borne	Yes
	2005	Chikungunya virus	Arthropod-borne	Yes
Poxviridae	1934	Buffalopox virus (orthopoxvirus)	Direct contact	Yes
	1958	Human monkey pox	Air-borne	
Parvoviridae	1975	Human parvovirus 4	Parenteral transmission?	Yes
Arenaviridae	1934	LCMV	Rodent-borne	Yes*
Herpesviridae	1934	CMV	Direct contact	Yes
	1974	Chickenpox (varicella) VZV	Air-borne, direct contact	Yes
Rhabdoviridae	1965	Chandipura virus	Arthropod-borne	Yes
Reoviridae	1963	Kammavanpettai virus (orbiviruses)	Tick-borne	No
Coronaviridae	2003	SARS Coronavirus	Air-borne	Yes
	2019	Coronavirus disease-2019 (COVID-19)	Air-borne	Yes
Polyomaviridae	1953	Polyoma-like virus	Human to human	Yes
Phenuiviridae	1931	Rift valley fever	Blood-borne	Yes

Table 1.
Emerging and re-emerging virus figure out with the inauguration periods [32, 33].

not only occurred by acute respiratory tract infection and gastrointestinal infections but also come out through tuberculosis and malaria that remained unchanged till now [35]. Many factors have been leading to emerging and re-emerging infectious diseases such as demographic factors, population distribution, sexual behavior, childcare, food-borne and water-borne diseases, ecological alteration and land use, chronic manifestations, enhanced pathogen detection, microbial evolution, and failure of community health scheme and bioterrorism shown in **Figure 1** [36]. The variations of the global population have been contributing to the growth and density in per capita, resettlement to the city area, international tourism, migration, and retaining density that directly or indirectly leads to the infectious virus disease [37]. However, there are some intentional reasons too responsible for the emerging and re-emerging virus such as the deliverance of sexual practice, enhanced childcare beyond the family, alcohol and drug abuse, food supply, transportation, and immunization practices [32]. Moreover, the environmental and land use causes of global warming, deforestation, and natural disasters such as floods, drought, and *El Nino* effect will be the lead to current and future infectious diseases [38]. The invention of modern technology can manifest the infectious diseases that are prolonging the life of people in the world. The use of new molecular techniques has enhanced to detection of fastidious and uncultivatable organisms [39]. As a result, a variety of pathogens were discovered in a short time. Nowadays, microbiomes naturally adapt to their environment for survival causing a wide range of microorganisms that

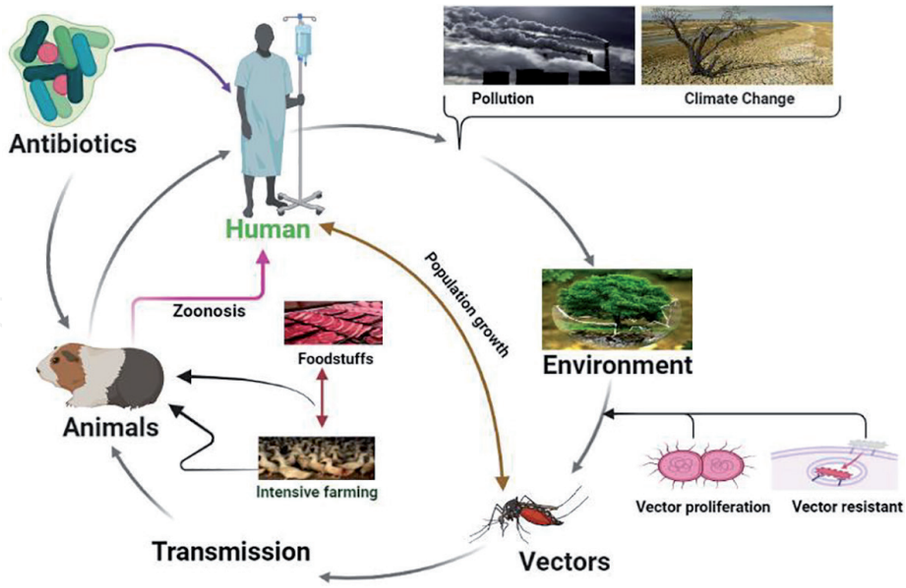

Figure 1.
Representing different factors that influence the activities of emerging and re-emerging viral bond diseases.

have become resistant to diseases [40]. Consequently, it can alter the present situation and convey the hazardous situation for human life.

2.5 Preventive measures of emerging and re-emerging disease

Due to the degradation of the environment, many contagious infections spread out the world for a long time. However, some diseases have been treated through the antibiotic and controlled with the vaccine but most of the disease's remedies remained unchanged still now [41]. Scientists and researchers have been searching for a new link in an infectious chain through their internal activities. The consumption of raw food is one of the triggers of infectious diseases. Raw food usually has lots of harmful microorganisms that can hamper your normal life within a short time [41]. Several factors have been contributing to the vast range of emerging and non-emerging diseases such as changes in human behaviors, enhancement of technology, change in the land pattern and economic progress, tourism, microbial change, and collapse of public health measures [41]. However, the prevention and control have been taken by the Pan American Health Organization (PAHO) that regulates some measures of emerging and re-emerging diseases [42]. First, there is need to increase and strengthen regional surveillance networks that control infectious diseases from one place to another place. Later, the rapid responses of infectious diseases thereby enhance the laboratory equipment and training. Moreover, the development of applied research fields can prevent the disease through the rapid diagnosis of epidemiology as well as prevention [43]. Finally, the enhancement of regional capacity and strength can control and prevent emerging and re-emerging diseases through effective implementation [44].

2.6 Traditional methods of preventing emerging and re-emerging disease

Emerging viral diseases have occurred previously and resultant pandemics where plant derived was the first choice for treatment. Around 1500 BC, Egyptians were started herbal drug preparation by the medicinal plant where later Greek and Roman

have improved it [45]. Emerging infectious diseases have been treated traditionally by the medicinal plant before inventing a drug or vaccine [46, 47]. In China, it was widely used to deal with infectious diseases. They believe that it boosts the immune system and protects the virus to enter the respiratory tract [48]. Many medicinal herbs have a unique antiviral effect and are used as a substitute for an antimicrobial drug against infectious diseases. They have used the whole body of herb or part of the plant such as leaves, roots, bark, fruit, seeds, flowers, and so on, for preventing and healing respiratory tract infections [49]. In the modern time, it has been perceived that the traditional drug safer and healthier than synthetic drug those comes from plant-based traditional medicine. Plant-derived drug discovery has been renowned for the last decade [50]. It is considered that plant products will be an indispensable source of a new drug in the future.

3. Computer-aided drug design approaches

3.1 Pharmacophore modeling

Pharmacophore is one of the most promising *in silico* concepts, which is utilized to screen large compound libraries. The process includes combining medicinal chemistry and computational chemistry that can screen and optimize lead compounds for the development of the final drug candidate [50]. The pharmacophore model can function in two ways such as ligand-based modeling and structure-based modeling (**Figure 2**). The ligand-based model is fully based on computerized for simplifying drug discovery in the macromolecular target structure [51]. It generates three-dimensional (3D) structures for interacting ligand and macromolecules. Software such as Schrödinger (https://www.schrodinger.com/) and so on are used for pharmacophore drug design. Furthermore, the direct interaction of 3D structure with macromolecule ligand complex is arranged by structure-based pharmacophore modeling. The investigation of the complementary chemical feature of the active site and their spatial relationships and assembly with the selected feature will be generated using the structure-based pharmacophore modeling [52]. Discovery studio is usually practiced for the implementation of the structure-based pharmacophore method. The catalyst feature of pharmacophoric is H-bond acceptor, H-bond donor, and hydrophobic. Virtual-based pharmacophore screening has been reducing the possibility of arising problems about inadequate consideration of protein selectivity with the optimizing

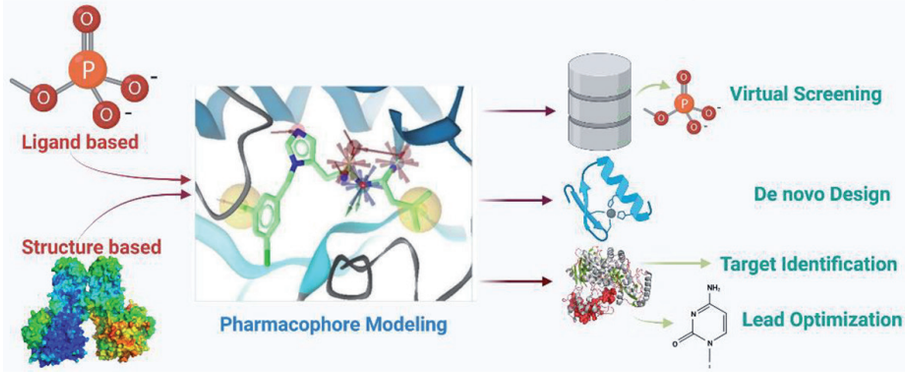

Figure 2.
Pharmacophore model-based virtual screening process for identification of small molecular candidates against a specific disease.

score and insufficient design by leading a tolerance radius for each feature [53]. The main purpose of pharmacophore model-based virtual screening is to count the highest molecules hit, which has similar or nearest the target.

3.2 Virtual screening

3.2.1 Molecular docking

In modern drug design and discovery, molecular docking is one of the foremost strategies to find the best molecules for a specific target. It assists to predict the interaction of protein and a ligand at the bond stage. Molecular docking is used to calculate the scoring function by sampling algorithms shown in **Figure 3** [54]. Furthermore, it is reasonable, time demanding, and effective more than any conventional technology. The computer-based drug designing method predicts the function of any individual protein of interest that conducts a very comprehensive approach [55]. It has various applications among them protein-ligand docking is one of them. It is primarily designed to predict the binding of small drug molecules from medicinal herbs or plants, invertebrates, and so on to target proteins [56]. The number of diseases is caused by the harmful receptors; hence, docking is designed to inhibit or induce the target protein. However, the discovery of drugs in the traditional way is very expensive because of the need to search a large volume of compounds to select against a particular protein for the proper binding interaction and targeting diseases [57]. Therefore, computerized docking can screen virtually thousands of compounds in a short time by experimental high-throughput screening and confirmed the ligand and receptor for stable binding. It also provides the knowledge-based scoring functions that interact with atom pairs between protein and ligand complexes along with three-dimensional structure. There are several purposes of molecular drug design [58]. Among them, three are main purposes such as predicting the active ligand, binding affinities, and identifying new ligand. Based on molecular

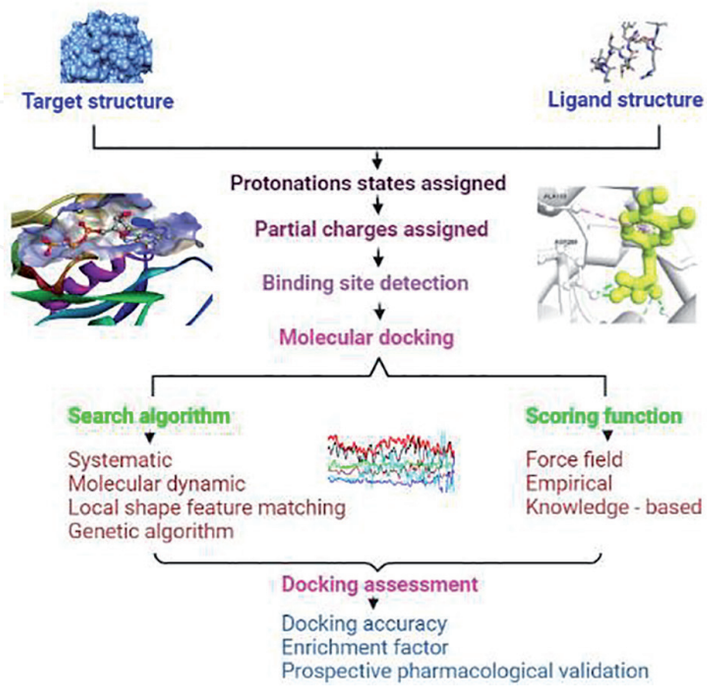

Figure 3.
Molecular docking-based screening approaches of small molecules against a specific target.

docking, it has numerous applications such as documenting the lowest free energy structure for the receptor-ligand complex, estimating the differential binding of a ligand of two separate macromolecular receptors, the geometry of the specific ligand-receptor complex, lead generation and optimization for future drug candidate, and so on [59].

3.2.2 Molecular dynamic simulation

Molecular dynamics (MD) simulation is a computer-based simulation technique that mainly analyzed the physical motion of atoms and molecules across a specific conformational space [60]. MD simulation is the unique way to drug discovery in the present era that led to work in a wet lab after computer simulation. The MD simulation ensures the detail of the dynamic properties of selected protein and plays a key role in the modeling and characterization of a protein [61]. The MD simulation also helps to determine the stability of a ligand to the active site of the targeted macromolecules. Moreover, MD simulation not only provides the information of the ligand optimization process at the qualitative level but also estimates accurately in ligand binding affinities. The tiny, microscopic event (protein-ligand interaction and molecular motion) occurs with a micro- or nano-second time scale that is not possible to determine without the technique [62]. Finally, dynamic simulation is a faster, reasonable, widely accessible, and perfect method for drug design *in silico* techniques. Moreover, it provides information of atomic position with respect to time. It usually explains the atomic and molecular properties of the protein, drug-target interaction, solvation of compound, and conformational changes that a receptor expresses in various conditions [63]. It works on the base of Newtonian mechanics (NM), which is related to the motion of large particles. The force fields are an important factor for MD simulation, which are mainly a set of the potential energy function for employing the relation between structure and potential energy. The particles are coordinated by the system of mathematical expression [64]. The computerized technique (force and energy) is used for building blocks that combined bonded and non-bonded interaction. Force acting on each atom was counted by using the force field of molecular machines that were developed through the four principal such as Born-Oppenheimer method, bond length, and bond angle, and potential energy of the surface molecule and atom type [65].

3.2.3 Quantum mechanics

Quantum mechanics has been leading a valuable method for drug discovery through characterizing the structure, dynamics, and energies of protein-ligand interaction [66]. In the medicinal industry and academic research, it is an inevitable part of drug design that fixes the problem by calculating chemical reactivity and helps to optimize structure [67]. The new drug candidate has been chosen by molecular mechanics (MM) but the quantum mechanics (QM)-based approach provides accurate accuracy and efficiency in the complexity of protein-ligand interactions [68]. Furthermore, it does not provide only the estimation of being affinities, determining ligand energies and bioactive conformations, refinement of molecular geometries but also added scoring docked ligand poses, describing molecular similarity, structure-activity, relationship analysis, and ADMET prediction in the activities of drug design [69]. QM is getting popular day by day in drug discovery because of the improving power or speed of the computer that led to advanced QM algorithm progress as well as a new application to address the shortcoming [70]. The popular method of fragment molecular orbital (FMO) offers a wide range of solutions where there are combined

accuracy, speed, and the ability to characterize important interaction such as strength in kcal/mol as well as hydrophobic, electrostatic, and so on. In summary, FMO analyzed the length such as polarization, desolation, and interaction with the illustrated for a water dimer and protein-ligand complex [71].

3.2.4 Pharmacokinetic properties

Pharmacokinetics is the unique part of the drug design where the time course study is done through the mathematical characterization for absorption of drug, distribution, metabolism as well as excretion (ADME) [72]. Therefore, before the clinical trial, it is the advanced procedure to select a drug for the development and decision-maker by AMDE test [73]. As a result, it is safe and effective for a specific patient by decreasing toxicity and increasing efficacy in drug therapy. However, the central compartment of the human body was interconnected by a series of compartments reversibly on the base of pharmacokinetic [74]. Therefore, drugs enter each compartment and are distributed homogenously to display consistent kinetics. Hence, it is separated by a mathematical model where AMDE can differ in each compartment and help to predict drug metabolisms or actions [75]. Moreover, the central compartment received drug and entry on the body called absorption. The drug is distributed to the peripheral compartment after absorbing into the body and beginning the metabolic processes. Finally, the excretion of the drug from the body is in three ways such as hydrophilic molecules by the renal system, hydrophobic molecules by the biliary system, and volatile substances by the pulmonary system [76].

4. Immunoinformatic

4.1 Peptide design

In the drug discovery, peptides are not new, but it makes a choice drug candidate in the challenging situation with the collaboration of immunoinformatics. Immunoinformatics can be developed as natural endogenous scaffolds with familiar biological activities for solving challenging medical problems by it distinguishing characteristics such as the ability to act firstly, more specific, the minimum range of toxicity, and so on [77]. Approximately 55 therapeutic peptides have been approved for clinical trial through the regulatory agency [78]. Currently, many researchers have been working to solve various diseases through antimicrobial peptide design. The target of antimicrobial peptides has accelerated through the deep generative models and molecular dynamics. By utilizing the immunoinformatic approach, the researcher has developed 20 novel peptides that were validated through deep learning and high-throughput molecular simulation [79]. The peptides are not only used in broad-spectrum potency but also lead to multi-drug resistant strain and low toxicity. Immunoinformatic approaches help to observe peptide activity, selectivity, toxicity, ease of synthesis stability, etc. During the present situation of COVID-19, immunoinformatics help to identify peptide candidates from diverse viral sequences as shown in **Figure 4**, which can be utilized for vaccine design [80]. It is identified and designed from the motifs and subsequently a peptide library. As a result, strong binding affinities of peptides had happened with the main protease of SARS-CoC-2 as well as maintained stability and physiological condition observed by molecular dynamic simulation [81].

4.2 Vaccine design

Vaccine design is a very powerful tool for saving human life in the world broadly. The advancement of technology has been trigger to develop new strategies by the target and the structures of antibodies, hitting conserved epitopes and controlling the usage of antigenic variation [82]. It designed immunogens for provoking foreign responses because of no single or best solution of immune drugs design till now [83]. However, artificial intelligence and system biology together make an opportunity for avoiding inefficiencies and failures that help to classical vaccine development pipeline [84]. *In silico* vaccine design process has been selecting well fragment of virus protein [85], thereby finally leading to a final vaccine as shown in **Figure 4** [86].

However, in the vaccine design process, DeepVacPerd is an efficient tool that predicts the best vaccine subunit candidates with 30 subunit candidates from the various protein sequences within a second by replacing the predicted and selected with deep neural network architecture [87]. Therefore, it has become a promising of higher efficiencies for the vaccine design and test process. Furthermore, systems biology developed various tools by analyzing large data set through the complex modeling interaction between the individual interaction [88]. The omics disciplines such as genomics, proteomics, metabolisms, and so on produced a simulation of the immune response, identified response-specific signature, and assessed their predictive value through the basilar idea with the integration of high-throughput data [89]. Therefore, several programs and consortiums have performed by developing novel analytic tools that may integrate the information from omics.

4.3 Future perspective of vaccine

Personalized vaccine candidates are developed against a specific "targeted" to maintain an optimized outcome. Failure of the vaccine candidates can increase immunogenicity subsequently reactogenicity and adverse effects [90]. Therefore, the individual level, the gender level, the racial/ethnic level, and the subpopulation

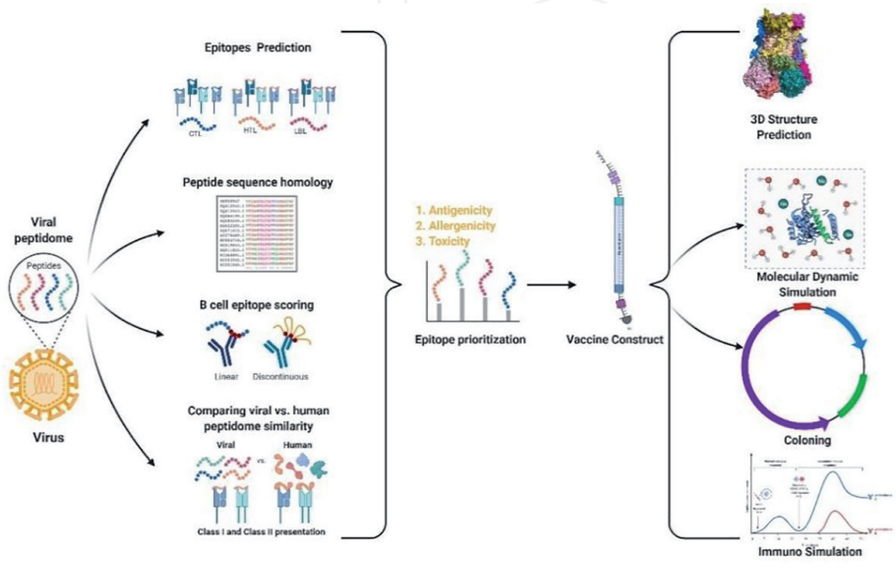

Figure 4.
Immunoinformatics aided identification of peptide candidates and procedure for designing multi-epitope vaccine by utilizing the peptide.

level should be considered during the personalized vaccine development process. Haplotype and polymorphism are mainly focused on the individual level selection as they can retard the formation of a protective immune response, where the gender level can determine the antibody tiger against a particular vaccine to males and females [91]. On the other hand, different human races or ethnic groups can show higher or lower immune responses to a specific vaccine candidate. Additionally, different interactions between host environmental, genetic, and some other factors may be influencing the vaccine immune responses; therefore, the subpopulation level should be also considered during vaccine design that can trigger an optimum immune response against a specific disease [92].

5. Conclusion

The study describes numerous computational tools that are widely used for drug and vaccine design against infectious viral diseases. However, improving ideas and methodologies can solve problems and provide system-level interconnected data. A promising idea accelerates the rational design of drug candidates that are used in the specific subfield. Here, we focused on computational methods that will help and provide a clear idea of modern drug and vaccine design approaches adequately.

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Conflict of interest

The authors declare no conflict of interest.

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