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.

CHAPTER

11

Molecular docking and molecular dynamic simulation approaches for drug development and repurposing of drugs for severe acute respiratory syndrome-Coronavirus-2

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11.1 Introduction

Since the beginning of the 21st century, the world has evidenced the occurrence of several disease outbreaks such as severe acute respiratory syndrome (SARS), H1N1 influenza pandemics, Zika virus (ZKV) disease, and Ebola virus epidemics. However, the world has not witnessed the state of emergency in the form of a pandemic until the emergence of SARS Coronavirus-2 (SARS-CoV-2) diseases until the first quarter of 2020 (Babore et al., 2020). As per the World Health Organization's (WHO) record, SARS-CoV-2 pandemics have resulted in infection to approximately 154.64 million people and the death of 3.23 million people worldwide to date. The occurrence of the corona pandemics has a catastrophic influence on the global healthcare settings and the economy as it has spread worldwide over 200 countries irrespective of their status being developed and developing countries (Pak et al., 2020). The COVID pandemic has worst affected the developed countries including superpower United States, Great Britain, Russia, etc. Similarly, in the category of developing countries, the worst affected countries are India and Brazil. India is recently witnessing the tendency of second wave of SARS-CoV-2 infection, which has shattered all the previous records with 0.38 million confirmed cases on a daily basis, thereby creating a traumatized situation of acute shortage of life-saving oxygen supplies, emergency drugs, and intensive care unit

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beds in the healthcare settings. Apart from the influence on healthcare settings, the uninterrupted service of healthcare professionals and other frontline warriors in these stressful critical conditions might lead to the development of psychological stress leading to anxiety and insomnia, which are categorized as mental health conditions (Babore et al., 2020; Liu et al., 2020; Vindegaard & Benros, 2020). The global burden of SARS-CoV-2 also seriously affected the functional attributes of pharmaceutical sectors thereby inferring considerable influence on drug development pipelines owing to the imbalance between the demand and supply with the limited resources available in developing countries (Ayati et al., 2020).

Amidst the pandemic situation, the scientific community continuously works in understanding the pathophysiology and transmission strategy of the COVID-19 virus and formulating putative therapeutic regimens to counteract the severity of viral infection. Though no specific antiviral therapies have been found to be influential to date, a series of proven scientific information such as focusing on the use of repurposed drugs (e.g., Redeliver, Virafin) for mitigation of infection severity and development of effective vaccines are important for the prevention of SARS-CoV-2 infection (Zhu et al., 2021). In the fight against SARS-CoV-2, the concept of repurposed drugs as a potential therapeutic regimen gained considerable interest. Hence, the repurposed medications are potential alternatives to target viral infection and thus require high throughput and robust clinical trials before being prescribed for medications (Shi et al., 2021). Since the clinically-approved antiviral drugs are found to be effective only against 4.54% of viruses infecting human hosts suggesting new avenues to decipher the putative antiviral drug candidates as potential antiviral therapeutics. The constant dedicated efforts and robust drug development strategies could accelerate the drug development process and can tackle any sort of epidemics and pandemics situation (Adamson et al., 2021; Meganck & Baric, 2021). Thus the current pandemic situation has offered learning avenues for proper management of healthcare settings with stringent surveillance strategy as well as rational development of putative drug candidates for mitigating the SARS-CoV-2 associated infection (Iyengar et al., 2020).

11.2 Drug discovery and development pipelines

From the beginning of human civilization, mankind has witnessed the wrath of several disorders and diseases. Several folkloric practices are being considered for minimizing the consequences of these health-associated ill effects. The advancement of chemistry in the early phase of the 19th century marks the beginning of the discovery of small compounds targeted toward the management of different health hazards. The discovery of small compounds as drug moieties has revolutionized the translation of scientific and folkloric knowledge into the wellbeing of human health and disease management. The drug discovery and development process is considered to be the backbone of pharmaceutical industries and includes sequential events of discovering putative drug targets, identification and optimization of lead compounds of natural and/or synthetic origin, followed by preclinical studies, and finally the highly robust phase of clinical trials (which is further categorized into four phases) (Salazar & Gormley, 2017). The drug discovery paradigms are considered to be critically influential when the human civilization is witnessing several disease outbreaks from time to time. No doubt, considerable progress has been made in the biotechnological and pharmaceutical sectors, the

number of approved drug moieties is constantly in a declining state due to productivity crisis and drug attrition (Cornet et al., 2018). In this context, it is important to look for alternative drug development regimens for the management of several health consequences and pandemic situations. The drug discovery and development regimens could be categorized into conventional and reverse pharmacology-based mechanisms.

11.2.1 Conventional drug development pipelines

Traditionally, the drug discovery regimens involve sequential events as per the stipulations laid down by US Food and Drug Administration (FDA). The drug discovery regimen includes the following stages, that is, (1) discovery and development (target identification, screening, and identification of potential drug candidates, validation and optimization of putative drug moieties), (2) preclinical research (involves the dosing regimen and toxicity aspects), (3) clinical phase (consisting of four phases), (4) FDA review process of clinically passed drug molecules, and (5) FDA postmarket drug safety monitoring (Rudrapal et al., 2020) (Fig. 11.1). The timeline spans from target identification to the approval of potential drug candidates for marketing purposes on an average account for 12 years or more. No doubt, among the thousands of potential drug candidates screened for a particular target, only 0.0001%–0.001% actually get approval for marketing and human consumption. In addition, the associated cost of the entire process stands approximately at $2.6 billion per molecule, but the crisis of productivity remains relatively nominal (Kiriiri et al., 2020;

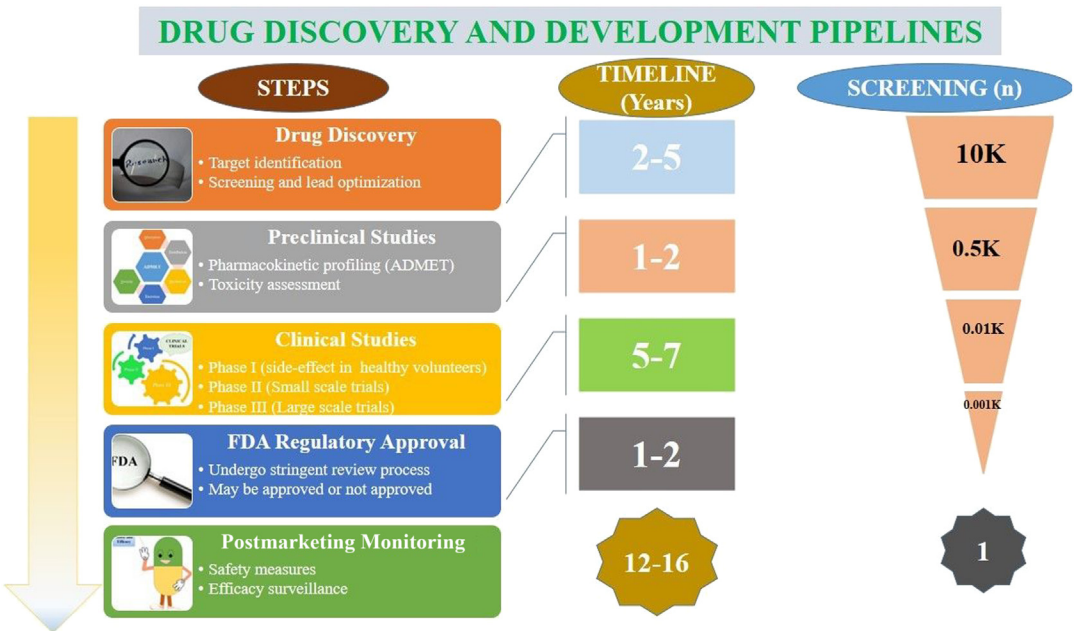

FIGURE 11.1 Schematic overview of the process of discovery and development of drugs starting from screening up to postmarket safety monitoring.

Mohs & Greig, 2017). Apart from cost-related limitations, possible toxicity profile, failure to pass pharmacokinetic filters, bioavailability issues, translational failures due to lack of proper model systems are considered to be influential in the failure of the majority of drug-like molecules over the drug development process. In this context, it is imperative to develop innovative approaches which not only minimize the relative cost of the drug development process but also improve productivity.

11.2.2 Reverse pharmacology-based drug development

As compared to the classical approach, reverse pharmacology-based approaches are considered to be highly significant in identifying the drug candidates and forming the basis of rational drug design. Reverse pharmacology approaches infer the robust exploration and documentation of data obtained from preclinical and clinical studies and translate the obtained information into the process of potential drug candidates as specific molecular targets (Patwardhan & Vaidya, 2010). The concept of reverse pharmacology-based drug discovery lies in the fact that, instead of pharmacological regimens, in the beginning, specific molecular targets are first identified using high throughput molecular genetics and computational tools. In the subsequent step, both target and ligand molecules are subjected to optimization. Once the optimization process is completed, a high throughput screening procedure is taken into consideration for the identification of potential lead molecules specific to the identified target. In the final step, the lead drug candidates are subjected to pharmacological activities (Takenaka, 2001) (Fig. 11.2). As per the trends received, the reverse

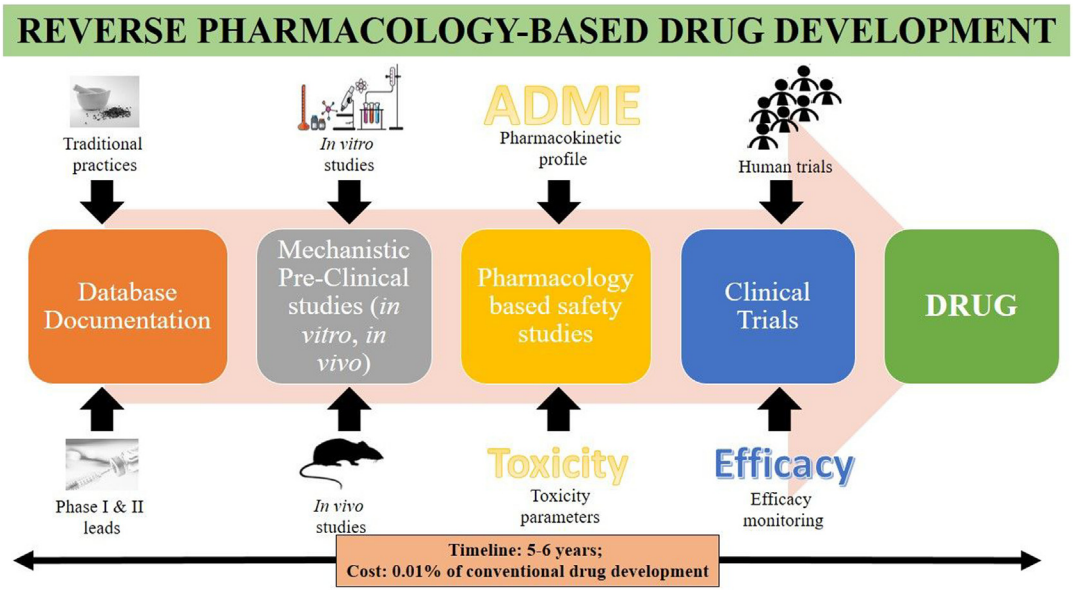

FIGURE 11.2 Schematic representation of reverse pharmacology-based rational drug design and its advantages.

pharmacology-based approaches for drug discovery are considered to be influential in terms of time and cost associated with the drug discovery process as in classical pharmacology-based approaches (Batool et al., 2019). As compared to the classical approach, the drug development process approximately takes 60% less time in reverse pharmacology-based approaches. Thus, the advent of reverse pharmacology has revolutionized the process of discovering potential drug candidates without compromising the safety and pharmacological efficacy (Arulsamy et al., 2016; Takenaka, 2001). Since the reverse pharmacology-based approaches are observed to be safer, effective, economical, and most importantly faster for validation of potential drug candidates, it is imperative to consider reverse pharmacology for identifying potential drug candidates in the emergency period such as epidemics and pandemics. The recent progress achieved in the advent of robust computational tools has significantly streamlined the complexity associated with rational drug design processes in terms of cost, engagement of human resources, and efficacy.

11.3 Computational approaches for drug discovery and development

Since the beginning of the 21st century, with the advancement in technological interventions, the concept of computational approaches is evolved as promising alternatives. These in silico approaches have revolutionized the current understanding of experimental drug discovery regimens by virtually estimating the possible associations between putative drug-like molecules and specific molecular targets of biological systems. Computational approaches-based drug discovery platforms provide avenues for screening thousands of drug-like molecules [termed as virtual screening (VS)] for specific biological activities (Rifaioglu et al., 2019). The intervention of computational tools in drug development regimens has radicalized the process of translating the obtained biological information toward the efficient management of particular diseases of interest at a faster rate as compared to classical methods (Agamah et al., 2020). The information obtained from in silico intervention in drug discovery programs, not only provides novel avenues for addressing the key aspects of drug development pipelines but also minimizes the limitations of conventional drug development in terms of drug attrition and probable toxicity (Wooler et al., 2017). The most noteworthy property of any potential drug candidates is their pharmacokinetic properties and toxicity. The pharmacokinetic properties (i.e., absorption, distribution, metabolism, and excretion) called ADME profiles of putative drug-like molecules are considered to be important parameters for consideration before being passed for their use as drugs. Secondly, the drug-like molecules should also not possess any toxicity profile. These features are found to be influential in the development of drug molecules for specific medications (Bergström & Larsson, 2018; Ferreira & Andricopulo, 2019). The advent of high throughput computational approaches has provided remarkable avenues for in silico determination of ADMET profiles, thereby screening the most potent drug candidates.

11.3.1 Computer-aided drug designing

Computer-aided drug design (CADD) infers the rational interference of computational approach-based information for the discovery and development of potential drug

candidates for specific activities to provide specific therapeutic solutions. In the last few decades, the involvement of several robust and high throughput computational tools have provided valuable information not only on putative drug candidates but also on therapeutic drug targets, screening of their interactions, and optimization processes. The CADD approach is the amalgamation of several concepts such as combinatorial chemistry, molecular databases, quantitative structure–active relationships (QSARs), and biological mechanisms. Basically, the CADD concept could be differentiated into structure-based drug design (SBDD) and ligand-based drug design (LBDD) (Yu & Mackerell, 2017). The SBDD concept applies in the situation where the structure of both ligand molecules (putative drug candidates) and target protein are known. As both ligand molecules and target proteins in the SBDD approach are known, the first step includes the identification of the binding site in the target protein where the ligand molecules are supposed to bind. In the subsequent step, the affinity of ligand molecules to bind the binding site of the target protein is calculated using specific computational tools, that is, molecular docking analysis, and the stability of the interactions was validated by molecular dynamics simulation (MDS). These tools play a pivotal role in screening the potential lead molecules for the purpose of drug development.

Meanwhile, the LBDD concept applies where the knowledge of the structure of ligand molecules is known but the structure related to the target site is not known. In this approach, the knowledge of ligand molecules could be considered either for pharmacophore-based Modeling (when the number of ligand molecules is confined to $n = 20$) or QSARs studies (when a number of ligands of interest are more than 20) for screening the potential lead molecules (Surabhi & Singh, 2018) (Fig. 11.3). Since the inception of QSAR-based modeling, it has been evolved from time to time and presently QSAR modeling is considered to be

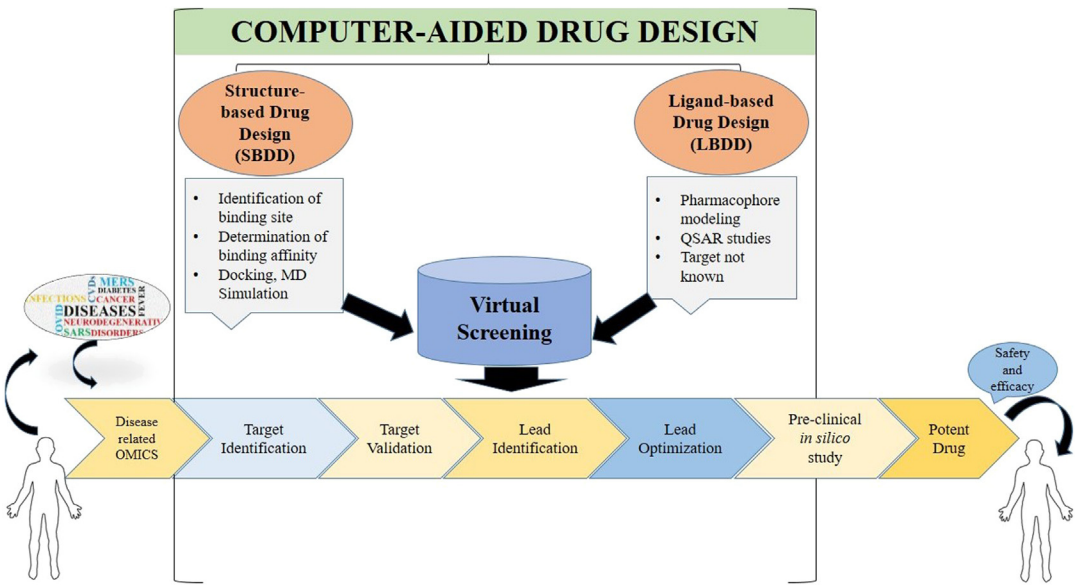

FIGURE 11.3 Schematic overview of in silico-based computer-aided drug design process and its applications.

instrumental in the VS of a large number of structurally diverse chemical compounds thus QSAR plays a pivotal role in analyzing large data sets. The combinatorial concept of QSAR using machine learning received considerable interest for rational drug design and development (Neves et al., 2018). Both the approaches of CADD, that is, SBDD and LBDD have received considerable attention from both academic research groups and pharmaceutical sectors for improving the efficacy of rational drug design regimens. The biggest advantage of considering CADD-based tools lies in the fact that these tools are ready to use and could complement the in vitro experimental data (Macalino et al., 2015).

11.3.2 Molecular docking approaches for drug discovery

Molecular docking forms the basis for the SBDD process and is explored as the computational tool for VS of thousands of drug-like candidates for their affinity toward a specific molecular target, provided that the structure of the target protein is available. Molecular docking is a fast, cost-effective, and simplified computational tool for predicting the scores associated with the association of putative ligand molecules and the target protein of interest. The generated docking score provides the basic information to identify potential lead molecules among the lot and could be considered for further therapeutic activities and drug development regimens (Wang & Zhu, 2016). In the last three decades, several molecular docking programs are being developed and these tools work on the principles of different algorithmic formulae. Among these programs, the most explored and effective docking tools are GLIDE (developed by Schrödinger), Auto Dock Vina (developed by Scripps Research Institute), GOLD (genetic algorithm-based), LeDock (for fast and accurate flexible docking) and MOE-Dock is considered to be the most accurate docking tools with both GLIDE (XP) and GOLD constantly exhibited more than 90% accuracy (Pagadala et al., 2017). Molecular docking-based VS when presented in combination with the data obtained from experimental studies (*in vitro* and *in vivo* analysis) could be instrumental in rational drug design and drug development process (Sethi et al., 2019).

Apart from VS, prediction of adverse drug reactions and relative toxicity, polypharmacology-based applications for identifying candidates modulating several targets associated with a particular pathophysiological condition, identifying alternative therapeutic modules of drugs through drug repositioning, target fishing and profiling, and rationalization of ligand−protein binding are the widespread applications of molecular docking (Lee et al., 2016; Pinzi & Rastelli, 2019). One of the most interesting aspects of molecular docking is the flexibility it provides in pose prediction for the determination of accurate ligand−protein binding. The algorithm associated with the particular molecular docking tools is responsible for predicting the pose of the ligand−protein complex through a series of trials and after a fixed threshold value or a sufficient number of poses being considered, the tool predicts the best orientation of ligands bound to the protein of interest through scoring functions and provides an affinity score (Kroemer, 2007; Meng et al., 2011). The exploration of conformational space associated when ligand molecule bound to the binding cavity of a target protein of interest, estimation of binding energy in different ligand conformations are the distinct phases in the entire process of molecular docking (dos Santos et al., 2018).

11.3.3 Molecular dynamics simulation tools for drug development

In the last few decades, considerable development has been observed in the SBDD approaches using computational tools. In addition to molecular docking, MDS also received considerable attention in the quest for potential drug candidates through the robust VS process, provided that the structure of the pathophysiological target is known. The advent of MDS complements the information received from docking analysis and thus provides a robust tool to screen the potent lead molecules. The MDSs not only provide an insight into the ligand–target protein interactions with the energy calculations but also confirms the stability associated with the formation of the ligand–protein complex. Hence, the MD simulation tools are considered to be instrumental in mediating the development of potential drug candidates for specific pathophysiological conditions (Ganesan et al., 2017).

The advantage of MD simulation in drug discovery pipelines lies in the fact that it provides dynamic structural information of the interactions between the drug-like candidates and target macromolecules with an assemblage of target protein conformations (Saurabh et al., 2020). MDS works on a different principle of mathematical algorithms and quantum mechanics. MDS tool utilizes "force-field" parameters (which ensembles different energy parameters such as binding energy, electrostatic, and van der Waal's energy) predicting the actual behavior of the formed complex in motion. The most widely used force-field parameters for MD simulations are AMBER, GROMOS, CHARMM, etc. Though these force fields are principally different from each other in terms of the way of utilizing the parameters, the results obtained from these approaches are more or less equivalent (Durrant & McCammon, 2011). In addition, the energetic information of the interactions in the dynamic state as obtained from energy calculations in MDS tools could play a pivotal role in determining the potential of any drug-like molecules (Liu et al., 2018). As per the recent trends, molecular docking in combination with MDS is being actively considered validating the possible interactions of ligand molecules and target protein and subsequently refining the existence of potent drug candidates (Gioia et al., 2017).

11.4 Drug repurposing: an overview

The concept of drug repurposing (also termed as drug repositioning and/or drug reprofiling) revolves around the use of potential drug candidates, which were earlier developed and passed the safety regulatory issues for the management of specific medical conditions, are repositioned for intended use against novel therapeutic target. Since the drugs of interest have already been tested in model systems and validated through clinical trials, repurposed drugs gained considerable attention in an emergency situations like pandemics (Jimenez-Alberto et al., 2020). The limitations associated with the drug development process such as probable side effects, systemic toxicity, pharmacokinetic failures, lack of efficiency could be resolved by diverting the clinically passed drug moieties and repositioning them for new therapeutic targets with lower risks of failures. The drug repurposing concept is generally categorized into drug-based or target-based based upon the availability of relative information. Drug-based repurposing approaches are considered

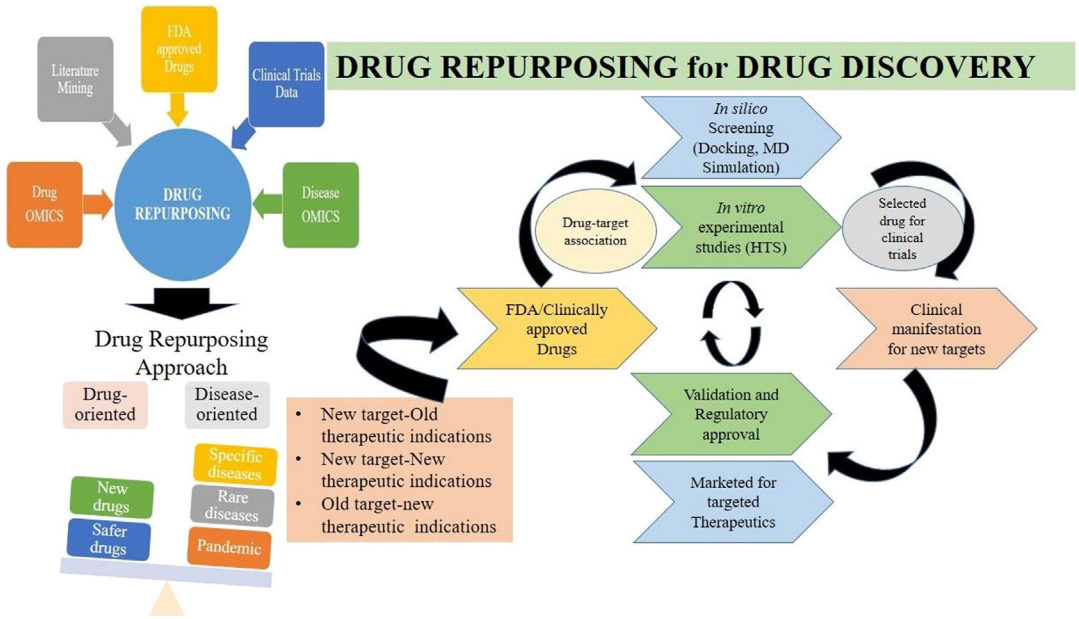

FIGURE 11.4 Schematic overview of drug repurposing or drug repositioning and its role in drug design and development.

when the information on drug-like candidates is available whereas the disease/target-based repurposing approaches are considered when the information on pharmacology of putative drug-like candidates are absent (Mohamed et al., 2021). Both the repurposing approaches have their specific advantages and limitations and hence, it is highly imperative to consider a combinatorial approach to decipher a strategic arsenal for the development of potential drugs for specific purposes (Peyvandipour et al., 2018; Pushpakom et al., 2018; Singh et al., 2020) (Fig. 11.4). From a historical perspective, the drug repurposing approach pioneered with the use of the anticancer drug, Zidovudine for efficient management of human immunodeficiency virus (HIV) causing acquire immunodeficiency syndrome (AIDS). Zidovudine was the first drug to be approved by FDA as an anti-HIV drug. Since then, several existing drugs were considered for repositioning to tackle new pathophysiological targets (Pushpakom et al., 2018). As per the estimates, approximately 75% of the existing drugs could be considered for repositioning for the management of several other pathophysiological conditions (Singh et al., 2020).

11.4.1 Drug repurposing for drug discovery

In the difficult period of pandemics, when the entire world is witnessing the upsurge of SARS-CoV-2 infections and the unavailability of potent drugs for COVID-19; the concept of drug repurposing could be deliberately used as the remedy in the context of modern drug development strategies to counteract viral infections. Drug repurposing not only

reduces the cost associated with the development of drugs but also substantiates the limitations associated with drug development by bypassing the safety, pharmacokinetics, and clinical trials of potent drug candidates (Ciliberto & Cardone, 2020). Since drug repurposing utilizing computational tools significantly reduces the drug development cost, it gained considerable attention from the scientific community for the effective treatment of several diseases particularly during epidemics and pandemics. Since the inception of first drug repurposing, several successful drug repurposing incidences were reported. For instance, the clinically approved drugs such as Favipiravir (originally approved for the treatment of the influenza virus) and sofosbuvir (originally approved for the treatment of hepatitis C) were successfully repurposed for efficient management of epidemics caused by Ebola and Zika viruses. Apart from these instances, other clinically approved drugs (nelfinavir, lopinavir, oseltamivir, atazanavir, and ritonavir) successfully repurposed for the treatment of Middle East respiratory syndrome and SARS (Dobson et al., 2015; Lv et al., 2015; Mercorelli et al., 2018; Muralidharan et al., 2021).

11.4.2 Drug repurposing and computational tools: a paradigm combination

From a historical perspective, drug repurposing utilizing the existing drugs toward other pharmacological and molecular targets received several transformations from time to time. The advent of high throughput OMICS-based approaches has provided a new dimension to the efficient use of genetic and molecular data from open sources and thus could be instrumental in the drug repurposing approach. Like that of OMICS-based approaches, the revolutionary computational tools with widespread mathematical algorithms also consider the available pharmacological and clinical evidence for drug repurposing. The combinatorial approaches of computational tools in combination with drug repurposing characteristically improve the use of existing drugs with increased efficiency. The computational tools assisted drug repurposing forms a lethal arsenal for drug discovery and development pipelines. Target-based, knowledge-based, signature-based, pathway- or network-based, and targeted-mechanism-based approaches are the different categories of drug repurposing. These differential approaches have given multifaceted platforms to screen out chemically diverse drug candidates to target many molecular targets of interest and thus significantly reduce the timeline for the design and development of repositioned drugs (Dotolo et al., 2021).

11.5 Molecular docking and molecular dynamics simulation tools for drug development against severe acute respiratory syndrome-Coronavirus-2 infections

11.5.1 Potential therapeutic drug targets in severe acute respiratory syndrome-Coronavirus-2

The OMICS-based mining of the SARS-CoV-2 genome, reveals the presence of six open reading frames (ORFs) in the conventional single-stranded (+) RNA. The ORFs code for different structural and nonstructural proteins (Nsps). The structural proteins are namely spike proteins (S), membrane proteins (M), an envelope protein (E), and nucleocapsid

proteins (N), all are being located toward the 3′end of the viral genome (Somboon et al., 2021). These structural proteins are responsible for the assemblage of virions and subsequent infections. Among the six identified ORFs, ORF 1a/b is considered to be influential in translating large Nsp which undergoes proteolysis to form the replicase complex, which plays a pivotal role in viral transcription and replication. Main protease (Mpro) or 3Chymotrypsin-like protease (3CLpro), RNA dependent RNA polymerase (designated as Nsp12), and Nsp13 helicase are the important and highly conserved nonstructural proteases responsible for the proteolytic processing and hence considered to be the potential therapeutic targets in the development of potential drug candidates (Zhu et al., 2021). Among the structural protein, the RNA dependent RNA polymerase (RdRp) is the most conserved enzyme across the different RNA viral species including coronavirus (CoV/SARS-CoV-2), Hepatitis C virus, and ZKV. Since RdRp is highly conserved and also plays a pivotal role in the viral replication cycle, the design and development of potential inhibitors specifically targeting RdRp could be instrumental in controlling viral infections (Mishra & Rathore, 2021; Wang et al., 2020) (Fig. 11.5).

The spike proteins of SARS-CoV-2 are a clove-shaped type I Transmembrane protein and have a significant role to play during the entry of the virus into the host cells. The association of these spike proteins provides a trimeric form to the virion particles and thus gives it a crown-like structure. The presence of receptor binding domain, S1 has the affinity to interact with angiotensin-converting enzyme 2 (ACE2) receptors on lung epithelial cells of the host organism. Once the SARS Spike glycoprotein forms complex with ACE2, the subunit S2 facilitates the release of genetic content (+ssRNA) into the host cell. Since the spike proteins are responsible for viral entry into the cell, these proteins are considered to be an efficient therapeutic target. As mentioned earlier, ACE2 proteins in the host are the receptor proteins where the spike proteins are assigned to bind. Hence, targeting these proteins could be an alternative mechanism (Narkhede et al., 2020; Tariq et al., 2020;

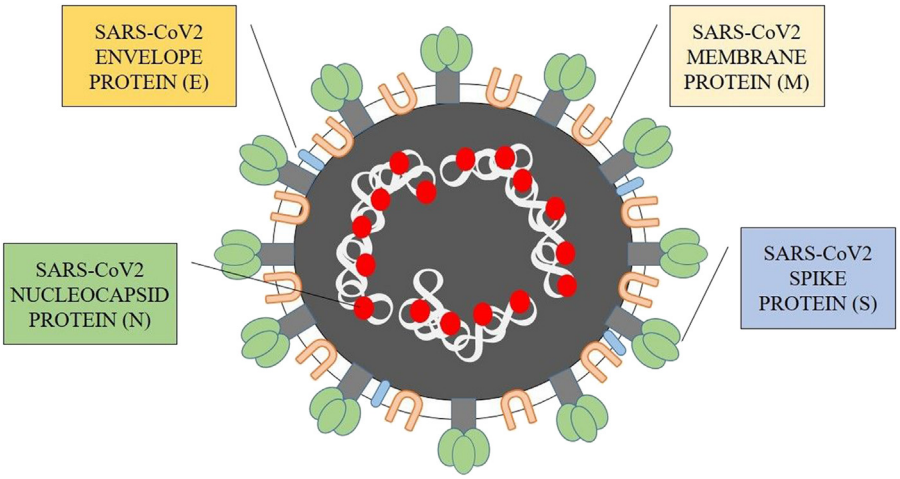

FIGURE 11.5 Schematic representation of potential therapeutic targets in severe acute respiratory syndrome-Coronavirus-2.

Walls et al., 2020). The envelope protein (E) of SARS-CoV-2 is a short, integral membrane protein and is highly conserved in terms of amino acid composition. The envelope protein is considered to be an integral part of viral assembly, viral morphological features, and pathogenesis. The envelope protein also significantly contributes during host association and thus could be considered as a potential therapeutic target (Das et al., 2021).

Among the Nsps, Nsp14 refers to the viral ribonuclease (RNase) which represents the most prominent arsenal of SARS-CoV-2 as an antagonist to interferons. The Nsp14 (RNase) is observed to be multifunctional as its N-terminal possesses the 3′-5′ exoribonuclease (exoNmm) activity whereas the C-terminal possesses N7-methyltransferase activity, and both these activities essentially control the viral replication cycle. Hence, Nsp14 emerges as a potential therapeutic target for the development of antiviral drugs (Narayanan & Nair, 2021; Ogando et al., 2020; Saramago et al., 2021).

Apart from these non-Nsps, papain-like protease (PLpro) is considered to be influential in the replication mechanism of SARS-CoV-2 and hence could be treated as a potential therapeutic target. The PLpro is one of the essential proteases of SARS-CoV-2 and was found to be essential in hydrolysis and maturation of viral polyproteins (e.g., ubiquitin, polyubiquitin) in order to generate functional replicase complex, which is essential for viral spread. In addition to deubiquitination, PLpro also exhibits DeISGylation activity which critically facilitates the viral invasion into the host cell. Hence, PLpro is considered to be a potential therapeutic target, and the inhibitors to PLpro could be instrumental in the fight against SARS-CoV-2 infections (Mirza et al., 2020; Osipiuk et al., 2021; Shin et al., 2020). Since the ligand-bound SARS-CoV-2 PLpro crystal structure is not available unlike that of Mpro; the development of potential inhibitors against PLpro remains limited. However, the advancement in the computational tools using the mathematical modeling workflow provided an alternative approach for identifying SARS-CoV-2 PLpro inhibitors (Amin et al., 2020).

11.5.2 *In silico* tools for identification of putative drug candidates targeting severe acute respiratory syndrome-Coronavirus-2

As discussed earlier, CADD-based rational drug design studies have provided novel avenues to decipher the therapeutic ability of thousands of lead molecules (natural and/or synthetic origin) against specific molecular targets. As we are witnessing the SARS-CoV-2 infections worldwide with a high rate of mortality and morbidity and thus provide ample opportunities to research scientists to decipher potential therapeutic targets in order to design and develop potential drug molecules. The advent of OMICS-based approaches has simplified in determining the sequence and structure of potential drug targets such as spike proteins, membrane protein, nucleocapsid proteins, helicase, etc. As the structural information is available for the target proteins, it is easier for the research groups to screen thousands of drug-like candidates for their affinity in binding to these proteins through computational approaches. In this context, recently marine-derived natural products were virtually screened using computational tools to identify their specificity to bind to the target protein, main protease (Mpro). Among the screened products, five products namely notoamide I, emindole SB β-mannoside, benzo[f]pyrano[4,3-b]chromene, and two

bromoindole derivatives exhibited promising aspects as potential SARS-CoV-2 Mpro inhibitors and could be considered for further studies in the management of viral infection (Gaudêncio & Pereira, 2020).

Plant-derived natural compounds are considered to be the most explored drug candidates for the management of several diseases and disorders from several decades. As per the estimates from WHO, approximately 80% of the world population still consider plant's based natural products and other plant-derived products for different health ailments. Plant-derived metabolites are considered to be instrumental in exhibiting widespread antimicrobial properties, particularly antibacterial and antiviral properties against an array of microbial pathogens. Considering the antiviral properties of plant-based metabolites could be evaluated for their role in the management of SARS-CoV-2 infections (Bhuiyan et al., 2020; Kumar Verma et al., 2021). In this context, it is imperative to the quest for plant-derived phytochemicals for their inhibitory effect on the SARS-CoV-2 infections by implementing the computational tools. In this regard, plant-derived Narcissoside (Isorhamnetin-3-O-rutinoside flavonoid) was identified from different medicinal plants subjected to SBDD tools using molecular docking analysis. Narcissoside exhibited promising affinity toward 3CLpro of SARS-CoV-2 and thus could be considered as a potential inhibitor against the Nsp, which is responsible for viral infections (Dubey & Dubey, 2020).

As discussed earlier, the structural Spike proteins of SARS-CoV-2 are found to be influential in the process of attachment to the host cells and subsequent pathogenesis. Hence, targeting these proteins could be instrumental in rational drug design utilizing computational tools. As evident from the exploration of plant-derived phytochemicals particularly epigallocatechin gallate, curcumin, apigenin, and Chrysophanol formed the basis of herbal medicines. When these phytochemicals were docked with viral spike proteins, they exhibited promising binding affinity with epigallocatechin gallate showing the highest affinity. Based upon the docking score obtained, it could be suggested that these phytochemicals could be considered for the efficient management of SARS-CoV-2 infections by specifically targeting the Spike proteins (Subbaiyan et al., 2020). Rutin, a highly decorated flavonoid reported from several medicinal plants is associated with antiviral, antibacterial, antitumor, antihypertensive, and antiinflammatory activities. Recently, the antiviral properties of rutin were repositioned to evaluate its effect on different therapeutic targets of SARS-CoV-2 using computational tools. As per the results, rutin exhibited a strong binding affinity toward the target proteins namely Chymotrypsin-like protease (3CLpro/Mpro), RNA-dependent RNA polymerase (RdRp), PLpro, and spike proteins of SARS-CoV-2. Thus the promising results obtained from computational approaches could be instrumental in developing rutin as a potential antiviral agent against the COVID-19 virus, provided that the computational results should be validated through experimental studies, both *in vitro* and *in vivo* (Rahman et al., 2021). More recently, cichoriin (coumarin glycosides), from Taraxacum officinale was also reported for its promising binding affinity toward several important targets of SARS-CoV-2. In particular, cichoriin exhibited the strongest affinity toward viral main protease, replication machinery (RdRp), Helicase, PLpro and also hampers the exonuclease activity by inhibiting Nsp14. As cichoriin is found to be safe for human consumption, it could be developed as a potent antiviral agent against SARS-CoV-2 infections (Rivero-Segura & Gomez-Verjan, 2021). In another study,

the broad-spectrum pharmacological properties of plant-derived phytochemical, curcumin (from *Curcuma longa*) and its derivatives are considered for their efficacy in binding to viral molecular targets and modulating viral infections. Bis-demethoxycurcumin, a derivative of curcumin exhibited the highest binding affinity toward both the full-length Spike protein and receptor binding domain of spike protein. Thus these bioactive secondary metabolites could be further developed as potential inhibitors of inhibition of viral entry through the involvement of spike protein (Patel et al., 2020). Lapachol (1,4-naphthoquinone) and its derivatives when evaluated computationally and observed that lapachol derivatives exhibited promising affinity toward Nsp9. Since, Nsp9 in SARS-CoV-2 plays a pivotal role in the transcription of the viral genome, modulating the Nsp9 protein response could block the viral transcription and thus could prevent the severity and progress of viral infection (Junior et al., 2021). The recent advancement in utilizing computational approaches for repurposing the existing drug molecules, secondary metabolites of plants have provided an atmosphere to consider them for widespread biomedical applications for repurposing toward the treatment of COVID-19 infection. The list of notable plant-derived secondary metabolites repurposed for efficient control of SARS-CoV-2 infection through computational approaches was listed in Table 11.1.

The recent trend in the pharmaceutical sector is the use of metal-based drugs for various biological activities. Vanadium complexes gained recent recognition owing to their low toxicity profiles as compared to other transition metal-based complexes. The interesting aspect of using Vanadium-based complexes is their widespread biomedical applications in the form of antidiabetic and antitumor activities. Hence, in the period SARS-CoV-2 pandemics, these complexes could also be considered for their probable therapeutic effect. In this regard, three vanadium complexes, that is, β-tocopherol and aliphatic lipid vanadium (IV) and (V) complexes along with xanthohumol vanadium (V) complex were evaluated for their affinity toward SARS-CoV-2 target proteins, that is, N-terminal domain of Nucleocapsid phosphoprotein, RNA dependent RNA polymerase, and main protease. The designed vanadium complexes exhibited promising affinity toward various targets and could be instrumental in developing novel antiviral agents (Vlasiou & Pafti, 2021).

Recently, chalcones (α,β-unsaturated ketones (1,3-diaryl-2-propene-1-one) were considered for their role in binding to potential therapeutic targets of SARS-CoV-2 through a computational approach. Basically, chalcones are naturally occurring flavonoids obtained from a wide range of fruits, vegetables, and tea. The chemical backbone of chalcones is responsible for their widespread biological activities. As per the literature available, antibacterial, antiinflammatory, antiparasitic, and antioxidant activities of chalcones were reported. In addition, the chalcones are found to exhibit promising antiviral properties against both plant and human viruses. In this context, acetamide chalcones were considered for their affinity to bind to the molecular targets, that is, main protease and spike protein of SARS-CoV-2 and ACE2 receptor protein associated with host cells. Molecular docking results conveyed the efficacy of 4′-acetamide chalcones toward ACE2 receptors of host cells and the Spike protein of the virus thereby altering the interactions between the virus and the host cells. The promising computational results could be translated into experimental studies to validate the pharmacological potential of acetamide chalcones in controlling the SARS-CoV-2 infections (Francisco et al., 2021).

TABLE 11.1 List of naturally derived plant-based phytochemicals screened for their affinity toward potential therapeutic drug targets of severe acute respiratory syndrome-Coronavirus-2.

Sl. no.	List of plant-derived phytochemicals	Chemical type	Biological activity	Computational tools used	Therapeutic target/ targets	Remarks	Reference
1.	Theaflavin digallate	Theaflavin Phenol derivative	Antioxidant	Molecular docking and Molecular dynamics Simulation (MDS)	SARS-CoV-2 Main Protease (M^{pro})	Activity: Theaflavin digallate > Biorobin > Hesperidin	Peele et al. (2020)
2.	Biorobin (Kaemferol 3-robinobioside)	Flavonoid-3-O-glycosides	Antimicrobial	Molecular docking and	SARS-CoV-2 Main Protease (Mpro)	Activity: Theaflavin digallate > Biorobin > Hesperidin	Peele et al. (2020); Surya and Praveen (2021)
3.	Hesperidin	Flavanone glycoside	Cardiovascular functions particularly hemorrhoids	Molecular docking and Molecular dynamics Simulation (MDS)	SARS-CoV-2 Main Protease (Mpro)	Activity: Theaflavin digallate > Biorobin > Hesperidin	Peele et al. (2020)
4.	Chlorogenic acid	Polyphenolic compound	Antioxidant, Antiinflammatory, Antimicrobial	Molecular docking	Angiotensin-converting enzyme 2 (ACE2) receptor protein	Blocks the binding of Spike protein and ACE2	Yu et al. (2020)
5.	Rutin	Flavonol	Antioxidant	molecular docking	SARS-CoV-2 Main Protease (M^{pro})	High binding affinity	Das et al. (2020)
6.	Andrographolide	Labdane ahlianoid from Andrographis paniculata	Antiviral, antiinflammatory, anticancer, antidiabetic	Molecular docking	SARS-CoV-2 Main Protease (M^{pro})	Docked efficiently in the binding site	Enmozhi et al. (2020)

(*Continued*)

TABLE 11.1 (Continued)

Sl. no.	List of plant-derived phytochemicals	Chemical type	Biological activity	Computational tools used	Therapeutic target/ targets	Remarks	Reference
7.	Asiatic acid	Pentacyclic triterpenoids	Wound-healing and Neuropsychiatric disease	Molecular docking	1. Main Protease (M^{pro}) 2. Nsp9 RNA dependent RNA polymerase (RdRp) 3. Spike receptor binding domain 4. Spike ectodomain 5. HR2 domain of spike protein	Asiatic acid exhibited the highest affinity against the main protease, Nsp9 RdRp, and spike ectodomain spike protein	Azim et al. (2020)
8.	Avicularin	Flavonol	Suppressed lipid accumulation	Molecular docking	1. Main Protease (Mpro) 2. Nsp9 RNA dependent RNA polymerase (RdRp) 3. Spike receptor binding domain 4. Spike ectodomain 5. HR2 domain of spike protein	Exhibited highest affinity toward main protease-N3 inhibitor complex	Azim et al. (2020)
9.	Guaijaverin	Quercetin 3-arabinopyranoside	Antiplaque effect	Molecular docking	1. Main Protease (Mpro) 2. Nsp9 RNA dependent RNA polymerase (RdRp) 3. Spike receptor binding domain 4. Spike ectodomain 5. HR2 domain of spike protein	Guaijaverin exhibited highest affinity toward HR2 domain	Azim et al. (2020)

10.	Withaferin	Steroidal lactone	Cytotoxic effect, antineoplastic agent	Molecular docking	1. Main Protease (Mpro) 2. Nsp9 RNA dependent RNA polymerase (RdRp) 3. Spike receptor binding domain 4. Spike ectodomain 5. HR2 domain of spike protein	Strong affinity toward HR2 domain after Guaijaverin	Azim et al. (2020)
11.	Hypericin	Napthodianthrone	Antibiotic, Antiviral	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Activity: Hypericin > Chrysanthemum	Pitsillou et al. (2020); Puttaswamy et al. (2020)
12.	Cyanidin-3-O-glycosides (Chrysanthemin)	Anthocyanin	Reducing oxidative stress	Molecular docking and MDS	SARS-CoV-2 Main protease (Mpro)	Activity: Hypericin > Chrysanthemum	Pitsillou et al. (2020)
13.	5,7,3′,4′-Tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone	Hydroxyflavone	Cytotoxic activity, Antileishmanial activity	Molecular docking and MDS	SARS-CoV-2 3 Chymotrypsin like protease	Form stable conformations when bound to 3C-like protease	Qamar et al. (2020)
14.	Myricitrin	Glycosyloxyflavone	Antiallergic agent	Molecular docking and MDS	SARS-CoV-2 3 Chymotrypsin like protease	Form stable conformations when bound to 3C-like protease	Qamar et al. (2020)
15.	Methyl rosmarinate	Coumarins derivatives	Antifungal and Antioxidant activities	Molecular docking and MDS	SARS-CoV-2 3 Chymotrypsin like protease	Form stable conformations when bound to 3C-like protease	Qamar et al. (2020)
16.	Sinapic acid	Phenylpropanoids	Antibacterial, Antioxidant	Molecular docking and MDS	SARS-CoV-2 Envelope protein I	Forms a stable interaction with the binding site of envelope protein with high-affinity	Orfali et al. (2021)
17.	Bismahanine	Carbazole alkaloid	Anticancer	Molecular Docking	SARS-CoV-2 Spike protein	High binding affinity	Puttaswamy et al. (2020)

(*Continued*)

TABLE 11.1 (Continued)

Sl. no.	List of plant-derived phytochemicals	Chemical type	Biological activity	Computational tools used	Therapeutic target/ targets	Remarks	Reference
18.	Eriodictyol-7-O-rutinoside	Flavanone	Antioxidant	Molecular docking	SARS-CoV-2 RdRp	High binding affinity	Puttaswamy et al. (2020)
19.	Quercetin	Flavonol	Antioxidant, Antimicrobial	Molecular docking	SARS-CoV-2 2 2′-O-Methyltransferase (Nsp16), Main protease	Potentially inhibits the target enzymes	Omotuyi et al. (2020)
20.	Letestuianin A	Diaryheptanoids	Trypanocidal property	Molecular docking	SARS-CoV-2 2 2′-O-Methyltransferase	Inhibits the target enzyme	Omotuyi et al. (2020)
21.	Apigenin	Trihydroxyflavone	Antimicrobial, Antioxidant, Antiinflammatory activites	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Inhibits the target enzyme	Omotuyi et al. (2020)
22.	Tectochrysin	Monohydroxyflavone	Anticancer activity	Molecular Docking	SARS-CoV-2 Spike glycoprotein (RBD) and Host ACE2 interface	High-affinity binding	Omotuyi et al. (2020)
23.	Amentoflavone	Biflavonoid	Antiviral, Antiinflammatory activities	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Formation of highly stable ligand-enzyme complex	Lokhande et al. (2020)
24.	Agathisflavone	Biflavonoid	Antiviral, Antineoplastic and Hepatoprotective	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Formation of highly stable ligand-enzyme complex	Lokhande et al. (2020)
25.	Eriodictyol	Flavanone	Antiinflammatory and Antioxidant activities	Molecular docking and MDS	SARS-CoV-2 Spike glycoprotein, main protease, RdRp, Nsp10-Nsp16 complex	Highest affinity for Nsp10-Nsp16 complex and Spike glycoprotein even more than that of FDA-approved drugs (Ribavirin, Lopinavir)	Deshpande et al. (2020)

Microbial secondary metabolites also gained considerable attention since microorganisms are the reservoir of structurally diverse bioactive metabolites. The biggest drawback is that majority of microbial-derived secondary metabolites remain unexplored and data mining of such undefined secondary metabolites could revolutionize the drug discovery pipelines. Microbial-derived antibiotics for therapeutics are considered to be revolutionary discoveries in the 20th century. The microbial metabolites exhibited promising biomedical and pharmaceutical activities such as antidiabetic, antimicrobial, anticancer, antiinflammatory properties, etc. (Knight et al., 2003; Liu et al., 2010; Pham et al., 2019). Fungi tend to produce an array of chemically diverse secondary metabolites. Fungal-derived metabolites are known for their widespread applications as antibiotics, flavoring agents, and food preservatives which are necessary for essential services for mankind (Rao et al., 2020a). The secondary metabolites reported from different microbial sources were reported for their promising antiviral properties against several pathogenic plant and human viruses. Hence, these microbial metabolites could be repurposed for the treatment of SARS-CoV-2 infections. The list of microbial secondary metabolites reported for their actions through computational approaches against SARS-CoV-2 are reported in Table 11.2.

11.5.3 Drug repurposing: new paradigm in rational drug design for targeting severe acute respiratory syndrome-Coronavirus-2

Since the inception of SARS-CoV-2 pandemics across the world, several reports were surfaced depicting the structure, routes of transmission, pathophysiological symptoms, and prevention guidelines from time to time. Though few vaccines came into existence in the last few months to prevent the infections' severity, we are still devoid of an appropriate therapeutic drug targeting the infections of SARS-CoV-2. Despite continuous efforts, the efficient management of SARS-CoV-2 infections remains unanswered to date thereby creating an uphill challenge to the healthcare systems as well as the economy as mentioned earlier. Considering the COVID-19 situation worldwide, the need of the hour is to develop potential drug candidates. In this tough time, drug repurposing could be instrumental in identifying the putative drug candidates. The drug repurposing considers the screening of clinically passed and FDA-approved drugs using computational tools which not only minimizes the drug development timeline and cost but also strongly reduces the risks of toxicity and further adverse effects. Hence, drug repurposing proved to be influential in developing the reuse of existing drugs for the efficient management of SARS-CoV-2 infections (Mohamed et al., 2021; Serafin et al., 2020). As mentioned earlier, SARS-CoV-2 infections in the host cells comprise several sequential pathophysiological events regulated by a number of enzyme complexes and thus considered to be potential therapeutic targets. In the fight against SARS-CoV-2 infections, the advent of repurposing of existing drug molecules targeting several targets could be instrumental in controlling the infections. The advanced molecular OMICS approaches and computational tools have provided the efficacy of several existing drugs in targeting multifaceted molecular targets and controlling the infection cycle. For example, the existing drug candidates exhibiting rational target-oriented approaches for affecting sequential infection steps through several mechanisms of action are as follows; (1) effect on viral entry through membrane fusion endocytosis

TABLE 11.2 List of naturally derived microbial secondary metabolites screened for their affinity toward potential therapeutic drug targets of severe acute respiratory syndrome-Coronavirus-2 using computational tools, molecular docking, and molecular dynamics simulation.

Sl. no.	List of microbial secondary metabolites	Chemical type	Source microorganism	Computational tools used	Therapeutic target/targets	Remarks	Reference
1.	Phillyrin	Natural Lignan	*Forsythia suspensa*	Molecular docking	Angiotensin-converting enzyme 2 (ACE2) receptor protein	Blocks the binding of Spike protein and ACE2	Yu et al. (2020)
2.	Citriquinochroman	Polyketide	*Penicillium citrinum*	molecular docking and molecular dynamics simulation (mds)	SARS-CoV-2 main protease	Strong binding affinity toward target protein	Sayed et al. (2020)
3.	Holyrine B	Indolocarbazole alkaloid	*Streptomyces actuosus*	Molecular docking and MDS	SARS-CoV-2 Main protease	Strong binding affinity toward target protein	Sayed et al. (2020)
4.	Proximicin C	Aminofuran antibiotic	*Verrucosispora* MG-37	Molecular docking and MDS	SARS-CoV-2 Main protease	Activity Proximicin C > Pityriacitrin B > (+) Anthrabenzoxocinone > Penimethavone A	Sayed et al. (2020)
5.	Pityriacitrin B	Indole alkaloid	*Malassezia furfur*	Molecular docking and MDS	SARS-CoV-2 Main protease	Activity Proximicin C > Pityriacitrin B > (+) Anthrabenzoxocinone > Penimethavone A	Sayed et al. (2020)
6.	(+) Anthrabenzoxocinone	Aromatic ketones	*Streptomyces* sp.	Molecular docking and MDS	SARS-CoV-2 Main protease	Activity Proximicin C > Pityriacitrin B > (+) Anthrabenzoxocinone > Penimethavone A	Sayed et al. (2020)
7.	Penimethavone A	Flavone	*Penicillium chrysogenum*	Molecular docking and MDS	SARS-CoV-2 Main protease	Activity Proximicin C > Pityriacitrin B > (+) Anthrabenzoxocinone > Penimethavone A	Sayed et al. (2020)

8.	Callophysin A	Indole carboxylic acid	*Callophycus oppositifolius*	Molecular docking and MDS	SARS-CoV-2 Main protease	High binding affinity with H-bonds and hydrophobic residues, Stable interactions	Muteeb et al. (2020)
9.	Flaviolin	Hydroxy-1,4-naphthoquinone	*Verticilliahliaiae*	Molecular docking and MDS	SARS-CoV-2 Main protease	Potentially inhibits 3C-like protease	Rao et al. (2020b)
10.	Jasmonic acid	Organic compound	*Lasiodiplodia mediterranea*	Molecular docking	SARS-CoV-2 Main protease	Exhibited greater affinity toward target protein, Mpro	Padhi et al. (2021)
11.	Putaminoxin B	Macrolide	*Phoma putaminum*	Molecular docking	SARS-CoV-2 Main protease	Exhibited greater affinity toward target protein, Mpro	Padhi et al. (2021)
12.	Putaminoxin D	Macrolide	*Phoma putaminum*	Molecular Docking	SARS-CoV-2 Main protease	Exhibited greater affinity toward target protein, Mpro	Padhi et al. (2021)
13.	Plantaricin W	Bacteriocin	*Lactobacillus plantarum*	Molecular docking and MDS	SARS-CoV-2 RNA dependent RNA polymerase (RdRp), Spike glycoprotein (RBD), and host ACE2 receptor	Activity: Plantaricin W > Plantaricin JLA-9 > Plantaricin D > Plantaricin BN	Anwar et al. (2020)
14.	Plantaricin JLA-9	Bacteriocin	*Lactobacillus plantarum*	Molecular docking and MDS	SARS-CoV-2 RNA dependent RNA polymerase (RdRp), Spike glycoprotein (RBD), and host ACE2 receptor	Activity: Plantaricin W > Plantaricin JLA-9 > Plantaricin D > Plantaricin BN	Anwar et al. (2020)
15.	Plantaricin D	Bacteriocin	*Lactobacillus plantarum*	Molecular docking and MDS	SARS-CoV-2 RNA dependent RNA polymerase (RdRp), Spike glycoprotein (RBD), and host ACE2 receptor	Activity: Plantaricin W > Plantaricin JLA-9 > Plantaricin D > Plantaricin BN	Anwar et al. (2020)

(*Continued*)

TABLE 11.2 (Continued)

Sl. no.	List of microbial secondary metabolites	Chemical type	Source microorganism	Computational tools used	Therapeutic target/targets	Remarks	Reference
16.	Plantaricin BN	Bacteriocin	*Lactobacillus plantarum*	Molecular docking and MDS	SARS-CoV-2 RNA dependent RNA polymerase (RdRp), Spike glycoprotein (RBD), and host ACE2 receptor	Activity: Plantaricin W > Plantaricin JLA-9 > Plantaricin D > Plantaricin BN	Anwar et al. (2020)
17.	Pyranonigrin A	Pyranopyrroles	*Penicillium thymicola*	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Possesses potential inhibitory effect on the main protease with stable interaction	Rao et al. (2020a)
18.	Colossolactone VIII	Tetracyclic triterpenoid	*Ganoderma colosum*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Colossolactone VIII exhibited the highest affinity	Rangsinth et al. (2021)
19.	Colossolactone E	Tetracyclic triterpenoid	*Ganoderma colosum*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Colossolactone VIII exhibited the highest affinity	Rangsinth et al. (2021)
20.	Colossolactone G	Tetracyclic triterpenoid	*Ganoderma colosum*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Showed potent interactions but less than that of Colossolactone VIII	Rangsinth et al. (2021)
21.	Ergosterol	Sterol	*Lentinula edodes*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Activity: Ergosterol > Heliantriol F > Velutin	Rangsinth et al. (2021)
22.	Heliantriol F	Triterpenoids	*Lignosus rhinocerus*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Activity: Ergosterol > Heliantriol F > Velutin	Rangsinth et al. (2021)
23.	Velutin	Flavone	*Flammulina velutipes*	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Activity: Ergosterol > Heliantriol F > Velutin	Rangsinth et al. (2021)

24.	Kanamycin	Aminoglycoside antibiotic	*Streptomyces kanamyceticus*	Molecular docking	SARS-CoV-2 3 CL-protease	Activity: Kanamycin > Oxytetracycline > Doxorubicin	Meyer-Almes (2020)
25.	Oxytetracycline	Aromatic polyketide	*Streptomyces rimosus*	Molecular docking	SARS-CoV-2 3 CL-protease	Activity: Kanamycin > Oxytetracycline > Doxorubicin	Meyer-Almes (2020)
26.	Doxorubicin	Anthracycline	*Streptomyces peucetius var. caesius*	Molecular docking	SARS-CoV-2 3 CL-protease	Activity: Kanamycin > Oxytetracycline > Doxorubicin	Meyer-Almes (2020)

(e.g., Aloxistatin), (2) effect on viral entry through membrane fusion (e.g., Nelfinavir), (3) modulation of viral replication and translation (e.g., Remdesivir, Emetine, Ribavarin), (4) modulation of only viral translation (e.g., Valrubicin, Perphenazine), (5) modulation of associated inflammatory responses (e.g., Fingolimod, Sarilumab, Tocilizumab, Colchicine), and (6) effect on the release of virions (e.g., Oseltamivir) (Yousefi et al., 2021).

Considering the current pandemic situation, the most regularly used term is the use of Remdesivir as a supplement to minimize the severity of SARS-CoV-2 infections. Remdesivir, originally approved for the treatment of Hepatitis C, is currently repurposed for emergency use in the treatment of SARS-CoV-2 infections and particularly to the hospitalized patients with evidence of lower respiratory tract infections (Beigel et al., 2020; Wang, Cao, et al., 2020). Similarly, an antimalarial drug, Chloroquine is also considered for drug repurposing against the management of SARS-CoV-2 infections. As per the results obtained from preliminary trials, chloroquine exhibited a promising antagonistic effect against the COVID-19 virus (Devaux et al., 2020; Wang, Anirudhan, et al., 2020). Similar to chloroquine, another antimalarial drug, hydroxychloroquine was also observed to characteristically reduce the viral load in the COVID-19 patients. The efficacy of hydroxychloroquine in minimizing viral load was significantly improved when used in combination with an antibiotic, azithromycin (Gautret et al., 2020; More et al., 2021). The list of FDA-approved drugs considered and evaluated as repurposed drugs against various molecular targets of SARS-CoV-2 through computational tools is mentioned in Table 11.3.

11.6 Current trends and future perspectives

In the last few decades, especially since the beginning of the 21st century, we have witnessed revolutionary advancement in both the biomedical and pharmaceutical sectors. The advancement in these sectors is amply complemented through the evolvement of high throughput knowledge in mathematical modeling, computational algorithms, quantum mechanics, combinatorial chemistry, structural biology, molecular dynamics, and machine learning approaches. The combinatorial approach of the experimental data with the advanced knowledge of computational tools has transformed our knowledge in the widespread use of CADD approaches for drug discovery and development pipelines (Hung & Chen, 2014). The rational exploration of the computational tools, quantum mechanics, mathematical modeling in understanding the molecular interactions and assumptions of stereotypical parameters (i.e., pharmacokinetic and pharmacodynamics properties) provides a new dimension to the drug discovery programs in the 21st century (Thomford et al., 2018).

Since the inception of the first anti-HIV drug way back in 1987 developed through the drug repurposing approach, the efficient reuse of existing drugs through computational tools gained considerable attention. The most important points to remember for a successful drug repurposing approach are finding the scientific and academic researchers with innovative ideas to answer unanswered pathophysiological conditions, providing incentives in the form of funding sources to establish scientific resources to avail benchmark experimental data, and involving enthusiastic collaborative stakeholders to translate the laboratory setup to market values. For an effective collaborative environment, it is highly important to work in coordination with all the stakeholders such as academic researchers,

TABLE 11.3 List of FDA-approved drugs repositioned as potential drug candidates using computational tools toward potential therapeutic drug targets of severe acute respiratory syndrome-Coronavirus-2.

Sl. no.	List of FDA-approved drugs	Intended original use	Computational tools for drug repositioning	Potential drug target/targets	Remarks	References
1.	Cangrelor	Antiplatelet drug	Molecular docking	Both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	High binding affinity toward both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	Ugurel et al. (2020)
2.	Fludarabine	Chronic lymphocytic leukemia	Molecular docking	Both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	High binding affinity toward both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	Ugurel et al. (2020)
3.	Folic acid	Nutritional supplement	Molecular docking	Both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	High binding affinity toward both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	Ugurel et al. (2020)
4.	Polydatin	Antitumor, Antioxidant, Antiinflammatory	Molecular docking	Both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	High binding affinity toward both wild type and mutant SARS-CoV-2 Helicase (Nsp13)	Ugurel et al. (2020)
5.	Doxycycline	Antibiotics with broad-spectrum antiviral properties	Molecular docking and Molecular dynamics simulation (MDS)	SARS-CoV-2 Main Protease (M^{pro})	Activity: Doxycycline > Minocycline> Demeclocycline > Tetracycline	Bharadwaj et al. (2020)
6.	Tetracycline	Antibiotics with broad-spectrum antiviral properties	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Doxycycline > Minocycline> Demeclocycline > Tetracycline	Bharadwaj et al. (2020)
7.	Demeclocycline	Antibiotics with broad-spectrum antiviral properties	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Doxycycline > Minocycline> Demeclocycline > Tetracycline	Bharadwaj et al. (2020)
8.	Minocyclin	Antibiotics with broad-spectrum antiviral properties	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Doxycycline > Minocycline> Demeclocycline > Tetracycline	Bharadwaj et al. (2020)

(*Continued*)

TABLE 11.3 (Continued)

Sl. no.	List of FDA-approved drugs	Intended original use	Computational tools for drug repositioning	Potential drug target/targets	Remarks	References
9.	Isavuconazonium	Antifungal	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Isavuconazonium > α-Ketoamide > Pentagastrin	Achilonu et al. (2020)
10.	Pentagastrin	Acidity	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Isavuconazonium > α-Ketoamide > Pentagastrin	Achilonu et al. (2020)
11.	α-Ketoamide	Peptidomimetic	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Isavuconazonium > α-Ketoamide > Pentagastrin	Achilonu et al. (2020)
12.	Carfilzomib	Anticancer drug with proteasome inhibitory potential	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Carfilzomib > Eravacycline	Wang (2020)
13.	Eravacycline	Antibiotic for complicated intra-abdominal infections	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Carfilzomib > Eravacycline	Wang (2020)
14.	Lopinavir	Antiviral	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Lopinavir > Camoquin	Peele et al. (2020)
15.	Amodiaquine (Camoquin)	Antimalarial	Molecular docking and MDS	SARS-CoV-2 Main Protease (Mpro)	Activity: Lopinavir > Camoquin	Peele et al. (2020)
16.	Paromomycin	Aminoglycoside antibiotic	Molecular docking and MDS	SARS-CoV-2 Main Protease (PDB ID: 6y84) and Spike protein (PDB ID: 6vw1)	High binding affinity toward both protease and Spike domain of SARS-CoV-2	Tariq et al. (2020)
17.	Indinavir	Antiviral drug	Molecular docking	SARS-CoV-2 Main Protease (PDB ID: 6y84)	High binding affinity with a more free energy score	Das et al. (2020)

18.	Casopitant	Neurokinin- 1 receptor antagonist	Molecular docking	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	Bind to the catalytic domain of RdRp and stabilized by the formation of H-bonds	Iftikhar et al. (2020)
19.	Meclonazepam	Antiparasitic	Molecular docking	SARS-CoV-2 Helicase (Nsp13)	Stabilized interactions with the formation of H-bonds and hydrophobic interactions	Iftikhar et al. (2020)
20.	Oxiphenisatin	Topical laxative	Molecular docking	SARS-CoV-2 Helicase (Nsp13)	Stabilized interactions with the formation of H-bonds and hydrophobic interactions	Iftikhar et al. (2020)
21.	Rimantadine	Antiflu drug against Influenza-A virus	Molecular docking	SARS-CoV-2 3C-like protease	Bound to substrate-binding site of the 3C-like protease	Iftikhar et al. (2020)
22.	Grazoprevir	Hepatitis C protease inhibitor	Molecular docking	SARS-CoV-2 3C-like protease	Bound to the allosteric site of the 3C-like protease	Iftikhar et al. (2020)
23.	Bagrosin	Antiepileptic drug	Molecular docking and MDS	SARS-CoV-2 3C-like protease, SARS-CoV-2 Spike protein	Bound to the allosteric site of 3C-like protease and C-terminal domain of S1 subunit of Spike protein	Iftikhar et al. (2020); Awad et al. (2020)
24.	Silodosin	For treatment of Benign Prostatic Hyperplasi (BPH)	Molecular docking and MDS	SARS-CoV-2 Spike protein	Preferentially binds to the S1 subunit of Spike protein and also interferes between the interaction between viral Spike protein and host ACE2 receptors	Awad et al. (2020)
25.	Ritonavir	Antiretroviral drug	Molecular docking and MDS	SARS-CoV-2 Nsp14 Viral ribonuclease (RNase)	Inhibit Nsp14 protein, thereby reducing the effect of Nsp14 in attenuating the drugs that function through premature termination of viral genome replication. Hence, Ritonavir could substantiate the therapeutic effect of Remdesivir, Favipiravir	Narayanan and Nair (2021)

(*Continued*)

TABLE 11.3 (Continued)

Sl. no.	List of FDA-approved drugs	Intended original use	Computational tools for drug repositioning	Potential drug target/targets	Remarks	References
26.	Aprepitant	Prevention of postoperative nausea and vomiting	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Exhibited strong and stable binding	Baby et al. (2021)
27.	Barnidipine	For hypertension	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Exhibited strong and stable binding	Baby et al. (2021)
28.	Tipiracil	For treatment of metastatic colorectal cancer	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Tipiracil > Terbutaline > Arbutin	Baby et al. (2021)
29.	Arbutin	Skin-lightening agent	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Tipiracil > Terbutaline > Arbutin	Baby et al. (2021)
30.	Terbutaline	Treatment of bronchospasm	Molecular docking and MDS	SARS-CoV-2 Main Protease (M^{pro})	Activity: Tipiracil > Terbutaline > Arbutin	Baby et al. (2021)
31.	Tigecycline	Antibacterial	Molecular docking	SARS-CoV-2 Papain-like protease (PLpro)	Potential inhibitors of PLpro	Wu et al. (2020)
32.	Valganciclovir	Antiviral	Molecular docking	SARS-CoV-2 Papain-like protease (PLpro)	Potential inhibitors of PLpro	Wu et al. (2020)
33.	Dexamethasone	Antiinflammatory drug	Molecular docking, MDS, Pharmacokinetic profiling	SARS-CoV-2 Main protease (M^{pro}), Host-secreted glucocorticoid receptor and interleukin-6 (IL-6)	Highest affinity toward glucocorticoid receptor also exhibited affinity toward Main protease (M^{pro})	Fadaka et al. (2020)
34.	Nafcillin	Antibacterial drug	Molecular docking	SARS-CoV-2 Envelope protein	Exhibited promising affinity in binding to the transmembrane domain of envelope protein	Das et al. (2021)

35.	Ribavirin	Antiviral drug for Hepatitis C	Molecular docking and MDS	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	Forms energetically stable interaction with RdRp	Singh et al. (2021)
36.	Saquinavir	Treatment of HIV/AIDS	Molecular docking	SARS-CoV-2 3C-like protease	Strongly interact with the active site of the 3C-like protease	Alexpandi et al. (2020)
37.	Elvitegravir	For HIV infections	Molecular docking	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	Interact with the NTP-entry channel and block RdRp activity	Alexpandi et al. (2020)
38.	Oxolinic acid	Antibiotic	Molecular docking	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	Interact with the NTP-entry channel and block RdRp activity	Alexpandi et al. (2020)
39.	Rilapladib	For Alzheimer's disease	Molecular docking	SARS-CoV-2 Spike glycoprotein (RBD) and Host ACE2 interface	Interferes strongly with the interface formed between viral spike protein and host ACE2	Alexpandi et al. (2020)
40.	Paritaprevir	Antiviral drug against Hepatitis C	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Formation of stable interactions	Indu et al. (2020); Khan et al. (2021)
41.	Raltegravir	Antiviral drug against HIV/AIDS	Molecular Docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Formation of stable interactions	Indu et al. (2020); Khan et al. (2021)
42.	Raltegravir	Antiviral drug against HIV/AIDS	Molecular docking and MDS	SARS-CoV-2 2 2′-O-Methyltransferase	Strong binding interactions with extended stability	Khan et al. (2021)
43.	Bictegravir	Antiviral drug against HIV/AIDS	Molecular docking and MDS	SARS-CoV-2 2 2′-O-Methyltransferase	Strong binding interactions with extended stability	Khan et al. (2021)
44.	Indinavir	Antiviral drug	Molecular docking	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	High binding affinity with H-bonding and interactions of hydrophobic residues	Indu et al. (2020)

(*Continued*)

TABLE 11.3 (Continued)

Sl. no.	List of FDA-approved drugs	Intended original use	Computational tools for drug repositioning	Potential drug target/targets	Remarks	References
45.	Paritaprevir	Antiviral drug	Molecular docking	SARS-CoV-2 RNA dependent RNA polymerase (RdRp)	High binding affinity with H-bonding and interactions of hydrophobic residues	Indu et al. (2020)
46.	Pibrentasvir	Antiviral drug	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Exhibited strong interactions with the main protease	Indu et al. (2020)
47.	Ergotamine	Used as vasoconstrictor	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Activity: Dihydrergotamine > Ergotamine	Gurung et al. (2020)
48.	Dihydrergotamine	Used as vasoconstrictor	Molecular docking	SARS-CoV-2 Main protease (M^{pro})	Activity: Dihydrergotamine > Ergotamine	Gurung et al.(2020)
49.	Tipranavir	Antiretroviral protease inhibitor	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro})	Exhibited promising binding affinity and forms stable interaction	Kumar et al. (2020)
50.	Lurasidone and derivatives	For treatment of Schizophrenia and bipolar disorder	Molecular docking and MDS	SARS-CoV-2 Main protease (M^{pro}), Papain-like protease (PLpro), Spike protein, RNA dependent RNA polymerase (RdRp), Helicase	Exhibited promising binding affinity and forms stable interaction, even better than the reference molecule	Thurakkal et al. (2021)

pharmaceutical companies, funding agencies, venture capitalists, etc. The co-ordinated collaborative work will provide an impetus to the existing gaps between the academic researchers and pharmaceutical sectors by sharing the scientific knowledge and thus could be instrumental in the fast-track development of drugs for efficient management of different pathophysiological conditions (Pushpakom et al., 2018). No doubt, drug repurposing has given a new ray of hope as an important arsenal against SARS-CoV-2 infections with advantageous characteristics such as fast-track drug development, economic, safety parameters; translating the drug repurposing information from laboratory setup to open market remains an uphill challenge. Particularly, the difference in scientific and regulatory parameters across the globe are observed to be the biggest challenge for successful implications of drug repurposing. In this context, a collaborative strategy should be developed under strict regulatory bodies. The most important task for such regulatory bodies should be focused not only on critically understanding the pre-clinical and clinical evidence and their efficacy and safety profiles for different targets but also on establishing an atmosphere for knowledge transfer with additional leverages through a collaborative approach (Sultana et al., 2020).

The recent advancement in computational tools, mathematical algorithms have provided novel avenues to develop multifaceted platforms for increasing the efficacy of drug discovery and development. In this context, recently, a group of scientists develops a robust webserver termed as D3Targets-2019-nCoV webserver which not only predicts putative drug targets through a single platform for drug-like candidates but also provides a platform for the identification of lead drug candidates against a specific molecular target or multiple therapeutic targets. Thus, the development of such a webserver provided a single platform for the identification of both targets and drug-like molecules for their interactions and thereby improving the computational arsenal against COVID-19 infections (Shi et al., 2020). The recent revolution in drug repurposing, as well as drug development pipelines, is the emergence of network pharmacology-based approaches. Recently, a network medicine-based algorithm termed Searching off-lAbel dRUg aNd NEtwoRk (SAveRUNNER) was designed and developed to provide a framework for the association of potential drug candidates (either approved or in clinical practice) with several disease-specific targets including SARS-CoV-2. Basically, SAveRUNNER works on a framework of 14 selected diseases that are directly or indirectly associated with SARS-CoV-2 infections. This network framework has provided an opportunity to predict the repurposing of approved drugs, off-label drugs as well as unexplored but promising drug candidates toward the treatment of COVID-19 and could be instrumental in the near future (Fiscon et al., 2021). Since the high throughput and robust computational tools and mathematical algorithms became an integral part of biomedical and pharmaceutical sectors as an interdisciplinary approach. The advancement of these tools resulted in the appearance of big data and to evaluate and validate the big data information, we require highly powerful and analytical tools. In this context, the artificial intelligence (AI)-based approach becomes a cutting-edge revolution in defining pathophysiological events, response to pathophysiological events, drug therapeutics management, and development of precision medicine using informatics. In the context of pandemics like SARS-CoV-2 infections, the advent of AI-based networks could also fulfill the demand for the use of repurposed drugs as an arsenal against viral infections in a précised manner (Lin et al., 2020; Zhou et al., 2020).

The scientific community is continuously working on the aspect of developing potential drug candidates specifically targeting novel coronavirus disease. On the other hand, pharmaceutical companies are coming up with the development of vaccines of different formulations for the prevention of disease severity and the development of herd immunity. But, in the meantime drug repurposing served as the most efficient solution for the treatment of SARS-CoV-2 infections and associated health ailments. OMICS-based approaches have given a new dimension in determining the structure and functional roles of potential molecular targets and thus facilitate the repositioning of existing drug candidates toward pathophysiological targets. However, more intensive work needs to be carried out to translate the use of repurposed drugs from laboratory setup to clinical settings. To achieve this target, the research scientists, academicians, funding agencies, pharmaceutical companies, government, and the health regulatory bodies should work in tandem and develop robust strategic formulations to fight against the pandemics. These collaborative approaches will not only facilitate tackling the current pandemic situation but also will provide new avenues for drug development and maintaining the healthcare systems in the future (Deshpande et al., 2020).

11.7 Conclusion

The journey of SARS-CoV-2 starting from Wuhan, China to more than 200 countries across the world since 2019–20 has imposed infections to hundreds of millions of people and resulted in a high rate of mortality and morbidity. The SARS-CoV-2 pandemics, apart from human life, also imposed a serious impact on our healthcare infrastructure, our preparedness to face such wrath of pandemics, the global economy with the rising incidence of unemployment, and increased pressure to the pharmaceutical industries for the development of new and effective drugs. The scientific community, no doubt is working continuously for the discovery of potential therapeutic agents for COVID-19, still, we have not encountered any specific therapeutic medications. In this context, computational tools-based drug repurposing could be a viable alternative to explore the already approved drugs toward screening against SARS-CoV-2 infection. Since drug repurposing approaches only consider the potential drug candidates being used and/or approved for some other therapeutic applications, the existing drugs could be directed toward the development of potential therapeutic agents on an urgent basis. No doubt, drug repurposing provides new avenues to drug development pipelines, the restrictions in scientific thinking and regulatory issues remain the important points to be taken care of. To avoid these complications in the wake of pandemics and associated health hazards, a collaborative approach should be strictly followed. The main objectives of such a collaborative approach should be centered on creating an environment for all the stakeholders starting from academic researchers, government organizations, pharmaceutical companies, funding agencies, and global regulatory bodies to work in tandem for global sharing of scientific knowledge for fast and effective development of potential drug candidates as arsenal against SARS-CoV-2 pandemic.

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