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EDITED BY
Bruno Villoutreix,
Institut National de la Santé et de la Recherche Médicale (INSERM), France

REVIEWED BY
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Tanta University, Egypt
Juan Fernandez-Recio,
Institute of Vine and Wine Sciences (CSIC), Spain

*CORRESPONDENCE
Emmanuel O. Ogbadoyi,
eogbadoyi@futminna.edu.ng

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The challenges and opportunities for the development of COVID-19 therapeutics and preparing for the next pandemic

Emmanuel O Ogbadoyi[1,2,3]* and Ndagi Umar[1,2,4]

[1]Deparment of Biochemistry, School of Life Sciences, Federal University of Technology, Minna, Nigeria, [2]Africa Centre of Excellence for Mycotoxin and Food Safety (ACEMFS), West African Network for Infectious Diseases ACEs (WANIDA), Federal University of Technology, Minna, Nigeria, [3]Global Institute for Bioexploration, Centre for Genetic Engineering and Biotechnology, Federal University of Technology, Minna, Nigeria, [4]Trans-Sahara Disease Research Centre, Ibrahim Badamasi Babangida University, Lapai Niger State, Nigeria

The disease which is today known as COVID-19 is caused by severe acute respiratory. Syndrome coronavirus 2 (SARS-COV-2), was first reported in Wuhan, China in December 2019. The disease has claimed well over six million lives from over 500 million cases. Vaccine hesitancy militates against successful mass vaccination. There is the rapid emergence of new SARS-COV-2 variants, constituting a challenge to the effectiveness of vaccines. Moreover, none of the available vaccines offers 100% protection and even the protection offered is of short duration necessitating booster doses to be taken. Moving forward, the development of plant-based edible vaccines will be a remarkable strategic approach to overcome vaccine hesitancy and improve vaccine uptake. So far only about nine drugs for COVID-19 treatment have approvals by either or both the European Medicines Agency and the FDA. While drug repurposing to address the emerging need in the early period of the COVID-19 pandemic has been contextually very useful, investment in it remains relatively low for commercial reasons arising from patenting issues. Embarking on new drug discovery and development strategies targeting both the virus and host factors is a very appealing option. Targeting druggable targets that are present across viruses, particularly the coronaviruses, for drug discovery and development represents an important strategy for pandemic preparedness. Natural products are an important reservoir of chemical scaffolds with huge potential for the discovery of novel chemical entities for development of novel therapeutics. Phytopharming is an available technology that can be used for mass and accelerated production of therapeutic molecules that will be required within short periods of time as is the case in pandemic outbreaks. Nanotechnology provides excellent platforms for formulating multivalent vaccines and pan-viral medicines for the treatment of COVID-19. Taken together, this review discusses the potential for the development of therapeutics by using the tools of biocomputing, nanotechnology, and phytopharming for accelerated therapeutic development to achieve effective COVID-19 treatment and associated complications, including new and emerging variants of SARS-COV-2 and other viral pandemics that may emerge or re-emerge.

KEYWORDS
COVID-19, SARS-CoV-2, Drug discovery, Natural products, Computational methods

Introduction

SARS-CoV-2 (COVID-19)

The ongoing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which started in the city of Wuhan in Hubei province, China with the earliest onset of symptoms on 1 December 2019 (Liu et al., 2020) has today spread to about 226 countries and territories worldwide. The disease which was initially diagnosed as viral pneumonia (Huang et al., 2020; Zhu et al., 2020) was referred to as Wuhan pneumonia by the press (Liu et al., 2020).

The virus was initially termed 2019 novel coronavirus (2019-nCoV) on 12 January 2020 and a month later, the World Health Organization officially named the disease coronavirus disease 2019 (COVID-19) and went on to declare it a pandemic on 11 March 2020. According to the World Health Organization, globally there are 497,960,492 confirmed cases with 6,181,850 deaths as of 12 April 2022. Horton (2020) described COVID- 19 as a triple crisis–medical, economic, and psychological.

Control measures

Generally, diseases are controlled through the use of both pharmaceutical and non-pharmaceutical approaches. COVID-19 is not an exception to this generalization. COVID-19 prevention is through a combination of vaccination, prophylactic or preventive treatment, and non-pharmaceutical measures of social distancing, quarantine, isolating infected persons and patients, lockdowns, avoiding crowding, wearing protective face masks, regular washing of hands with soap, use of hand sanitizers, and not touching the face with hands, particularly the mouth, nose and the eyes which are ready and easy viral entry points into the body. Implementation of these were very challenging, particularly in low- and middle-income countries and among the unscientifically minded populations. This was most common with the use of face masks where: materials that will readily allow entry of the virus are used for the face masks; many people touched the masks that may have been infected with the virus with their bare hands thereby possibly carrying the viruses in their hands and then touching their faces with unwashed and unsanitized hands; inappropriate disposal of used face masks which become potential sources of spread of the virus within the population as children and even some adults pick up discarded used masks from roadsides and waste bins (this is common in poor resource settings and among individuals with a low level of education). The pharmaceutical approaches involve the use of therapeutics, which in a broad sense can be described as medications or remedies taken to prevent, treat, or remediate a health problem. Therapeutics include but are not limited to, vaccines, monoclonal antibodies, drugs, functional foods, and nutraceuticals.

Vaccine development: General approaches

The field of vaccinology came into being in 1796 with the discovery of the smallpox vaccine by Edward Jenner in which he used the whole live organism that causes smallpox, cowpox virus, to develop the vaccine. This was followed by the formulation of the polio vaccine using the killed or inactivated polio virus to develop the polio vaccine. Then there came the live attenuated vaccines in which the infectious agent is neither killed nor inactivated but rendered non-infective. Some examples include measles, mumps, and rubella vaccine (MMR). Following this are the toxoid vaccines which are based on inactivated toxins of pathogenic microorganisms such as tetanus and diphtheria. In more recent times, subunit vaccines (an example is the HPV vaccine), in which components of the pathogen antigen to which immune response is stimulated are used in developing the vaccines. The components of the pathogen antigen can also be produced as recombinants and used for vaccine production. Subunit vaccines have excellent safety profiles but are generally less immunogenic compared with inactivated or attenuated vaccines and require much stronger adjuvants for enhanced immunogenicity. Other forms of vaccine platforms include conjugate vaccines in which poorly immunogenic surface molecules, such as polysaccharides of many bacteria, are synthesized and conjugated to strongly immunogenic proteins and are then used for vaccine development. Some examples include HiB, meningitis C, and pneumococcal vaccines; the next generation vaccines: vectored vaccines which involve putting vaccine antigens inside replication-deficient microorganisms such as Adenoviruses and modified Vaccinia Ankara capable of triggering an immune response and the antigen is then vectored into the host cells; The genome-based approach (nucleic acid approach) which is based on the use of DNA or RNA to make desired antigens in the host thereby prompting an immune response; Reverse vaccinology in which vaccine candidates are selected on the basis of predicted immunogenicity emanating from sequence information obtained from the use of modern sequencing technology. This was successfully used in developing a

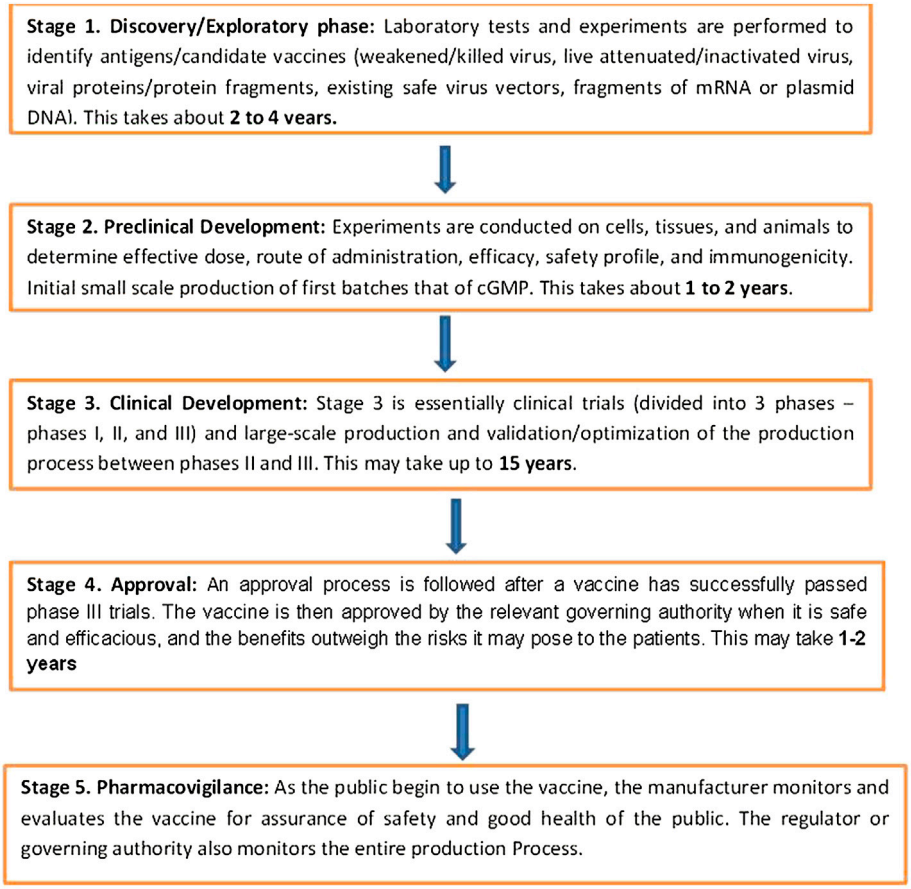

FIGURE 1
Stages of traditional vaccine discovery and devolopment process.

vaccine against meningococcus B, which, till then, was difficult to be achieved using conventional vaccine technologies (Rappuolia et al., 2021); Structural vaccinology (structure-based antigen design) which can also be considered as a variant of reverse vaccinology uses information on the structure of antigenic epitopes and protein conformation in the design of vaccines. Some examples include the design of a single meningococcal antigen containing the epitopes of three antigenic variants of the same molecule, and a host of others (reviewed by Rappuolia et al., 2021). The stages involved in traditional vaccine discovery and development are shown in Figure 1.

Structural vaccinology is novel and innovative and particularly potentially very useful in antiviral vaccine development to combat very challenging viruses that traditional approaches have failed or may fail to produce effective vaccines. Essentially, the process involves four stages: determining the atomic structure of the antigen or antigen-antibody complex; remodeling the antigen or the epitope by reverse molecular engineering; incorporating the re-engineered antigen or epitope into one of the vaccine platforms; and testing the safety and efficacy of the candidate vaccine *in vivo* (Anasir and Poh 2019).

In summarizing, three broad platforms can be used for the design of vaccines: the whole organism (virus or bacterium), the parts of the organism (subunits and recombinants), and the genetic material (DNA or RNA). These are illustrated in Figure 2.

Drug discovery and development: General approaches

Broadly, drug discovery involves the following approaches: Screening extracts of natural origin for bioactivity and then isolating bioactive compounds from potent extracts for drug development. Opium and taxol are a good testimony to this; Random synthesis and screening in which several organic compounds are synthesized and pharmacologically screened for therapeutic potentials. The efficiency of this approach has been greatly enhanced by automated high throughput screening

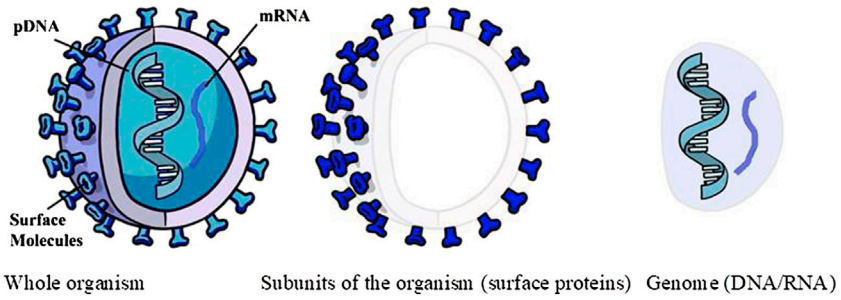

FIGURE 2
The three broad platforms for vaccine design and devolopment.

Step 1. Discovery: In vitro and in vivo experiments for target identification and validation; Assay development for High Throughput Screening (HTS) and *In silico*/virtual screening of **5,000-10,000 compounds** for Hit discovery; Secondary screening for Hit-to-Lead (H2L) and lead generation; Lead optimization, involving synthetic chemistry to improve potency and reduce side effects; **Up to 250 compounds may be obtained for preclinical studies**. The discovery process takes **3-5 years.**

Step 2. Development/Preclinical studies: In vitro, In vivo, and Ex vivo experiments are conducted on **up to 250 compounds** to determine ADME/PK/PD properties, safety profile, proof of concept, dose range, route of administration/delivery, effects on gender, race/ethnic groups, drug-drug interactions, effectiveness in comparison to similar drugs, formulation, optimization, and bioavailability, IND- or BLA-enabling studies, and IND or BLA application. **Up to 5 compounds may make it to clinical trials.** The preclinical development takes **1-2 years.**

Step 3. Clinical Development/Clinical Trials: This stage of development is done in humans and includes IND studies, the 3 phases (Phase I, Phase II, and Phase III) of clinical trials, and **may involve up to 5 compounds.** *Phase I:* This first in human studies is done in 20-100 healthy volunteers to determine safety and dosage through examination of dose escalation, single ascending and multiple dose studies. Phase I takes **1.5 years.** *Phase II:* Done in 100-500 patient volunteers to evaluate safety and efficacy and may take up to **2 years.** *Phase III:* Studies in 1,000-5,000 patient volunteers to confirm efficacy and safety upon long-term use; Bioanalytical method development and validation. This takes **3-5 years**. Phases I, II, and III may take up to **6-7 years.** Only 1 compound may enter step 4.

Step 4. Regulatory Review and Approval: Submission of New Drug Application (NDA), including: preclinical data, results of phase III clinical trial, proposed labeling, updates on safety, information on drug abuse, patent information, directions for use. Approval is then done if outcome of review is satisfactory. The approval timeline may be standard, fast track, breakthrough, accelerated approval, or priority review depending on its intended uses and necessity for patients. Review and approval takes **1-2 years** and the drug is then registered.

Step 5. Post Market Surveillance/Pharmacovgilance: The drug manufacturer conducts post marketing testing to monitor the safety its drug in line with guidelines provided by the regulatory agency that gave the approval. For example the FDA Adverse Event Reporting System (FAERS).

FIGURE 3
Summary of traditional drug discovery and devolopment process.

technology and combinatorial chemistry which has greatly accelerated synthetic methods, enabling the synthesis of a huge library of compounds that can then be screened for bioactivity. However, this approach is not a successful path to drug discovery; Rational drug design is dependent on several determinants such as the pathophysiology of the disease against which the drug is being developed. This uses the tools of genomics, structural biology, synthetic biology, medicinal

TABLE 1 Candidate vaccines in clinical development indicating platforms, number and percentage.

Platform	Candidate vaccines	
	Number	Percentage
Protein subunit (PS)	52	33
RNA	31	20
Viral Vector, non-replicating (VVnr)	21	13
Inactivated Virus (IV)	21	13
DNA	16	10
Virus Like Particle (VLP)	06	04
Viral Vector, replicating (VVr)	04	03
VVr + Antigen Presenting Cell (VVr + APC)	02	01
Live Attenuated Virus (LAV)	02	01
VVnr + Antigen Presenting Cell (VVnr + APC)	01	01
Bacterial antigen-spore expression Vector (BacAg-SpV)	01	01

Modified from WHO (2022) at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

chemistry, computational biology/bioinformatics, and cheminformatics. Rational drug design is a very efficient and successful approach as the innovative tools mentioned can significantly reduce the time for the discovery process. The steps involved in the drug discovery and development process are summarized in Figure 3.

Drug repurposing, though not drug discovery per se, is a useful approach to obtaining drugs for meeting unmet medical treatment needs.

Development of COVID-19 therapeutics and the challenges: The state-of-the-art

COVID-19 vaccine development

The world was unprepared to immediately and adequately mitigate the catastrophic consequences of the outbreak of COVID-19. Since there was no specific treatment for the disease at the onset, the most appropriate control method was to develop vaccines for mass immunization to prevent transmission and bring the disease under control. The response was massive as researchers in academia, research institutes, and industries worked together with manufacturing companies to produce various vaccines using eleven different platforms (Table 1). These platforms can be classified into conventional vaccines (live attenuated virus, inactivated virus, virus-like particle, and protein subunit) and next-generation vaccines (Gene-based vaccine platforms based on viral vectors, DNA, and RNA). The international coordinated efforts led to the unprecedented scientific achievement of getting a vaccine (Comirnaty vaccine of Pfizer/BioNTech) for use in just about a year of the pandemic outbreak and many others followed (Table 2). As of 20 May 2022, there were 157 vaccines in clinical development (Table 1) and 198 in preclinical development (World Health Organization, 2021). The percentage of vaccines in each platform is summarized in Figure 4. Two vaccine platforms, mRNA and viral vectors particularly stand out in the fight against COVID-19. Despite this remarkable progress, there are still serious challenges of limited efficacy (Table 2), waning protection over short periods of time, and rapid emergence of new variants that may further reduce the efficacy of existing vaccines. These inadequacies can be overcome by developing platforms for polyvalent vaccines using CRISPR-engineered viral vectors and/or nanomedicine. Furthermore, the availability of vaccines alone cannot prevent the disease unless people get vaccinated. However, vaccine hesitancy continues to remain a serious challenge militating against vaccine acceptance and uptake by the general population. The SAGE working group on vaccine hesitancy describes vaccine hesitancy as the "delay in acceptance or refusal of vaccination despite the availability of vaccination services" (MacDonald, 2015). Vaccine hesitancy, driven largely by misinformation and disinformation, has been described as one of the top ten global health threats (Scheres and Kuszewski, 2019). Although globally a total of 11,250,782,214 vaccine doses had been administered as of 5 April 2022, the dream of herd immunity is far from being realized. This is compounded by "vaccine nationalism and regionalism" and a lack of production capacity in many countries, particularly the low- and middle-income countries. For instance, there are only 24 countries out of the total of 235 countries and territories in the world that produce World Health Organization prequalified vaccines and none of the 24 countries is in Africa with twelve countries leading vaccine production as shown in Table 3. However, in February 2022, the

TABLE 2 Vaccines granted Emergency Use Listings as at16 March 2022.

Company	Vaccine	Platform	Date of EUL	Efficacy
Pfizer/BioNTech	Comirnaty vaccine	mRNA (nucleoside modified)	31 December 2020	95%
The SII/COVISHIELD and AstraZeneca	AZD1222 vaccines	Viral Vector (non-replicating)	16 February 2021	76%–100%
Johnson & Johnson	Janssen/Ad26.COV 2.S	Viral Vector (non- replicating	12 March 2021	85.4%–93.1%
Moderna	Moderna COVID-19 vaccine (mRNA 1273)	mRNA (nucleoside modified)	30 April 2021	94.1%
Sinopharm	Sinopharm COVID-19 vaccine	Inactivated virus	7 Ma y 2021	79%
Sinovac	CoronaVac	Inactivated virus	1 June 2021	51%–100%
Bharat Biotech	BBV152 COVAXIN vaccine	Inactivated virus	3 November 2021	78%–93%
Novavax-COVAX	Covovax (NVX-CoV2373) vaccine	Protein subunit	17 December2021	90%
Novavax	Nuvaxovid (NVX-CoV2373) vaccine		20 December 2021	90%–100%

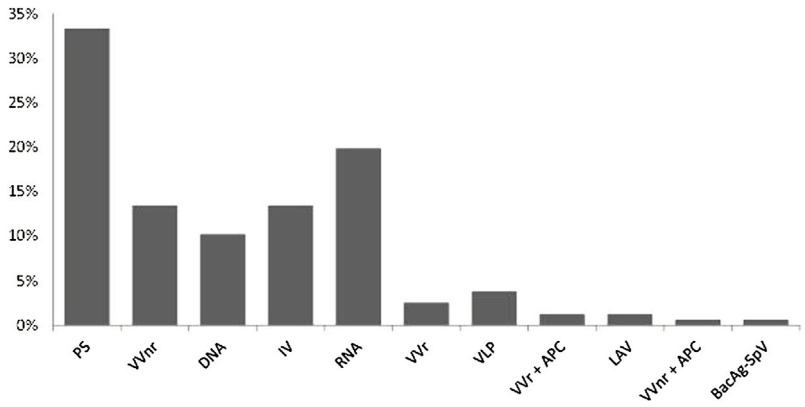

FIGURE 4
COVID-19 vaccines in clinical devolopment,the devolopmental platforms (*x* axis), and the percentage of vaccines in each devoloment platform (*y* axis). Key: PS=Protein subunit; VVnr= Viral Vector, non-replicating; DNA; IV= Inactivated virus; RNA; VVr = Viral Vector, replicating; VLP = Virus Like Particle; VVr + APC = VVr + Antigen Presenting Cell; LAV = Live Attenuated Virus; VVnr+ APC + VVnr + Antigen Presenting Cell; BacAg-SpV = Bacterial antigen-spore expression Vector. Based on data obtained from WHO (2022) at https://www.who.int/publications/m/item/draft-landscape-of covid-19-candidate-vaccines.

technology for the production of mRNA vaccines was given to six countries in Africa (Egypt, Kenya, Nigeria, Senegal, South Africa, and Tunisia) to enable the production of mRNA vaccines in these countries.

Drug development

Although the rollout of vaccines and non-pharmaceutical interventions are significantly helping to contain the COVID-19 pandemic, treatment remains a major control measure. However, it is an understatement to say that COVID-19 chemotherapeutic armory is grossly inadequate at the moment. There is huge potential to successfully address this inadequacy by providing solutions for COVID-19 treatment using drug repurposing and traditional drug discovery approaches.

TABLE 3 A total number of COVID-19 vaccine doses produced by the top 12 producing countries as of 03 March 2021.

Country	Number of doses
China	141,624,000
United States	103,000,000
Germany/Belgium	70,534,055
India	42,390,000
United Kingdom	12,200,000
Netherlands/Belgium	10,496,982
Russia	10,492,500
Switzerland	5,462,338
South Korea	1,617,000
Brazil	200,000
South Africa	160,000

https://www.statista.com/chart/24492/total-covid-19-vaccine-production-by-country/ (accessed 21 May 2022).

Drug repurposing

The outbreak of the COVID-19 pandemic can be said to have taken the world unaware and unprepared to contain it and there was more or less pandemonium at the onset as there was neither vaccine nor any specific treatment. While scientists and researchers immediately began efforts in collaborative vaccine development, intensified and concerted efforts were also made by scientists and researchers to evaluate pre-existing approved drugs for efficacy against COVID-19 so that they could be used for the treatment of the disease in what is known as drug repurposing (also referred to as repositioning, re-profiling, re-tasking, indication expansion, indication shift, or rescue of drugs). Drug repurposing has also been described as establishing new medical uses for already known drugs, including approved, discontinued, shelved, and experimental drugs (Talevi and Bellera, 2020). Therefore, in response to the immense pressure the disease placed on world health systems, the World Health Organization rationally established an international "Solidarity" clinical trial to accelerate the finding of an effective treatment for the disease (World Health Organization, 2020). What followed were clinical trials of pre-existing multiple antiviral medications that had been used for SARS-CoV, MERS-CoV, and antimalarials (Li and De Clercq, 2020). The initial repurposing efforts involved remdesivir, the malaria medications hydroxychloroquine and chloroquine, the combination of HIV drugs called Kaletra, consisting of lopinavir and ritonavir, and other combinations, including interferon beta-1a (Savi et al., 2020). Candidates for clinical trials came from the deployment of available screening techniques of current pharmacopoeia to reveal novel drug indications of already established drugs (Jarada et al., 2020).

The methodologies used for drug repurposing can be broadly categorized into three depending on available information in the context of pharmacological, toxicological, and biological activity. They include those based on the: drug, drug target, and disease/therapy. Three fundamental steps are involved before a potential drug for repurposing can be developed and marketed. These are: identifying the candidate drug; evaluating mechanistically, the drug effects in preclinical models; and evaluating the efficacy of candidate drugs in phase II clinical trials (Khataniar et al., 2022). There are two alternative but complementary approaches that can and have been used for drug repurposing: an experimental approach which is also referred to as the activity-based approach, and the computational methods (*in silico*) approach (Lipinski, 2011; Senanayake, 2020; Dhaneshwar and Bhasin, 2021; Naasani, 2021; Ng et al., 2021; Khataniar et al., 2022). Whichever approach is chosen, the process begins with the selection of the drug for repurposing followed by the identification of the drug target(s). From what is known about the biology of SARS-CoV-2, the drug targets frequently mentioned are: Spike (S) protein receptor binding domain (RBD), RNA-dependent RNA polymerases (RdRps), helicase; SARS-CoV Chymotrypsin-like cysteine protease, $3CL^{pro}$ (also known as M^{PRO}); papain-like cysteine protease (PL^{pro}), which are all important for viral replication and they are therefore viral-based targets. This has been reviewed in the literature (Jang et al., 2021; Nawaz, 2021; Yang and Rao, 2021; Khataniar et al., 2022) and will not be discussed in detail in the current review. There are also host factors that can be targeted for therapeutic intervention and they include, but are not limited to: transmembrane protease serine 2 (TMPRSS2) for viral entry; NF-κB, IL-1β, and IL-6, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and Janus kinase (JAK) for immunomodulation and cytokine storm prevention and control; superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSPHx), reduced glutathione (GSH), glutathione reductase (GR) and lipid peroxidation (LPO) for mitigating against oxidative stress.

In the experimental approaches, either phenotypic or target-based screening can be done to identify potent drug candidates for validation, optimization, selection, and repositioning. Phenotypic screening is followed by target deconvolution (retrospective identification of molecular targets) using appropriate deconvolution strategies involving binding assays for identification of target interactions, in which techniques such as affinity chromatography and mass spectrometry, and other techniques such as three-hybrid systems, phage, and mRNA display, protein and "reverse transfected" cell microarrays, and biochemical suppression are frequently used. The targets can then be validated by functional studies that use methods such as RNA interference and protein overexpression.

Although drug repurposing has the advantages of saving time and cost (Pushpakom et al., 2018) and therefore a very compelling approach to drug discovery in emergencies as was the case in the early phase of COVID-19 drug discovery, it is not without shortcomings. The shortcomings include intellectual property and economic considerations (legal and commercial barriers); data and compound availability; and fear of exhausting the repurposing space (Talevi and Bellera, 2020). In spite of these challenges, remarkable success stories abound, including repurposed drugs for COVID-19 treatment (Remdesivir has got FDA approval) and some others have been granted emergency use authorization.

Computational methods are today used in both traditional drug discovery processes and drug repurposing and it is extensively discussed in another section of this review. Suffice it to mention here that the most common techniques used in computational methods include target-based, network or pathway-based, knowledge-based, signature-based, and artificial-intelligence-based techniques which rely largely on docking and molecular dynamics simulations.

Apart from drug repurposing, there have also been efforts in developing antibody therapies using blood samples obtained from recovered patients. These involve the isolation and identification of antibodies including neutralizing monoclonal antibodies and nanobodies for the

treatment of COVID-19 (Huo et al., 2020; Renn et al., 2020; Adamson et al., 2021).

Traditional drug discovery approach

The trajectories for drug repurposing and traditional drug discovery are essentially the same, differing mainly in speed and cost. While drug repurposing was going on, scientists across the globe were intensifying strategic basic research efforts to accumulate knowledge about SARS-CoV-2 and the pathophysiology of COVID-19 to allow for the commencement of the drug discovery process specifically for COVID-19. Technologies generally involved in drug discovery include various screening techniques such as phenotypic, CRISPR, and target-based screening; structure-based drug discovery; and Biocomputing/bioinformatics. Typically, the drug discovery and development process involve the following key steps: target (a biological molecule, usually a protein but can also be DNA or RNA or gene whose function is to be modulated to bring about a desired or beneficial therapeutic effect to the patient) discovery, identification, and validation; assay (investigative procedures for the qualitative evaluation of the effects of a compound on identified molecular, cellular, or biochemical targets) development; screening to obtain molecules or extracts with a promising activity which are referred to as hits; counter-screening to identify compounds that may interfere with the primary assay used in the primary screen and to eliminate cytotoxic compounds; hit-to-lead and lead optimization to obtain a compound with suitable properties that can be modified to produce a drug candidate. The drug candidate then goes into development and progresses into clinical trials.

Whatever the drug discovery approach used, challenges abound. A major factor militating against anti-SARS-CoV-2 drug discovery is the requirement for Category three containment level which is expensive and difficult to maintain and therefore not within the reach of many scientists, particularly in poor resource settings. Screening of compounds against live SARS-CoV-2 is therefore problematic. The alternatives are to use *ex vivo* systems such as pseudoviruses and/or perform inhibition studies against SARS-CoV-2 enzymes such as RNA-dependent RNA polymerases (RdRps) and proteases or block critical protein-protein interactions. SARS-CoV-2 is not an exception to drug resistance which is a major problem in antiviral therapy generally. This is particularly so with respect to RNA viruses as a consequence of the error-prone nature of RNA-dependent RNA polymerases (RdRps), the rapid rate of viral replication, and the high frequency of recombination events. The deployment of nanotechnology to formulate multi-component and multi-target nanoparticle cocktails will produce medicines to which resistance will be much less likely.

Natural products are compounds or substances produced by living organisms which include plants, animals, and microorganisms. The use of natural products for the treatment of diseases dates back to prehistoric times. Scientists are digging into nature to harness the "goldmine" of healing molecules to meet various unmet medical treatment needs. Natural products continue to be major sources of prototypes of antimicrobial and antiviral drugs (Adalja and Inglesby, 2019) and represent viable sources of therapeutic alternatives for many diseases (González-Maldonado et al., 2022). It is estimated that over 70% of all existing pharmaceutical products are of natural product origin (Wangchuk, 2018; Abd et al., 2019). In the United States, approximately 118 of the top 150 prescription drugs are based on natural sources (Chen et al., 2016). Several classes of natural compounds such as flavonoids, alkaloids, peptides, and others have been tested against COVID-19 (Antonio et al., 2020; Verma et al., 2020; Antonio et al., 2021; González-Maldonado et al., 2022) with promising outcomes.

Medicinal plants are globally recognized as valuable sources of new medicines with up to 80% of people in developing countries relying on herbal medicines for their primary health care needs. Additionally, more than 25% of medicines prescribed in developed countries are derived from wild plant species (reviewed by Chen et al., 2016). At the dawn of the 21st century, 11% of the 252 drugs considered basic and essential by the WHO were exclusive of flowering plant origin (Veeresham, 2012). Some plants known to have antiviral and immunomodulatory properties include *Glycyrrhiza glabra, Azadirachta indica, Andrographis paniculata, Calotropis gigantea, Ocimum sanctum, Curcuma longa, Withania somnifera, Zingiber officinale, Allium sativum, Tinospora cordifolia, Moringa oleifera* (Ganjhu et al., 2015; Tiwari et al., 2018). There are a number of plant-specific compounds such as lignans, saponins, alkaloids, flavonoids (kaempferol, luteolin, apigenin, baicalin, quercetin, catechins), and polysulphates (sulphated polysaccharides) that are known to destroy the nucleocapsid and genetic material, inhibit viral entry and inhibit the replication of viruses such as dengue, herpes simplex virus (HSV), hepatitis C virus (HCV), influenza, chikungunya, SARS, etc. (Dhama et al., 2018). Exploiting medicinal plants for the development of COVID-19 therapeutics is therefore a very attractive option.

In the early days of the heat of the COVID-19 pandemic when no specific treatment was available, many countries explored the potential of phytochemicals obtained from medicinal plants and herbs for treating COVID-19 patients (Aanouz et al., 2020; Divya et al., 2020; Jahan and Onay, 2020; Qamar et al., 2020; Xu and Zhang, 2020). Significant progress has already been made in COVID-19 drug discovery from medicinal plants. Polyphenols have been shown to inhibit coronaviruses (Mani et al., 2020) while virtual screening has demonstrated the strong binding potential of absinthin, quercetin 3-glucuronide-7-glucoside, and quercetin 3-

TABLE 4 Herbal medicines and efficacy levels as adjuvant symptomatic therapies in early COVID-19 (Silveira et al., 2020).

Plant	Efficacy
Althaea officinalis	Positive
Commiphora molmol	Positive
Glycyrrhiza glabra	Positive
Hedera helix	Positive
Sambucus nigra	Positive
Allium sativum	Promising
Andrographis paniculata	Promising
Echinacea angustifolia	Promising
Echinacea purpurea	Promising
Eucalyptus globulus essential oil	Promising
Justicia pectoralis	Promising
Magnolia officinalis	Promising
Mikania glomerata	Promising
Pelargonium sidoides	Promising
Pimpinella anisum	Promising
Salix sp	Promising
Zingiber officinale	Promising

vicianoside to SARS-CoV-2 main protease (Mpro) and angiotensin-converting enzyme 2 (Joshi et al., 2020). It is documented in the literature that 83 phytocompounds with anti-COVID-19 activity, the most potent being the alkaloid, lycorine, lignan, savinin, and a total of 39 herbal medicines (listed by WHO and European Medicines agency, EMA) which are indicated for "respiratory diseases" that were evaluated for efficacy as an adjuvant symptomatic therapy for COVID-19 the results of which are shown in Table 4 (Silveira et al., 2020). Thymoquinone obtained from natural *Nigella sativa* has also been documented to be potentially useful for the treatment of COVID-19 (Abdelrahim et al., 2022). Additionally, several plant-derived bioactive compounds from traditional herbal medicine include andrographolide, panduratin A, baicalein, digoxin, and digitoxin, have demonstrated potent SARS-CoV-2 antiviral activity comparable with some repurposed FDA-approved drugs (Liana and Phanumartwiwath, 2021). Methanolic extract of *Stachytarpheta cayennensis* remarkably inhibited SARS-CoV-2 entry (González-Maldonado et al., 2022). The Lamiaceae family members, *Zingiber officinale*, and *Glycyrrhiza* spp. are known to be particularly good as sources of medicines for the treatment of COVID-19.

While the descriptions of the huge potentials of natural products-derived anti-COVID-19 medicines are heartwarming, only Lianhuaqingwen, a Chinese herbal mixture of 11 medicinal species containing 61 compounds (Wang et al., 2016) has recommendation (by the Chinese National Health Commission) for clinical application to treat or manage COVID-19 (Yang et al., 2020). The herbal mixture inhibited SARS-CoV-2 replication in a dose-dependent manner with an IC50 of 411.2 μg/ml. Furthermore, the mixture was able to suppress the release of pro-inflammatory cytokines (TNF-a, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) in a dose-dependent manner (Runfeng et al., 2020).

Terpenoids, lectins, glycoproteins, lentinan, galactomannan, and polysaccharides from mushrooms (*Agaricus subrufescens* Peck, *Agaricus blazei* Murill, *Cordyceps sinensis* (Berk.) Sacc., *Ganoderma lucidum* (Curtis.) P. Karst., *Grifola frondosa* (Dicks.) Gray, *Hericium erinaceus* (Bull.) Pers., *Inonotus obliquus* (Arch. Ex Pers.) Pilát., *Lentinula edodes* (Berk.) Pegler, *Pleurotus ostreatus* (Jacq.) P. Kumm., *Poria cocos* F.A. Wolf, and *Trametes versicolor* (L.) Lloyd are promising prophylactic or therapeutic agents against COVID-19 (Arunachalam et al., 2022). The terpene, erylosides B from Red Sea invertebrate inhibits SARS-CoV-2 main protease (MPro) and identified as a promising anti-COVID-19 drug lead (Ibrahim et al., 2021).

Novavax vaccine consisting of proteins has been created in cultures of Fall armyworm (*Spodoptera frugiperda*) cells where the cells produce protein spikes that coat SARS-CoV-2 when infected with an engineered virus. The vaccine is achieving high success rates against all main variants of the virus and is entering authorization processes around the world. Peptides from animal venoms (snake, scorpion, frog, insect venoms) are rich sources of antiviral drugs.

Flavonoids, phlorotannins, alkaloids, terpenoids, peptides, lectins, polysaccharides, lipids and others substances of marine origin have been shown to exert desirable effects on coronaviruses penetration and entry into the cell, replication of the viral nucleic acid and release of the virion from the cell also can act on the host's cellular targets (Zaporozhets and Besednova, 2020). Similarly, several classes of compounds from various marine organisms (diverse sponges and algae and bacteria) have been shown to affect various virulence factors of SARS-CoV-2 and also induce the innate immune response and downregulate human ACE-2 (Geahchan et al., 2021).

As good and attractive as drug repurposing and other drug discovery processes are, drug discovery from natural sources is even more attractive and very compelling. This is because of the rich chemical diversity and the huge potential for the discovery of novel chemical scaffolds for discovery of novel drugs. The application of computational methods has made the discovery process much more robust and it is described in the section that follows.

BIOCOMPUTING/BIOINFORMATICS/ ARTIFICIAL intelligence

The availability of many untapped floral and faunal bioactive compounds (phytochemicals) in Africa and gradual understanding of the use of bioinformatics tools in drug discovery, drug design, and

computer applications in a genetic study is opening a new chapter of scientific understanding (gradual shift) from conventional laboratory investigation to *in silico* approach to drug discovery and molecular biology. In most African drug research centers, computer-aided drug design (CADD) is now being used to facilitate the process of drug discovery. Though the method is predictable the precision and its efficiency have been ascertained by various researchers. In the last decade, bioinformatics-based models of specific biomolecules have offered rapid and inexpensive methods for the discovery of effective viral therapies. In the presence of a target biomolecule, these models are capable of predicting inhibitor candidates in a structure-based manner. The inhibitors can also be used to predict the specific target (ligand-based) if enough data are presented to a model and it can aid the search for a drug or vaccine candidate by identifying patterns within the data. The availability of enormous data from African bioactive compounds (phytomedicines) provides a baseline for which bioinformatics tools can be used to explore inhibitors of various micro-organisms including viruses like SARS-CoV-2. Database, like phytochemical database, management system has been successfully developed and used in *in silico* drug design.

Phytochemicals database, a platform for virtual screening and computer-aided drug design

The phytomedicines derived from medicinal plants have proven to be a rich source of diverse chemical agents that have been used as drugs and supplements in the millennium (Mahmud et al., 2022). The dependence of Africans on phytomedicines as the first line in the treatment of disease conditions and perhaps the consumption of various vegetables with medicinal properties must have contributed to the low incidence of SARS-CoV-2 in most African countries relative to European countries despite a devastating prediction from World Health Organisation (WHO). It is therefore important to explore the efficacy of different African phytochemicals as inhibitors of SARS-CoV-2 using an already established phytochemical database and bioinformatics tools. In recent times, statistics of newly approved drugs by the United States Food and Drug Administration (FDA) shows that Phytomedicines account for a large number of the approved drugs used as general tonics, antioxidants, cell protectives, and immune stimulants (Kandeel et al., 2020) in the management of SARS-CoV-2, even in this era of combinatorial chemical drugs (Mahmud et al., 2022). Information relating to biological activity, molecular weight, and molecular structure of phytomedicines are deposited in the various databases. Few phytomedicine databases include:

Phytochemdb (Mahmud et al., 2022) is a database that is manually managed and compiles 525 lists of plants and their corresponding 8093 phytochemicals (Mahmud et al., 2022). It is a comprehensive database that gathers most of the information about medicinal plants in one platform, which is considered to be very beneficial to the work of researchers on medicinal plants. "Phytochemdb" is available for free *at* https://phytochemdb.com/.

TarNet

This is an evidence-based database for research on natural medicine. It is a cataloged database that provides information on traditional medicinal plants with natural compounds that includes potential bio-target information (Hu et al., 2016). Comprehensive information on a plant-compound-protein relationship can be accessed from the TarNet platform. TarNet is freely available at http://www.herbbol.org:8001/tarnet.

Ethiopian-Traditional Medicine Database

ETM-DB is the largest web-based integrated resource of Ethiopian traditional medicine (Bultum et al., 2019), freely accessible, and provides traditional herbal medicine entities and their relationships in well-structured forms including references (Bultum et al., 2019). The ETM-DB website interface is user-friendly and allows the users to search the entities using various options provided by the search menu. ETM-DB is expected to expedite the process of drug discovery and development and also promote *in silico* research from Ethiopian natural products leveraging information on the chemical composition and related human target gene/proteins. Phytochemicals from this database can be virtually screened against different targets of SARS-CoV-2. Therefore, this database is key in the discovery of antiviral drugs including RNA viruses such as SARS-Cov-2. The current version of ETM-DB is openly accessible at http://biosoft.kaist.ac.kr/etm.

African natural product database (AfroDb)

This is a database of selected highly potent and diverse natural product libraries from African medicinal plants (Ntie-Kang et al., 2013). AfroDb is said to represent the largest "drug-like" and diverse collection of 3D structures of natural products (NPs) covering the geographical region of the entire African continent (Ntie-Kang et al., 2013). The database is readily accessible and can be used in the integrated virtual screening program. The huge information on phytochemicals in this database can be leveraged in the discovery of antiviral drugs. This drug bank could serve as a reservoir of potent molecules active against most viral infections including SARS-CoV-2 and its variants. Since it is possible to predict the variants of SARS-CoV-2 by inducing mutation on SARS-CoV-2 main targets using *in silico* method, the targets from these variants can be used as reference targets for the virtual screening (target-based virtual screening) or the molecules from the database can be screened against targets (ligand-based virtual screening). AfroDb is therefore a drug bank in which artificial intelligence (bioinformatics tools) can be used to explore huge information on African phytochemicals to aid in drug

TABLE 5 Binding energies of some phytochemicals docked in the active sites of 3-chymotrypsin-like proteases of coronaviruses (Gyebi et al., 2021).

S/NO	Plant name	Compound	Binding energy (kcal/mol)
1	Vernonia amygdalina	Vernolide	−8.0
2	Vernonia amygdalina	Vernomygdin	−7.9
3	Occinum gratissimum	Chicoric acid	−7.7
4	Occinum gratissimum	Rosmarinic acid	−7.7
5	Vernonia amygdalina	Neoandrographolide	−7.7
6	Occinum gratissimum	Luteolin	−7.7
7	Vernonia amygdalina	Vernomenin	−7.7
8	Vernonia amygdalina	Isorhamnetin	−7.6

discovery and drug design, particularly in the pre and post pandemic period.

Computer-aided drug design and its application to COVID-19 drug discovery

Computer-aided drug design (CADD) has helped to facilitate the process of drug discovery and development by minimizing the cost and time (Gurung et al., 2021). The availability of a drug data bank (phytochemical database) also enhances the process of drug discovery. In the search for antiviral drugs, two important methods of computer-aided drug design (CADD) is key to the discovery of potent anti Covid-19 drugs (Gurung et al., 2021): the ligand-based and structure-based virtual screening. Molecular docking and molecular dynamic simulation are important techniques in structure-based drug design whereas ligand-based drug design includes pharmacophore modeling, quantitative structure-activity relationships (QSARs), and artificial intelligence (AI) (Gurung et al., 2021). The CADD plays a significant role in the design and discovery of promising drug candidates against various drug targets implicated in the pathogenesis of SARS-CoV-2 (Gurung et al., 2021).

Structure-based drug design

The availability of the three-dimensional crystal structure of the therapeutic target proteins and exploration of the binding site or active site residues forms the basis of structure-based drug design (SBDD) (Batool et al., 2019). This approach is highly selective and effectively fast in the identification of lead molecules and their optimization which has led to a better understanding of diseases at a molecular level (Lionta et al., 2014). Some of the common methods used in SBDD include structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations (Gurung et al., 2021). A lot of information can be extracted from these methods, some of which include assessment of binding energetics, principal component analysis (PCA), dynamics cross-correlation, protein-ligand interactions, and conformational changes in the receptor upon ligand binding (Batool et al., 2019). SBDD is a computational technique has greatly helped in the discovery of several drugs available on the market today. For example, the discovery of Amprenavir as a potential inhibitor of the human immunodeficiency virus (HIV) protease using the crystallized protein model and molecular dynamics (MD) simulations (Adamson et al., 2009; Liao and Nicklaus, 2010). Others include thymidylate synthase inhibitor, an anticancer agent, and Raltitrexed implicated in the treatment of HIV-infected cancer patients using the SBDD approach (Anderson, 2003; Medina-Moreno et al., 2019). Norfloxacin a topoisomerases II and IV inhibitor was also discovered through SBVS (Batool *et al*., 2019). In recent time, SBVS conducted using different protein targets of SARS-CoV-2 and phytochemical database revealed high binding energy and very good interaction with the residues of the active site target protein such as 3-Chymotrypsin-like proteases ($3CL^{pro}$) of SARS-CoV-2 (Gyebi et al., 2021). Some of the phytochemical agents that show good binding energy and ligand-residue interaction are shown in Table 5.

These plants, native to most of the African countries, demonstrate the reservoir of phytochemicals in Africa with potent inhibitory activity against target proteins in SARS-CoV-2. The basic steps involved in Covid-19 drug discovery using bioinformatics tools (SBDD) consist of the preparation of target structure, identification of the ligand-binding site, compound library preparation, molecular docking and scoring functions, molecular dynamic simulation, and binding free energy calculation (Gurung et al., 2021).

Ligand-based drug design

Ligand-based drug design is a computer-aided drug design technique that is widely used in drug discovery and design. It is employed when the three-dimensional structure of the target receptor is not available. The information

obtained from a set of active compounds against a specific target receptor is useful in the identification of physicochemical and structural properties that are responsible for the specific biological activity which is based on the structure-activity relationship (Prathipati et al., 2007; Gurung et al., 2021). The commonest techniques used in the ligand-based virtual screening approach include pharmacophore modeling, quantitative structure-activity relationships (QSARs), and artificial intelligence (AI).

Artificial intelligence (AI) and prospects in Covid-19 drug discovery

Artificial intelligence (AI) is a machine learning intelligence that depends on the ability of computers to learn from existing data (Gurung et al., 2021). AI has been used in various computational modeling methods to predict the biological activities and toxicity profiles of drug molecules (Patel et al., 2014). In addition, AI has also been widely used in the prediction of protein folding, protein-protein interaction, virtual screening, Quantitative Structural Activity Relationship (QSAR), evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the drug molecule, and *de novo* drug design (Gurung et al., 2021).

There are two major methods of AI that are widely used in rational drug design: machine learning (ML) and deep learning (DL) (Cortes and Vapnik, 1995). A support vector machine (SVM) is an ML algorithm that has been extensively used in drug discovery (Cortes and Vapnik, 1995). Others include Random Forest (RF) (Breiman, 2001) and Naive Bayesian (NB) (Sammut and Webb, 2017). Deep learning methods include convolutional neural network (CNN), deep neural network (DNN), recurrent neural network (RNN), autoencoder, and restricted Boltzmann machine (RBN) (Gurung et al., 2021). In summary, artificial intelligence has been widely used in drug discovery and vaccine development (Arshadi et al., 2020). As has been documented (Keshavarzi et al., 2022), this advancement in therapeutics research is critical for the current situation of pandemic and urgent need for the SARS-COV-2 therapy discovery for the following reasons (1) deep learning has an automatic feature extraction ability that can support models with better accuracy and deliver good reliable results (2) deep learning models demonstrate the generative ability that can be utilized to create more druggable molecules and better epitope prediction, (3) reduced chances of failure in the drug pipeline, and (4) because of the novelty of the virus the data related to its therapies remain scarce, which is a suitable scenario for knowledge transfer while leveraging on the learned knowledge from previous tasks (e.g., TranscreenTM) (Salem et al., 2020). Transfer learning is very effective in the transferring of learned knowledge and parameters from a secondary task with big data available to the task at hand (Weiss et al., 2016). Therefore, the use of deep learning in the discovery of therapies for SARS-COV-2 is necessary for a timely and accurate response to the viral pandemic (Arshadi et al., 2020).

Strength and challenges of CADD in the discovery of COVID-19 drugs

With the increase in the number of confirmed positive and death cases from SARS-CoV-2 infection with related evidence of viral mutation, computer-aided drug design (CADD) is the most viable and reliable technique in drug and medicinal research because of its attributed time saving and cost reduction in the design of therapeutic agents (Gurung et al., 2021; Ojha et al., 2021). In addition, the high impact of the pandemic resulting from COVID-19 infection and the relative lack of approved drugs create room for drugs to be repurposed within a short period of time. The CADD enhances this method by facilitating the discovery of new drugs or repurposing FDA-approved drugs whose safety and adverse effects are already known (Basak et al., 2021; Gurung et al., 2021). Since SARS-CoV-2, an RNA virus, poses a high mutation rate, the genome may hinder disease prevention and treatment (Gurung et al., 2021). CADD can be used efficiently to induce mutation on the existing targets, allowing for *in silico* prediction of the possible SARS-CoV-2 variant and subsequently developing potent molecules against these variants that are likely to cause a future pandemic (Gurung et al., 2021; Sharma et al., 2021). This is one of the major advantages (strength) of CADD in the discovery of COVID-19 drugs. Therefore, CADD is an asset in the drug discovery and development process. However, the CADD method is limited by the inability to validate its lead compound through clinical trials before market approval (Ojha et al., 2021). The molecular understanding of the disease pathogenesis of COVID-19 are still been strengthened, and the existence of the limited data on variants of COVID-19 can have a major impact on the precision and accuracy of CADD methods such as artificial intelligence (Ojha et al., 2021).

COVID-19 and beyond

In spite of the odds, tremendous opportunities exist to overcome the challenges by integrating advances in science and technology such as Genomics (including CRISPR-Cas system) Phytopharming/Molecular farming, Biocomputing, and nanomedicine to develop novel and innovative antiviral therapies with broad-spectrum activities against human

pathogenic viruses of the present and those that may emerge or re-emerge in the future.

Phytopharming/plant molecular farming for increased and accelerated production of COVID-19 therapeutics

Phytopharming or plant molecular farming is the production of biopharmaceuticals in plants using the tools of plant metabolic engineering and plant biotechnology. It is intended to overcome the limitations of high operating cost, prolonged production time, low yield, chances of contamination with pathogenic microorganisms, and limited posttranslational modifications of the current platforms that use bacterial systems, microbial eukaryotes, insect cells, and mammalian cells (Shanmugaraj et al., 2020). The use of plants as a platform for the production of diagnostic reagents and pharmaceutical proteins has been around for well over 30 years (Schillberg et al., 2019; Fischer and Buyel, 2020). The Israeli biotech company Protalix and Pfizer got FDA approval for the first drug, Elelyso (taliglucerase alfa), developed in plant cells (cells from carrot) in 2012. In February 2022, the Canadian biotech company, Medicago, got approval for its two-dose COVID-19 vaccine, the first world's plant-based COVID-19 vaccine (The Pharmaeutical Journal, 2022). The rapidity with which this feat was achieved is outstanding, taking just over 2 weeks. This is what the executive vice president of Medicago, Marc-André D'Aoust said. "From the moment we had the sequence on our computer, to the moment we [had the] first purified product, it took 19 days". Comparing this speed with five to 6 months for a conventional egg-grown vaccine, the plant-based approach will be of great advantage in potential future pandemics. This is particularly useful in poor and developing countries where the cost of the infrastructure of conventional platforms for the production of biopharmaceuticals is out of reach. Living plants have therefore effectively become bioreactors for the production of biopharmaceuticals. It may well be that plants may offer the only platform that can be used to manufacture COVID-19 diagnostic reagents and therapeutics at scale in a timeframe of weeks, compared with months or even years for cell-based systems (Capell et al., 2020). Lico and other colleagues in Italy made a case for molecular farming to complement conventional methods of production for the rapid and scalable supply of protein antigens as reagents and vaccine candidates, antibodies for virus detection and passive immunotherapy, other therapeutic proteins, and virus-like particles as novel vaccine platforms to meet the urgent therapeutic needs imposed by COVID-19 (Lico et al., 2020).

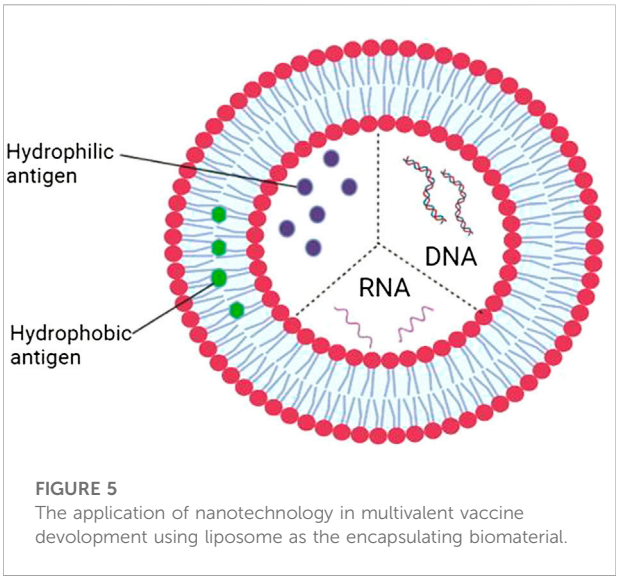

FIGURE 5
The application of nanotechnology in multivalent vaccine devolopment using liposome as the encapsulating biomaterial.

Edible vaccines in the battle against COVID-19

The concept is not different from molecular farming except that in this case the vaccine is produced in edible crops such as tomatoes, banana, potatoes, rice, carrot, corn, cucumber, lettuce, and spinach. Tomato has the advantages of having excellent biomass, being easy to transform and the whole plant can be generated within a short period. Tomato has therefore been described as a green vaccine factory (Sohrab, 2020). Sohrab and other colleagues listed the advantages of plant-based vaccines to include: oral use as fruits and vegetables; obtainable as capsules from dried leaf tissue powder; no requirement for adjuvants to enhance immune responses; mucosal immunity elicited by orally-introduced antigens; bulk production on site is easy and can be transported and stored at less cost and without cold chain requirement; not administered by injection and therefore no need for a trained medical person; easy to express, separate and purify; they can be stored as seeds and oils and dried tissue without any refrigeration; They do not have any risk of microbial contamination and disease spread; There is the possibility of enhanced compliance, especially in children (Sohrab et al., 2017). Significant progress has been made as scientists from the Centre for Genomics and Bioinformatics of the Academy of Sciences at Uzbekistan have developed a tomato-based vaccine against COVID-19 as of 2021. Seedlings in the laboratory are grown in the form of a vaccine from seedlings in the Centre after 2 months, and people who eat these tomatoes are expected to produce antibodies against the virus (Abdulkerimov, 2021).

Nanomedicine and enhancement of COVID-19 therapeutics

Nanomedicine is a branch of medicine that applies nanotechnology, which is essentially the manipulation and manufacture of materials and devices that are in the size range of 1–100 nm, to the diagnosis, prevention, treatment, and monitoring (follow-ups) of diseases and also for medical imaging and the repair and regeneration of biological systems (regenerative medicine). It uses the properties developed by a material at its nanometric scale which is different from those of the same material at a bigger scale in terms of physics, chemis,try or biology to achieve the many intended aims of nanomedicine applications. At the nano-scale, the surface-to-volume ratio is such that the surface properties become an intrinsic parameter of the potential actions of a particle or material. Therefore, coating the nanoparticles and functionalizing their surfaces enhance the biocompatibility of the particle and its circulation time in the blood, as well as ensuring a highly selective binding to the target of choice. The design and development of nanoparticles containing drug(s) (nanoparticulate nanomedicines) for drug delivery is an aspect of nanomedicine that has attracted tremendous attention. Nanoparticulate nanomedicines are designed and developed to deliver drugs through various mechanisms such as solubilization, passive targeting, active targeting, and triggered release which will ultimately increase therapeutic efficacy, decrease the therapeutically effective dose, and/or reduce the risk of systemic side effects (Hua et al., 2018). The nanomaterials of choice will include, but not limited to, liposomes (Figure 5), solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles. As of 2012, the global nanomedicine market stood at about 78 billion dollars (Viseu, 2022). In 2022, this stands at 159.43 billion dollars and this is expected to rise to $291.15 billion by 2027 (Market Data Forcast, 2022). This means that the market outlook for investors is bright and attractive and funding may not be a problem. Moreover, any investment in health is an economic investment because of the intricate relationship between health and the national economy.

Development of nanomedicine-based therapeutics against a variety of viral infections, including hepatitis B virus, human immunodeficiency virus, respiratory syncytial virus, influenza virus, and coronaviruses are already known. The attraction for the use of nanoparticles in nanomedicine is in their unique physicochemical properties: the small size which is also the scale of many biological mechanisms in the human body allows them to easily cross intracellular barriers/membranes to access new sites of delivery and interact with a variety of biological components of similar size, interacting with DNA or small proteins at different levels, in blood or within organs, tissues or cells; the surface polarity which can be modified by various functional groups to increase their binding efficacy and stability and reduce aggregation and precipitation (Dutta, 2022, ETPN, 2022).

Metallic nanoparticles such as iron-oxide, copper-oxide, and silver nanoparticles with antiviral properties can be used to entrap and inactivate SARS-CoV-2. These particles disrupt the cell membrane, damage proteins, and DNA, form free radicals, inhibit biofilm formation, and/or exert heavy metal toxicity in viruses thereby destroying the viruses. Iron-oxide nanoparticles have been shown to interact with the spike protein of SARS-CoV-2, altering its structural conformation. So have lipid nanoparticles loaded with SARS-CoV-2-specific small-interfering RNAs (siRNAs) for targeted delivery to the lungs to suppress viral replication and prevent the establishment of infection and disease. Poly lactic-co-glycolic acid polymer-based nanosponge coated with human lung epithelial cell and macrophage membrane to mimic the cellular physiology required for SARS-CoV-2 host cell entry is a good target for SARS-CoV-2. The binding of SARS-CoV-2 to this synthetic cellular nanosponge leads to the neutralization of the virus and infection of cells is blocked.

Apart from targeting SARS-CoV-2 directly, nanoparticulate nanomedicines can also be used to modulate the immune system in such a way that hyperinflammation and the consequent cytokine storm in COVID-19 patients can be prevented. Graphene-oxide nanoparticles are known to increase the levels of macrophages and T cells thereby enhancing adaptive immune response and viral clearance. Similarly nano-diamonds induce anti-inflammatory macrophages to reduce hyperinflammation. In the same way, carbon and graphene sheets can be modified to eliminate cytokines and interleukins (pro-inflammatory mediators) from the blood (reviewed by Dutta, 2022).

Concluding remarks and moving forward

Natural products represent a large reservoir of chemicals from which new chemical scaffolds can be obtained for the discovery of novel drugs, not only for COVID-19 but for other infectious diseases, including emerging and re-emerging diseases. Monotherapy in which one drug to one target approach is used is no longer a viable option. A strategic therapeutic approach in which a multicomponent and multi-target pan-viral therapy is developed for the treatment of COVID-19 and associated complications and future viral pandemics is a very compelling option and the drug discovery and development community should embrace it. Nanomedicine presents an excellent platform to achieve this as different drugs each with different targets can be loaded into a drugs-nanoparticle complex formulation as shown in Figure 5. This is also useful for the development of multivalent vaccines for activity against existing human pathogenic viruses and those that may emerge or re-emerge in the future. Plant molecular farming is undoubtedly a very useful technology for relatively cheap, fast, and large-scale production of biopharmaceuticals and relevant stakeholders should ensure that the required infrastructure for this is put in place in countries across the world for pandemic preparedness. After the “hype” about edible vaccines in the 90s,

it is now becoming a reality and should be vigorously pursued for COVID-19 vaccine production particularly in poor resource settings, and quick response in the future should there be an outbreak of a pandemic. Edible vaccines will be an important strategy to significantly reduce vaccine hesitancy. However, worries about GMO foods are a potential problem but strong advocacy may be able to remove or significantly reduce these worries. Finally, it is important to sustain and improve on the coordinated global effort by all stakeholders in the development of COVID-19 therapeutics so that the several decades of accumulated knowledge from previous epidemics and pandemics can be effectively combined with the tremendous advances in science and technology to develop therapeutics of the present and the future.

Author contributions

NU wrote the Biocomputing and Bioinformatics section while EO wrote the other portions of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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