Drug Discovery and Development - with Special Focus on COVID-19

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Abstract: From target identification to product launch, drug discovery and development is a lengthy process. Each stage is divided into sub-stages, each with its own set of tests and trials. Each year, hundreds of medications are approved for sale, with 10,000 candidates being denied. Advances in technology and a broadening of knowledge in numerous domains ensure that safer drugs are produced. The scientific community is working to develop treatments and vaccinations to combat the present COVID-19 pandemic. COVID has impacted people's lives in a variety of ways, from a market in China to isolated slums in our own country. We hope to find a cure soon thanks to ongoing vaccine phase II and III trials.

Keywords: Drug Discovery, SARS, MERS, SARS-Cov2, drug target, vaccine, clinical research

1. Introduction

Diseases are unavoidable and have been in human life since the dawn of mankind. A disease is any adverse divergence from an organism's normal structural or functional condition, which is usually accompanied by particular signs and symptoms and differs from physical injury in origin. [1]

Drug discovery in the modern era is a crucial idea in the fight against sickness. It's a complicated procedure that takes several years to create and costs billions of dollars. It might take anywhere from 10-15 years for a new drug to reach the market after years of research and development. Drug discovery and development is the most important step of the drug life cycle, requiring collaboration and interaction between several departments, typically between academia and industry [2]. From target to market, drug discovery and development undergoes series of trials and test to ensure maximum safety and efficacy.

A new viral disease was discovered in a wholesale market in Wuhan, China's southernmost province, at the end of 2019. The World Health Organization (WHO) designated the virus to be a novel coronavirus strain on January 7, 2020, and named it 2019 COVID-19. SARS-CoV, a coronavirus, first appeared in different parts of the world in 2002, causing severe acute

respiratory syndrome and killing approximately 900 individuals. MERSCoV infections first appeared in 2012, resulting in 1401 cases, with approximately 500 deaths[3]. All of these incidents demonstrate that coronaviruses are a constant threat to humans and the economy, as they appear out of nowhere and have catastrophic repercussions.

Coronaviruses are a group of enclosed, non-segmented, positive-sense single-strand RNA viruses with genomes ranging from 26 to 32 kilobases in size. There is no effective vaccination to treat or inhibit Covid-19, and countries all over the world, including India, are racing to develop one. Several candidates are in the works, with promising outcomes thus far. This article will focus on the complete drug development process, covering the many phases involved from the moment a molecule is recognised as a drug candidate until the time it is approved for use.

2. Drug discovery and development

Introducing a drug to the market is a complex, expensive, and time-consuming process. It takes 12-15 years from the identification of the target to launching the product and costs the pharmaceutical industries billions of dollars. Each year dozens of new drugs are available in the market. But in their wake, thousands of candidate drugs are rejected. [4]

Drug discovery is patient-focused, to help them overcome disease and improve their quality of life. The goal of the drug development process is to provide patients with effective, safe, and low-cost medicines as quickly as possible. A drug undergoes a succession of rigorous testing and analysis to ensure its efficacy and safety, from target discovery to FDA review and market introduction. Before making it available to patients, adverse side effects, the proper dosage for high therapeutic results, and the administration route are all understood.

According to Intercontinental Marketing Services, global pharmaceutical sales in 2012 were predicted to be $965 billion, with the majority of sales occurring in North America, Japan, and China.[5] The irony of this innovation investment is that, despite various targets, increased funding, and improved technology, the number of compound approvals has been falling. Between 1995 and 1999, the average annual number of novel molecular entities (NMEs) approved in the United States was 37.6; between 2004 and 2012, it was 26[6].

The search for a prospective "druggable" target whose activation or inhibition can cure an illness begins with the identification of a potential "druggable" target. In the search for new targets, bioinformatics, genetic association research, and phenotypic screening are all useful methods. Once a target has been discovered, researchers will look for a molecule or compound that can effectively operate on the target. They go through additional validation methods after target selection, which leads to the lead discovery phase. During lead discovery, a comprehensive search is conducted to identify a drug-like small molecule or biological therapy, referred to as a development candidate, that will progress through preclinical testing, clinical development, and, if successful, commercialization[7].

The pharmaceutical sector is currently confronting obstacles such as identifying new therapeutic targets, obtaining government permission, and implementing innovative technologies in drug discovery and development. In order to eradicate diseases all across the world, advancements in technology and the pharmaceutical sector are required. Medication discovery nowadays entails hit screening, medicinal chemistry, and hit optimization to limit potential drug adverse effects[8]. Every country has its own regulatory authority, which is known as the US Food and Drug Administration (FDA) in the United States and the Medicines and Healthcare Regulatory Agency (MHRA) in the United Kingdom.

2.1. STEP 1: Discovery and Development

2.1.1. Target Discovery: Identification and Validation: Target discovery aids in the identification of an appropriate target whose activation or inhibition can cause or prevent a disease. A target is frequently a nucleic acid sequence or protein that plays a role in gene regulation or intracellular signalling [9]. The study target must be safe, effective, and "druggable," meaning that its activity can be controlled by an external substance. A medicine must be able to bind to its target and impact its function in some way. Enzymes, cell signalling receptors, structural proteins, and regulatory factors such as protein kinases are the most prevalent targets. Nucleic acids, such as mRNA, lipids, and carbohydrates are among the other targets that are increasingly being studied[10]. GPCRs (G-protein-coupled receptors) are one type of pharmacological target. The different technologies utilised to discover a prospective target include genomics, proteomics, genetic association, and reverse genetics, as well as clinical and in vivo research. Good target identification and validation guarantees a secure relationship between the target and the disease, as well as aiding in the cure of the disease by modulation of the target. Researchers have traditionally used natural substances from plants, fungi, or marine animals as the basis for these candidate medications, but scientists are increasingly harnessing knowledge gathered from genetics and protein research to design novel molecules using computers. There could be as many as 10,000 chemicals evaluated, with only 10 to 20 potentially interfering with the illness process [7]. Most of the targets are originally identified using public databases and scientific literature such as Drug bank and TTD. Target deconvolution or target discovery can both be used to identify a target.

Deconvolution of the target begins with a medicine that looks to be effective, and the target is then identified retrospectively. There are several approaches to achieve target deconvolution, including affinity chromatography, expression cloning, protein microarray, reverse transfected cell microarray, and biochemical suppression.

The phenotypic method to drug development is part of the target deconvolution field, and it entails exposing cells, isolated tissues, or animal models to small compounds to see if they have the intended impact, which is manifested as a change in phenotype [9]. The capacity to find molecules and pathways that were previously unknown to be involved in a disease is the most significant benefit of phenotypic screening.

A novel target is discovered in the target discovery procedure in order to create a new drug. Each candidate target in target-based screening is validated using a variety of experimental methods, including modification of the target, to show that it is directly or indirectly implicated in the disease or condition of interest [9].

2.1.2. Hit discovery and lead identification: To find naturally occurring chemicals that can be repurposed as medications, screening experiments are carried out. Synthetic chemicals can also be created to interact with the predicted target while without interfering with other biological processes. In addition to determining the drug's mechanism of action, preliminary safety tests are carried out in cell culture. The drug's pharmacokinetics and pharmacodynamics — how it is metabolised and how it affects various biological functions — are being investigated [9]. During the hit discovery and lead identification phases of the drug discovery process, compound screening assays are created after target validation. The primary goal is to discover compounds that interact with the drug's target. Assays are test methods that evaluate a new drug candidate's efficacy and potency at the cellular, molecular, and biochemical levels. A chemical that interacts with the target of interest is referred to as a "hit" [7]. By refining the screening criteria to pick more promising molecules for subsequent development, lead compounds are selected from a succession of "hits." Off-target effects, as well as Physico-chemical and ADME (absorption, distribution, metabolism, and excretion) properties, may be screened for in secondary tests used for lead selection [9]. In a screening library, there will be 30,000 to one million compounds, of which 10,000 will interact positively with the target of interest. Small molecule hits from an HTS are reviewed and optimised in a restricted way into the lead compound in the hit to Lead process. The hit-to-lead process aims to boost a compound's potency, selectivity, and physicochemical qualities (such as solubility and stability) in preparation for in vitro and in vivo testing [8]. A promising lead should be taken into the bloodstream, delivered to the site of action, efficiently digested, and eliminated from the body. To determine the toxicity of a substance, cytotoxicity and genotoxicity tests are performed. The lead optimization procedure is then applied to these compounds.

2.1.3. Lead Optimisation: The hit-to-lead method produces lead compounds that are changed to boost efficacy and potency while reducing negative effects. Lead optimization designs the drug candidate by conducting experimental testing utilising animal efficacy models and ADMET tools. The goal of lead optimization is to improve the most promising compounds' efficacy, reduce toxicity, or boost absorption. Properties of lead series and biological activity are studied using in vitro and in vivo tests. To quickly evaluate and move the compounds, and the series, toward the optimal candidate profile, rigorous and important data must be gathered in a precise, timely manner. The identification of a preclinical candidate is the result of lead optimization [11]. Drug development begins when a lead chemical for a drug candidate is discovered.

2.2. STEP 2: Preclinical Research

Preclinical studies entail comprehensive testing on animal models to determine efficacy, safety, toxicity, and pharmacokinetic (PK) information. At this point, the drug's side effects are being monitored. Preclinical research isn't usually extremely long. These studies go into great detail about dose and toxicity levels. Researchers compile and examine their findings after completing a preclinical test. Preclinical studies entail comprehensive testing on animal models to determine efficacy, safety, toxicity, and pharmacokinetic (PK) information. At this point, the drug's side effects are being monitored. Preclinical research isn't usually extremely long. These studies go into great detail about dose and toxicity levels. Researchers assemble and examine their findings after completing a preclinical test to determine whether the medicine should be tried in humans. To achieve trustworthy results, preclinical research must follow Good Laboratory Practice (GLP) guidelines, which are needed by authorities such as the FDA before filing for approval as Investigational New Drugs (IND). The relationship between a drug's concentration in the body and its biological action is described by pharmacodynamics[12]. The therapeutic index of a medicine is determined by pharmacodynamics, which describes the quantity of dose that causes toxicity as well as a therapeutic benefit. Changes in plasma concentrations over time as a result of absorption, distribution, disposition, metabolism, and excretion are described in pharmacokinetics (ADME). For later rounds of the clinical study, ADME profiling is crucial for determining the dose range and administration schedule [11]. In vitro, in vivo, and, more recently, in silico models with controlled dosages are used in preclinical trials.

Because in vitro investigations use cell, tissue, or organ cultures, or focus on specific cell components such as protein, they are quick, simple, and cost-effective. Isolated cells in a Petri dish may behave differently than cells in the body, where they interact with millions of others. As a result, in vitro models are unable to anticipate results, necessitating more sophisticated preclinical testing.

In vivo research for the discovery of novel medications involve animal models. This study [13] uses animal models that replicate human circumstances, such as knockouts or genetically engineered mice. In vivo studies are carried out in rodents such as the mouse, guinea pig, hamster, and non-rodents to comply with FDA regulations. Primates such as monkeys, apes, and others are occasionally utilised to study bigger compounds. Mice are the most commonly utilised animal models because 99 percent of all mouse genes overlap with human genes. To avoid sex-based prejudices, the most appropriate animal must be used. A medication could cause a male animal to behave differently than a female. The selection of relevant animal models is based on a number of factors, including species-specific physiology, similarity of the target organ, metabolic pathways, and financial, regulatory, and ethical considerations [11]. Animal testing, like human testing, is rigorously controlled in most countries and requires clearance from local ethical review committees to ensure that the experimental subject is not harmed unnecessarily. The IACUC, as well as other international and domestic bodies, regulates animal use in drug development and ensures that specified rules are followed. Skin equivalent systems, quantitative structure-activity-relationship (QSAR),

virtual trials, patient-drug database research, stem cell and genetic testing, and MRIs, CT scans, and micro-dosing are all alternatives to using animals [8]. In silico experiments are now more relevant than in vivo and in vitro research, thanks to advances in bioinformatics and computer technology. In silico investigations employ computer modelling to see how a candidate might react in in vitro and in vivo tests. These computer simulations necessitate specialist understanding in biochemistry and molecular biology in addition to technology requirements [11].

Despite the best attempts to find the right animal model, medicines often have different pharmacodynamic features when given to humans. As a result, one out of every five preclinical medications is approved for clinical usage. [4]

2.3. STEP 3: Clinical Trials

Following the completion of preclinical research, researchers move on to clinical drug development, which involves studying the effects of medications on humans using human volunteers. Preclinical research can help answer basic issues about a medicine's safety, but it can't replace studies of how the drug will interact with the human body. The term "clinical research" refers to human studies or trials [14]. An Investigational New Drug (IND) must be submitted to the FDA before clinical studies can commence [15]. The FDA undertakes a thorough assessment of the IND and responds within thirty days. The FDA either accepts the IND for the start of the clinical trial or places it on hold until more information is received. It is uncommon for FDA to cancel an IND submitted because to the high expenditure of time and money up to the preclinical stage. Before starting a clinical trial, the FDA usually makes suggestions for improvements. Clinical trials identify the ideal pharmacological dosage for a positive therapeutic effect. The clinical trial is divided into three stages. Before moving on to the next phase, researchers must submit their report to the FDA after completing each phase.

2.3.1. Phase 1: Small doses of medicines are given to 20-100 healthy participants during phase 1 of clinical trials. This phase aids researchers in determining the drug's safety, pharmacokinetics, absorption, metabolism, and elimination effects on the human body. There are adverse effects to be aware of, as well as safe dosage limits. The phase takes anywhere from a few months to two years to complete. Around 70% of the compounds will be deemed safe enough to move through to phase 2 trials. Carcinogenicity testing on mouse animal models, specifically the Tg rasH2 mouse, which is used to predict the carcinogenic risk of substances, is also done during this phase. The time required for carcinogenicity testing was reduced from two years to six months using this methodology [13].

2.3.2. Phase 2: Phase 2 evaluates the drug's safety and efficacy in a group of 100-500 patients over a period of months to years. These people have the ailment that the new medicine is supposed to help with. Phase 2 will identify the most effective dose and administration route (oral or intravenous), as well as the optimal dosing interval and product safety [8]. In this phase, adverse events, side effects, and efficacy are all monitored. Because of safety concerns or unacceptable side effects, the majority of medications fail in phase 2 clinical trials.

2.3.3. Phase 3: Only about 12% of medications make it past this stage. To acquire statistically significant data, researchers test the medication on 1000-5000 patients across several international sites. If the drug successfully completes this phase, data from a larger number of patients is used to determine the proper dose for a high therapeutic effect in the future. In preparation for full-scale production after drug approval, phase 3 studies necessitate substantial collaboration, organisation, and coordination and control by an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB). Phase 3 confirms the results of phase 2 in a broader population and determines the most appropriate dose scale. In phase 1 and 2 trials, a larger number of participants aids in the detection of any undetected side effects. Good Clinical Practices (GCP), the Health Insurance Portability and Accountability Act (HIPAA), and adverse event reporting to the IEC/IRB all govern and safeguard the safety of human patients throughout clinical studies [8].

Despite all of these efforts, medicine will fail 10% of the time at this level. A pharmaceutical company can obtain FDA approval to market a medicine once phase 3 is completed.

2.4. STEP 4: FDA Review

Following the completion of clinical studies, the FDA receives a New Medicine Application (NDA) for review and approval of the drug. In the United States, the application procedure for marketing permission is known as a New Drug Application. This process is known as Marketing Authorization Application (MAA) in the European Union and other nations [9]. Only if the medicine has been shown to be safe and effective in clinical trials can an NDA be filed. This will necessitate a large amount of data, including information on all phases and trials, preclinical and clinical results, animal models, safety precautions, and potential drug interactions. The FDA examines the study's findings before deciding whether or not to approve it. Before a decision is made, more research or an expert advisory panel may be required. The review team has 6 to 10 months to make a decision on whether or not to approve the application. A number of factors can cause a New Drug Application to fail. Some of them are toxicity effectiveness, PK characteristics, bioavailability, or poor drug performance. When it comes to safety concerns, the FDA has the authority to reject the NDA if toxicity is excessive in animals or human patients. PK characteristics or poor bioavailability due to low water solubility or high first-pass metabolism can also lead a medicine to be rejected by the FDA. Inadequate action duration and unforeseen human drug interactions are two PK explanations of medication failure [13]. When a medicine is approved, the process of "labelling" begins. The grounds for approval and the optimum way to take the drug are accurately and honestly described on the label [14]. Before the product is launched, other actions such as manufacturing scale-up and sterilisation, product storage, shipping and distribution arrangements, production staff, and quality team availability must be started.

2.5. STEP 5: Post-Marketing Monitoring

While a medicine is on the market, pharmaceutical companies conduct post-marketing surveillance. The term "post-marketing safety surveillance" refers to the monitoring of a drug after it has been approved and released into the market [9]. Unexpected adverse effects and

potential other uses of the medicine have been observed in the population following the debut of the product. Clinical studies give valuable information on safety and efficacy, but they have some drawbacks when applied to a larger population. As a result, a product can only be considered safe after months or years on the market. Clinical trials are useful in a variety of ways. Following drug approval and production, the FDA mandates drug companies to use the FDA Adverse Event Reporting System (FAERS) database to track the medicine's safety. FAERS assists the FDA in the implementation of its post-market safety surveillance programme. Manufacturers, health professionals, and customers can all report concerns with licenced pharmaceuticals using this service [8]. When the FDA receives reports of a prescription problem, it corrects the information and adds further caution as well as other measures to address more serious issues.

2.5.1 Phase 4: After the medicine has been approved, phase 4 studies are carried out. Thousands of volunteers will be diagnosed with the illness for which the medicine has been licenced. Phase 4's key goal is to learn more about the drug's long-term risks and other benefits as it becomes more commonly used. The data gathered in the "real world" will also aid in the drug's development.

Only 25 of the 25,000 chemicals chosen are tested on people, and only 5 of them make it to market, with only one recouping the investment. To better mirror the complexity of human disease pathways, current standard preclinical techniques must be improved. It takes a long time to find and develop a new drug. A drug undergoes a sequence of tests and alterations from the laboratory to our bedside to ensure optimal safety and efficacy. Due to a variety of reasons such as technology advancements, emerging new diseases, and so on, the drug development process has always been large and dynamic. Safety and efficacy should never be sacrificed during the development of a drug, regardless of how long or how much time it takes. Drug research and development will become considerably easier in the future, thanks to new technologies.

Modern Technologies in Drug Discovery

The process of discovering new candidate pharmaceuticals is known as drug discovery. It entails a wide range of tasks, including candidate identification, synthesis, optimization, and therapeutic efficacy testing. Drug development might take anything from 12 to 15 years from product identification to commercialization.

The field of drug development is a difficult one. Identification of a new drug, high throughput screening, structure-based drug design, molecular modelling, and translation medicine are all processes in the creation of marketable treatments. Technological advancements are critical in creating pharmaceuticals in a short amount of time. A few technologies that enhance drug discovery and development include high throughput screening (HTS), computer-assisted drug discovery (CADD), and molecular docking.

3.1. High Throughput Screening

HTS is a method of employing an HTS platform to test various pharmaceuticals, mainly drugs. The drug response curves for each molecule examined are created immediately after the screen is completed. A gadget that allows for the rapid testing of a large variety of chemical and biological tests.

It is primarily used in the pharmaceutical sector to rapidly test a large number of biological compounds, which is typically employed in medication development. Because of its speed, efficiency, and low cost, it has acquired widespread acceptance and has become a common method for drug discovery in the pharmaceutical sector. Scientific research and biological testing have both changed as a result of it.

With better efficiency and cheaper costs, HTS intends to screen 1,00,000 or more samples each day. Because of the great sensitivity and speed of assays, HTS is becoming increasingly important. With the latest technologies on the market, it has become a competitive technique. [9]

3.2. Computer Aided Drug Discovery

The imaginative process of generating and designing novel pharmaceuticals utilising a wide range of computational tools is known as computer aided drug discovery (CADD). Another term for computer-aided drug design is in silico drug design.

A drug's development is a lengthy and time-consuming process that takes more than a decade. Computers, on the other hand, are now playing an increasingly crucial role in many research fields and are being utilised to speed up pharmaceutical research. From the first idea to clinical testing, scientists use computers in every phase of medication development. Scientists can develop prospective active candidates more quickly with the use of fast computer systems. Researchers can screen millions of chemicals in seconds using computer-assisted techniques.

CADD is projected to grow as a large technology in today's world as it gains popularity, implementation, and recognition. Researchers are interested in using computational tools to advance drug discovery because CADD identifies the most promising drug candidate by eliminating all unwanted molecules. It decreases the amount of time and money spent on chemical and biological testing. It is distinguished by its speed, cost-effectiveness, time-consuming nature, and automatic nature. It lowers the number of drug discovery failures.

In silico technologies based on knowledge of the target receptor structure or the chemical structure of active small molecules (ligand based) are frequently employed in the early stages of drug development projects for discovering and optimising hit or lead compounds of pharmaceutical research institutes. Computational techniques to drug design include ligand-based and structure-based approaches. It provides useful data on target molecules, lead

compounds, screening, and optimization. The most recent breakthroughs and newly available software tools provide a foundation for creating specificity-required ligands and inhibitors.

3.3. Molecular docking

Molecular docking is a computer-assisted method for simulating the interaction of two or more molecules to produce a three-dimensional structure of an intermolecular complex.

It's utilised to see if the ligand and target molecule could work together as a binding site for two or more constituent molecules with the same structure. During docking, several conformers interact and are compared to one another. The molecules that bind to the target molecules, which are usually tiny molecules, are known as ligands. The receiving molecules, which are mainly proteins, are known as target molecules. It's similar to "lock and key," in which the target has a certain form that corresponds to the shape of the ligand. Essentially, the ligand fits into the target like a key does into a lock.

3. Earlier Coronaviruses: History

Coronaviruses are a large virus family with hundreds of distinct viruses. Bats, chickens, camels, and cats are all affected by the bulk of them. Viruses that infect one species can occasionally mutate and infect another. "Spillover" or "cross-species transmission" is the term for this. Coronaviruses are a type of RNA virus that causes infections in the respiratory tract in birds and mammals. Coronaviridae is a family of Nidovirales that includes these viruses. Because of the crown-like spikes on the virus's outer surface, it was given the name Coronavirus. These viruses have a single-stranded RNA nucleic material with a length ranging from 26 to 32 kbs and are tiny (65-125nm in diameter). [16] Along with infecting birds and mammals, SARS-CoV, MERS-CoV, and the more recent COVID-19 infection infect people. A moderate infection causes the common cold, but severe strains can cause SARS-CoV, MERS-CoV, and the more recent COVID-19 infection. There are no antiviral medications or vaccines available to treat or prevent human coronavirus infections as of yet.

The coronavirus family has its origins on Earth a long time ago. The corona virus was first reported in the 1920s, when a respiratory ailment spread among hens in North America. Two other animal corona virus stains affecting mice were found in the late 1940s. After decades of investigation, the first human coronaviruses were found in the 1960s. In 1965, Tyrell and Bynoe were the first to identify coronavirus, which they discovered in the respiratory tract of a patient who had a common cold. B815, the virus's moniker, was given to it. Almost simultaneously, Hamre and Procknow described a similar virus, which they dubbed 229E [17]. Electron microscope analysis revealed that both viruses had a similar shape and a size range of 80-150 nm. When a group of virologists looked at several strains of human and animal viruses, they discovered the same results. As a result, a new genus of virus was found, and it was given the name "CORONA" because of its crown-like look.

Seven distinct coronaviruses are currently infecting humans. Four are endemic (occurring exclusively in a single group of people or in a specific location) and normally produce only little illness, whereas three are significantly more serious and even fatal, as discussed below. In addition, coronaviruses are commonly divided into three groups, as shown in the table: 1.

Table 1. Category of Human and Animal Coronaviruses

Category	Coronavirus
Group I (α-CoVs)	229E and other similar viruses
Group II (β-CoVs)	OC43
Group III (γ-CoVs)	(IBV) Avian infectious bronchitis virus and other related avian viruses

4.1. Severe Acute Respiratory Syndrome (SARS)

SARS, or severe acute respiratory syndrome, began in small mammals and was later spread to humans. It was the first new disease to develop in the twenty-first century that was both severe and easily transmissible, and it had a clear ability to spread via international air transport routes. SARS was first discovered in Southern China in 2002, and it soon spread over 29 nations in North America, South America, Europe, and Asia. In total, 8422 persons were infected in 32 nations, with 919 (11%) of them dying. [18] Between November 16, 2002 and June 3, 2003, 5328 cases were documented in China, with 349 (6.5%) deaths. in a flash Even SARS is thought to have originated in Himalayan palm civets, yet its cause remains unknown. Fever, chills, and body pains are among the symptoms of SARS, which can progress to pneumonia. SARS infection produces acute respiratory distress (severe breathing problems) and has a death rate of roughly 10%. [19]

4.2. Middle East Respiratory Syndrome (MERS)

A new virus emerged towards the end of December 2012, affecting 2279 people, 806 of whom died. Middle East respiratory syndrome coronavirus was the virus in question (MERS-CoV). This virus posed a significant risk to those aged 50 to 59 years old. MERS began in camels and then spread to humans. The cellular receptor dipeptidyl peptidase 4 was the target (DPP4). [20] Fever, cough, and shortness of breath are common symptoms of this virus, which can lead to pneumonia. MERS has claimed the lives of about three or four out of every ten patients. MERS cases continue to emerge, particularly on the Arabian Peninsula; however, there have only been two confirmed MERS cases in the United States as of 2019, both in 2014. [21]

4.3 SARS-nCoV 2 – THE COVID-19 VIRUS

A zoonotic coronavirus has crossed species to infect human populations for the third time in the last two decades. In Wuhan, China, this virus, also known as 2019-nCoV, was discovered for the first time. Surprisingly, this virus resembles infections caused by the SARS coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). [22] Fever, trouble breathing, and, in the most severe cases, bilateral lung infiltration are signs of viral pneumonia, which are comparable to those of the two previous infective coronaviruses. The fast demise of the public health, clinical, and scientific communities resulted in the identification of the virus and sickness, as well as a grasp of the infection's epidemiology [23]. On the 9th of January 2020, the Chinese Center for Disease Control and Prevention (CDC) confirmed and declared the virus's likeness to new CoV after much uncertainty about the causative agent. 2019-nCoV is said to be identical to SARS-CoV and even more closely related to many bat Coronaviruses, according to reports. The nucleotide alignment suggests that this new virus belongs to CoV group 2B and is 80 percent similar to SARS. SARS-nCoV 2 causes COVID-19, an infectious disease that has now become a pandemic. The COVID-19 virus, according to the WHO, can persist for up to 72 hours on plastic and stainless steel. Furthermore, it can stay on copper for less than 4 hours and on cardboard for less than 24 hours.

4. Differences between SARS-nCoV AND SARS-nCoV 2

Both viruses are members of the same family and hence have a lot in common, aside from their structural similarities, such as the fact that they both infect lung alveolar epithelial cells by receptormediated endocytosis and employ the angiotensin converting enzyme II (ACE2) as an entrance receptor. [24] Despite significant similarities, SARS-CoV and SARS-CoV 2 have a number of differences, which are listed below:

Table 1 Differences between SARS and SARS 2

	SARS-CoV 2	**SARS-CoV**
First detection place	Wuhan, China	Guangdong, China
Incubation Period	2-10 years (mean of 4-5 days)	1–14 years (mean of 5.1 days)
Mortality	4.6%	10.8%
Median Age	59 years (range between 15 to 89 years)	35 years (range between 0 to 92)
Male to female ratio	2.7:1	1:1.25
Deaths	649K and still growing	916

R_0	1.4 to 2.5 (median: 1.95)	3
Intestinal symptoms	Rare	20-25% of cases

Table 2 shows that SARS and SARS 2 have differing incubation periods of 5.1 days and 4-5 days, respectively. Thus indicates that the time between being exposed to an illness and experiencing symptoms in the human body is this long. The COVID-19 virus has a lower fatality rate than SARS because SARS-CoV was highly lethal but not very transmissible, which is why it did not trigger a pandemic at the time.

The R0 value, commonly known as the 'Reproduction number,' determines how contagious and infectious a disease is. It indicates the average number of people who will become infected with an infectious disease after being exposed to one person who has the condition. As a result, the R0 with a median of 3.28 shows that each patient infects an extra 3.28 persons. [25]

Fever, cough, headache, shortness of breath, and breathing difficulties are common early signs of SARS and SARS 2. Diarrhea was recorded in roughly 20% to 25% of SARS patients at the time. Intestinal problems are rarely reported in COVID19 individuals. Furthermore, most SARS and COVID19 patients developed lymphopenia and had high levels of proinflammatory cytokines such as interleukin (IL) 1b and IL6 [26].

Structure and Parameters of SARS-CoV 2

Coronaviruses are RNA viruses that are related to one another. These viruses can cause infections in the respiratory tract that vary from moderate to fatal. It belongs to the order Nidovirals, the coronaviridae family, and the coronavirinas subfamily. The method of phylogenetic clustering further divides it into alpha, beta, gamma, and delta Coronaviruses. Its genomic material is single-stranded RNA with a size range of 26-32 kilobases. To enter the host cell, these viruses bind to receptors on cell membranes. By modifying the genomic sequence within the cell, they take over the machinery and make viruses. They reproduce in order to produce a vast number of copies. This enormous number of copies then impacts other cells, causing serious changes in our body's respiratory organs. Accessory proteins found in Corona do not help with replication. Corona's genetic material is protected by a helical symmetry nucleocapsid. They have distinctive club-shaped spikes that help Coronaviruses adhere to the cell receptors of their hosts.

SARS-CoV-2 is a coronavirus with a genome of 29,903 bytes of single-stranded RNA (ss-RNA). Beta-Coronaviruses typically create an 800 kDa polypeptide during genome transcription. This polypeptide is broken by proteases to produce a variety of proteins. Papain-like protease (PLpro) and 3-chymotrypsin-like protease are responsible for the proteolytic processing (3CLpro). The 3CLpro cleaves the polyprotein at 11 different places, resulting in a variety of non-structural proteins that are critical for virus particle replication [27]. Multiple sequence alignment revealed that 3CLpro was preserved with 100% identity across the entire SARS-CoV 2 genome. The SARS-CoV-2 3CLpro polypeptide is 306 amino

acids long, has a molecular weight of 33,796.64 Da, and a GRAVY score of 0.019, according to the study. As a result, the protein is classified as a stable, hydrophilic molecule capable of forming hydrogen bonds [28].

Target Cells

Data was retrieved from human protein databases to reveal SARS-CoV 2 neurovirulence and ACE2 expression in neurological tissue. Literature and mammalian tissue expression databases provide the majority of evidence for ACE2 expression in the brain. As a result, the neurotropic effects of SARS-CoV-2 have been investigated, as well as its contribution to the morbidity and death of COVID-19 patients.

The brain has ACE 2 receptors, which can be found on glial cells and neurons, making them a possible target for COVID-19. The role of SARS-neurotropic CoV-2's potential in patients is still unknown. The 2019-nCoV spike protein ectodomain had a 10–20-fold higher ACE2 binding affinity than the SARS-CoV spike protein. [29]

The cribriform plate of the ethmoid bone has a systemic circulation that might lead to brain involvement. One of the characteristics that may increase the interaction of the COVID-19 virus spike protein with ACE2 produced in the capillary endothelium is the slow movement of blood inside the microcirculation. Despite the fact that cerebral damage may cause COVID-19 disease, it appears that the overall dysregulation of homeostasis caused by pneumonic, renal, cardiovascular, and circulatory damage is what causes COIVD-19 to be fatal in patients. COVID-19 viral access to the brain via the transcranial route could have been the situation in a recently described hyposmia patient and COVID-19 cases of abrupt respiratory failure. [30] The virus is thought to be able to go from the periphery to the CNS via retrograde neuronal transport and synaptic connections, particularly through lung vagal nerve afferents. [31]

5. Various Modes of Transmission of Covid-19

Every living thing is currently terrified of the fatal corona virus. Furthermore, an individual has no knowledge how it spreads or what the symptoms are. In general, a virus can be transmitted through direct and indirect contact, droplets that can be sprayed for short-range transmission, and aerosol for long-range transmission. The virus-infected mucus, which contains huge droplets, is a main mechanism of transmission. To avoid the transmission of COVID-19, we must keep a social distance of 6 feet. In the case of air currents, virus-laden little aerosolized droplets can stay in the air for a long period and travel great distances, whereas larger respiratory droplets can only travel short distances and stay in the air for a short time. According to the World Health Organization, respiratory diseases can be spread through droplets of various sizes. COVID-19 is largely transferred among humans through respiratory droplets and contact routes, according to existing data. The SARS COV-2 aerosol can travel a maximum distance of 4 metres (13 ft). The virus can survive in aerosols for up to

three hours. There's a potential the virus will spread if you touch a surface or object that has the virus on it from an infected person.[32]

DURATION OF CONTAMINATION ON OBJECTS AND SURFACES:[32]

- Plastic : up to 2-3 days
- Stainless Steel : up to 2-3 days
- Cardboard : up to 1 day
- Copper : up to 4 hours

It's vital to remember that the identification of RNA in environmental samples using polymerase chain reaction (PCR) or PCR-based assays isn't always indicative of a living, transmissible virus. It can also spread via fomite, fecal-oral, blood-borne, mother-to-child, and animal-to-human transmission.

Hands should be washed often with soap and water or an alcohol-based sanitizer to avoid the current situation. According to reports, the COVID-19 is caused by people talking, shouting, dancing, or singing with their colic in a closed environment such as hotels, nightclubs, worship places such as temples, mosques, and churches, and workplaces where people used to talk, yell, dance, or sing with their colic. During this time, aerosol transmission between people occurs primarily in crowded and improperly ventilated interior areas where the sick person used to come and spend longer periods of time with other people, where it cannot be ruled out. We can't even guarantee that we'll be able to defeat COVID-19 because it can propagate in any case. Hands should be washed regularly and thoroughly, and the mask should be worn at all times while standing at least 1 metre away. People who are asymptomatic can also spread the infection. Infected people can spread the virus even if they don't show any symptoms. Even those who have been diagnosed with COVID-19 but do not exhibit any symptoms must be isolated to restrict their interaction with others. COVID-19 is a new form of disease, according to WHO officials, and they are all eagerly awaiting new information day by day. [33]

The COVID-19 transmission brief outlines how the virus spreads among humans and the implications for preventive measures that must be taken. An individual should always check to see if they are safe, and should always listen to the government and follow the preventive measures to avoid disease. As a result, we are forced to break the chain.

Current Drugs

9.1. REMDESIVIR

REMDESIVIR, also known as GS-5734, is an Adenosine Triphosphate (ATP) analogue prodrug. It has the potential to be employed as an antiviral agent against a range of different

viruses, primarily RNA viruses. It is broken down into its basic active form, GS-441524, because it is a prodrug. REMDESIVIR is being studied as a possible treatment for SARS COV-2, the corona virus that causes COVID-19. On May 1, 2020, the FDA granted it an emergency use authorization. A broad spectrum antiviral prodrug with significant in vitro antiviral activity against a variety of RNA viruses, including Ebola, MERS-COV, and SARS-COV. In human clinical trials, it is now employed in the phase 111 procedure of identifying COVID-19. As an ANTICORONAVIRAL AGENT, it is extremely important. It's made up of a carboxylic ester, pyrrolotriazine, nitrile, phosphoramidate ester, C-nucleoside, and aromatic amine. They're all descended from GS-441524. [34]

The medicine is offered in the form of a 100mg injectable for COVID-19 patients. As these states are the epicentre of the virus outbreak, the business has given 166 medications to Maharashtra hospitals and 53 to national capitals. REMDESIVIR is the only medicine approved for use in the treatment of adults and other paediatric patients who have been hospitalised with COVID-19 infections, whether suspected or proven.

9.2 DEXAMETHASONE

DEXAMETHASONE, also known as corticosteroids, has anti-inflammatory and immunosuppressive properties. According to preliminary studies from the World Health Organization, the medication has been proven to lower mortality by approximately one-third for patients on ventilators and by around one-fifth for persons who merely require oxygen. DEXAMETHASONE was administered as a liquid, pill, or injectable preparation at a count dose of 6 mg per day for ten days. Women who were pregnant or breastfeeding were given randomised prednisolone, a milder corticosteroid with a 40mg dose in the mouth. DEXAMETHASONE has been found as an injectable formulation for the treatment of respiratory distress syndrome in newborns. The WHO has given it their stamp of approval. In comparison to the others, it is generally safe. DEXAMETHASONE has a favourable benefit-risk profile only in patients with severe types of pneumonia, whereas those with non-severe pneumonia have a lower benefit-risk profile. Higher daily doses of DEXAMETHASONE have been used for other indications for a long time and are also safe. DEXAMETHASONE is now available all over the world. It is an off-patent drug that has been used in a variety of forms for many years, including tablets, liquid solutions, and injections. They are both simple to obtain and effective.

9.3.HYDROXYCHLOROQUINE

The 4-aminoquinoline HYDROXYCHLOROQUINE exhibits immunosuppressive, anti-autophagy, and antimalarial properties. It's a chloroquine derivative with anti-inflammatory and antimalarial properties. In systmic lupus erythematosus and rheumatoid arthritis, it is utilised as an anti-rheumatologic drug. This medicine is extremely effective against the erythrocytic forms of Plasmodium vivax and Plasmodium malariae. It is effective against Plasmodium falciparum strains, but not against Plasmodium falciparum gametocytes. The parasite's erythrocytes have been found to take up HYDROXYCHLOROQUINE into acidic food vacuoles. It's a chemotherapeutic drug that's often used to treat malarial parasites that

take the erythrocytic form. This raises the pH of the parasites' acid vesicles by slowly interfering with vesicle synthesis and inhibiting the phospholipid metabolism that must occur. This medicine inhibits the erythrocytic stage of plasmodium formation when used as a suppressive therapy.

Global Efforts on Vaccine

Is India capable of defeating COVID-19? We are all very happy to announce that India is home to one of the top pharmacies on the planet. India supplies over 60% of the vaccines used around the world. India has played a key role in the development of a vaccine to combat COVID-19 and has a large portion of the global effort to create the vaccine. The government, in partnership with business organisations, is attempting to expedite the approval process that is required for the development of a potential COVID vaccine. India is a key player in the development of a COVID-19 vaccine. Many clinical trials are under underway across the country to determine the efficacy of these prospective vaccines. The government has vowed to promote all of the country's basic needs at various levels. In addition, the government will ensure and assist the regulatory process for vaccine development. Companies such as BHARAT BIOTECH and ZYDUS CADILLA have received government approval and are conducting human clinical trials. COVAXIN, a vaccine for COVID-19, was developed by BHARAT BIOTECH and the Indian Council of Medical Research (ICMR). [35] Meanwhile, the Department of Biotechnology has partially sponsored the ZYDUS vaccine known as ZYCOV-D. Furthermore, Serum Institute, a well-known Indian pharmaceutical company, has won a deal with Astra Zeneca, a British pharmaceutical company, to supply one billion doses of the COVID-19 vaccine developed by Oxford University. This vaccine is currently in the third stage of human clinical trials. The Indian government has stated that developing a COVID-19 vaccine is the most difficult task it faces. According to the Director of the Apex Medical Research Institute, the medicine used in the United States was primarily created in India. This alone demonstrates India's importance in the field of pharmacy. [36] People's safety and interests are of paramount significance to the ICMR. They also stated that the Drug Controller General of India has approved 12 clinical trial locations, such as medical institutes and hospitals, for performing different phase trials on humans for COVID-19 vaccine, 'COVAXIN,' based on past clinical research. The ICMR has declared that BHARAT BIOTECH plans to enrol 375 people in the first phase and 750 people in the second phase. We are all waiting for the vaccine to be approved for general use, which is contingent on the results of human clinical trials. The SARS-CoV-2 strain identified by the ICMR was used to develop this vaccine (National Institute of Virology, Pune).

The ASTRA ZENECA, or Oxford vaccine, has showed encouraging results in human testing, and Oxford University officials have stated that they will apply for a permission to conduct studies in India as well. They will conduct trials for the vaccine in India as soon as they receive clearance. The authorities have stated in the present report that they expect to obtain

one billion doses of ASTRA ZENECA, the Oxford vaccine, over the next year. They intend to begin human clinical trials in India in August 2020, and they intend to market these vaccines to India and other low-income countries throughout the world.

Conclusion

We've given you an overview of how drug discovery works and how it gets started in this article. When a vaccine is made, it goes through a lot of steps, which can be dangerous and expensive. It also benefits those who are in need. We can only hope that everyone will be able to resume their usual lives as soon as possible. Let's hoping India recovers quickly from COVID-19. Modern technology not only saves time and effort for researchers, but it also makes other areas of drug discovery easier. Researchers' joint efforts, as well as internet accessibility, will provide them more control over experimental data. It provides a flexible approach to conducting an experiment, which is important in difficult circumstances like the one people are facing today. COVID-19 has caused devastation, and a speedy cure, such as a therapeutic treatment, is required to bring this epidemic to an end. With the support of technology advancements and increasing computer capacity, it has pursued researchers to develop a new medicine for quick antiviral treatment. Many clinical trials are being place at various levels around the world to give the vaccine a name. It is not an exaggeration to argue that the digital world holds the future of drug research.

Declaration

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