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Anti-SARS-CoV-2 Biotherapeutics and Chemotherapeutics: An Insight into Product Specifications and Marketing Dynamics

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Abstract: Chemotherapeutics and biotherapeutics agents have been explored as a potential treatment for COVID-19. This study was aimed to elucidate latest update related to biotherapeutics and chemotherapeutics against COVID-19 and its variants as well as the product specifications and marketing dynamics of its pharmacotherapies. There are several chemotherapeutics that have been studied for the treatment of COVID-19, including Paxlovid (Nirmatrelvir & Ritonavir) fixed dose combination, nirmatrelvir and ritonavir fixed dose combination, Remdesivir (Vekulary/Covifor) fixed dose combination, chloroquine and hydroxychloroquine, molnupiravir, favipiravir, Infliximab (Remsima®) fixed dose

combination tocilizumab (Actimera), casirivimab+imdevimab (Ronapreve) fixed dose combination, ivermectin, methylprednisole. These drugs have been repurposed for use in COVID-19 due to their antiviral properties and ability to reduce inflammation. The COVID-19 death cases have significantly reduced because of tested efficacy of advanced biotherapeutics and chemotherapeutics. As for marketing dynamics, the demand for chemotherapeutics for the treatment of COVID-19 has increased significantly since the outbreak of the pandemic. Hence, the prices of anti-viral and monoclonal antibodies in top COVID-19 affected countries is also presented here. Considering the molecular interactions, therapeutic activity, efficacy, and adverse effects, the USFDA and the WHO recommended the aforementioned drugs. The chances of approval seems favouring biotherapeutics as these have the best characteristics among the chemotherapeutics. Overall, this review contributes to the scientific understanding of the COVID-19. This can help to inform future research and development efforts and contribute to the overall advancement of knowledge in the field of medicine.

Keywords: Paxlovid ; nirmatrelvir and ritonavir; Remdesivir; chloroquine and hydroxychloroquine; molnupiravir; favipiravir; infliximab; ivermectin

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or commonly known as COVID-19 has claimed millions lives worldwide [1, 2]. The coronavirus causing COVID-19 mutated over time, resulting in genetic variation in the population of revolving viral strains across the host. The continuously changing mutations will adversely affect human health and disease progression. Due to this, the drug development for COVID-19 is challenging for scientists and industries worldwide; therefore, medical professionals serve patients with prequalified treatment protocols by using existing therapeutics, including convalescent plasma treatment rather than developing new drugs [3, 4]. With the support of a professional team of methodologists, the WHO 'Guideline Development Group' (GDG) meets regularly to prepare for and review evidence summaries from international clinical trials. The GDG then develops clinical practice recommendations for the use of therapeutics to treat patients with COVID-19 of any disease severity. To improve patient outcomes, it is crucial that WHO-recommended medications are promptly adapted and integrated into the COVID-19 clinical care pathways at both the national and local levels [5-8].

In December 2021, the United States Food and Drug Administration (US FDA) approved the 'Emergency Use Authorization' (EUA) of the antiviral chemotherapeutic drug Paxlovid, along with a few other chemotherapeutics to incorporate in standardized treatment protocols for COVID-19 [9]. The significant concerns raised with chemotherapeutics are due to the potential reactivity to synthetic chemicals. On the other hand, biotherapeutics are made

up of natural agents, which are more effective and exhibit almost no or lesser side effects than chemotherapeutics [9]. Tocilizumab, a monoclonal antibody that inhibits the interleukin-6 (IL-6) receptor activity, was the first biologic agent to be largely evaluated in COVID-19 patients; and was also approved by the WHO for prequalified treatments for n-COVID-19 [10]. Two biosimilars are under clinical trials; one is Celltrion Healthcare's Infliximab biosimilar, Remsima®, and CinnaGen's biosimilar interferon (IFN) β-1a (ReciGen®). ReciGen is an anti-inflammatory drug prescribed for patients with multiple sclerosis. ReciGen® was part of the first published study to evaluate the therapeutic efficacy of Interferon (IFN) molecules in patients with COVID-19 [11, 12] .

Before analyzing the findings of current research work, it is essential to understand the history, structure and morphology of the novel coronavirus (Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), in brief. Investigations associated with the structure and morphology of the novel coronavirus revealed that the viral strain belongs to the oldest group of viruses dates back to the late 1920s rather than a new class of virus. However, there was no evidence of coronaviruses that infects humans until the discovery of human coronaviruses in the late 1960s. Coronaviruses belong to a group of RNA viruses that infects mammals; they cause respiratory tract infections that may last from mild to lethal. Mild illnesses in humans include the common cold and fever [13, 14]. In contrast, lethal varieties are SARS, Middle East respiratory syndrome (MERS), and an ongoing pandemic COVID-19, which can infect the lower respiratory tract and lungs and eventually creates respiratory distress and kill human beings. This virus can commonly infect diarrhea in pigs and cows; hepatitis and encephalomyelitis in mice and rats [15].Meanwhile, the emergence of monkeypox also caused a menace to the public health which casualty is on the rise [16].

Various drugs have been repurposed for use in COVID-19 due to their antiviral properties and ability to reduce inflammation. The analysis revealed that the demand for COVID-19 therapeutics is growing as the COVID-19 pandemic has not subsided yet [2]. Pandemic is rising continuously in some or other corners of the world despite the availability of multiple varieties of vaccines [17-20]. However, the death cases are significantly reduced because of release of advanced biotherapeutics and chemotherapeutics into the market to treat the disease effectively This study was aimed to elucidate latest update related to biotherapeutics and chemotherapeutics against COVID-19 and its variants as well as the product specifications and marketing dynamics of its pharmacotherapies.

2. Literature Search

We performed a comprehensive review of literature from all peer-reviewed journals published since January 2020 when COVID-19 first made the headline. We reviewed the articles from different journal databases like Nature, Lancet, Pubmed, Scopus, Science direct, Bentham Science, DOAJ, Clarivate Web of Science, and many more, used Google translator to translate the foreign language into English. The keywords used for the search include, "COVID-19", "Biosimilars", "Biologics", "COVID-19 treatment", "adverse effects of COVID-19 drugs" etc.

3. Classification

Coronaviruses constitute the subfamily Orthocoronavirinae, in the family Corona viridae with order Nidovirales and realm Riboviria. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of coronaviruses ranges from nearly 26 to 32 kb, one of the largest among RNA viruses. They have characteristic club-shaped spikes that project from their surface, which in electron micrographs create an image reminiscent of the solar corona, from which their name derives. They are further classified into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. α- and β-coronaviruses infect mammals, while γ - and δ - coronaviruses primarily infect birds [21].

3.1. Structure & Morphology

Coronavirus is structurally large and morphologically spherical particles with unique surface projections. The size of each virus particle varies from 50 to 120 nm in diameter. The virus is mainly composed of different proteins which make up the structure and function for the maximum survival rates and viral replication, which are the lipid bilayer viral envelope, membrane proteins, and nucleocapsid proteins [22].

3.2. Structure of a COVID-19 virus

The external envelope of the virus is purely made up of lipid bilayer, which is mainly composed of structural proteins, namely membrane protein (M), envelope protein (E), and functional proteins, namely spike glycoprotein (S). The structural proteins membrane protein (M) and envelope protein (E) form the shape of the viral envelope and maintain a specific size and shape for the identity of the virion. On the other hand, the spike glycoprotein (S) is functionally required for host cell interaction. The nucleocapsid resides inside the envelope, formed by multiple copies of nucleoproteins (N) bound to the genetic material that is the single-stranded genomic RNA. Most coronavirus strains have spike-like proteins called hemagglutinin esterase (HE); these are functional proteins consisting of about 400 amino acids per single peptide chain that helps to interact with host cells and spike glycoproteins [22] .

3.3. Viral Transmission

When COVID-19 infected person coughs, sneezes, or communicate without personnel protective equipments such as nose masks, face shield, hand gloves, etc., the tiny particles known as aerosols carry the viral strains into the environment from their nose and mouth. The healthy person who is in contact with the infected person without social & physical distancing and personnel protective equipments is susceptible to becoming infected by COVID-19. Researchers demonstrated that the viral particles could live in the air for nearly three hours [23].

3.4. Lifecycle

The lifecycle of COVID-19 is a three-phase process. The first phase of the process initiates with the entry of a viral particle into the host cell through cellular receptors on the host cell, followed by several biosynthetic pathways of the virus in the cytoplasm of the host cell with the help of some cell organelles and enzymes in the host cell favoring the biosynthesis of the foreign viral particle. The final stage of viral replication in the host cell ends with the assembly and exit of the new virions through budding [6, 24].

3.5. Viral entry

The infection in the body begins when the virus enters and starts to bind with the host cellular receptors on the cell. The spike glycoprotein (S) located on the virus's surface helps the virus attach the receptors, namely Angiotensin-converting enzyme 2 (ACE2), to the complementary host cell. After successfully attaching the virus to the ACE2 receptor, an enzyme called protease from the host cell cleaves and activates spike glycoprotein (S) attached to the ACE2. When the attachment and activation of the spike glycoprotein (S) are completed, the virus crosses the cell wall and enters the host cell through direct fusion or endocytosis [25, 26].

3.6. Biosynthesis

Upon entry into the host cell's cytoplasm, certain enzymes cleave the virus's membrane and help to release genetic material into it. COVID-19 belongs to RNA viruses, and the RNA of its genome allows it to act like a messenger RNA or mRNA and helps in the translation into polyproteins, namely pp1a and pp1ab, by the host cell ribosomes. These polyproteins undergo proteolysis, which is a hydrolysis reaction of peptide bonds in which complex protein molecules break down into smaller peptides or individual proteins to yield small proteins [27].

3.7. Replication & Transcription

The replicase transcriptase complex is an enzyme responsible for the replication and transcription of the viral genome into genomic RNA and mRNA, respectively, which will enhance the translation process further. The enzyme transcriptase converts the genomic RNA into four mRNAs, which will be translated into respective proteins for packing and assembly. The subgenomic RNA is replicated over time to produce the genomic RNA [27].

3.8. Translation

The four transcribed spike glycoprotein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N) mRNAs then translated into proteins by two different pathways. Nucleocapsid protein (N) mRNA is directly translated into nucleocapsid proteins (N) by attaching with the genomic RNA replicated from the virus's genome. The remaining three mRNA's translated through Endoplasmic reticulum and Golgi complex mediated

biosynthesis. During this process, three mRNA's go inside ER and subsequently with the Golgi resulting in the formation of Endoplasmic reticulum Golgi intermediate complex (ERGIC).

3.9. Assembly and Exit

Assembly is a featured step in the viral life cycle, which is a dynamic process through morphogenetic reactions involving peptide associations between viral genome (N) and core structural proteins. Cellular vesicles help to deliver the viral genome (N) into the core structure. This ERGIC packed with the nucleocapsid proteins (N) is assembled in a vesicle, ready to exit the host cell. The exit of progeny viruses is by means of exocytosis through budding to cross the cell wall once the new virus exits the host cell, which enables viruses to infect other cells in the body [25].

4. Drugs for Treatment of COVID-19

Unfortunately, there is no specific drug available on the market till now to treat COVID-19, except prequalified and emergency authorized medications; due to this, scientists are unable to find the efficacy and adverse effects of these drugs used for COVID-19 treatment. We can estimate the quality and quantity of use for these drugs as these are within our hands. Developing an efficient drug for the treatment of COVID-19 is now a global challenge, but unlike many other diseases, it is a severe pandemic and spreads quickly; thus, there is not enough time to spend researching a new drug instead using the existing drugs. The US FDA approved a few drugs for emergency use authorization, but one does not know the efficacy of these drugs [28]. Developing a new drug for a specific disease takes several years to study the physicochemical properties, efficacy, and adverse reactions. In the COVID-19 case, there is no choice for WHO and USFDA except for the approval of prequalified and emergency use medicines. Here, in this case, those drugs are tested preliminary on the COVID-19 virus and related proteins to determine the activity; once they ascertain the beneficial results, they can be approved for emergency use. Of all the drugs, chemotherapeutics or chemo drugs have more adverse effects than biotherapeutics or bio-based drugs.

Thus, here in this article, we present the drugs available for COVID-19 treatment, which are already approved or under research, and their adverse and positive effects are identified, as summarized in Table 1.

Table 1. Characteristics and summaries of chemotherapeutics and biotherapeutics agents.

No.	Name	Category	Activity	Side effects	Status
1	Paxlovid (Nirmatrelvir + Ritonavir)	Chemotherapeutics (Antiviral)	Protease inhibitor	Alteration in sense of Taste, Diarrhea Increased blood pressure. Muscle aches	Approved
2	Remdesivir	Chemotherapeutics (Antiviral)	Nucleotide analog RNA polymerase inhibitor	Respiratory failure, Electro cardiogram abnormalities, Juandice	Approved
3	Favipiravir	Chemotherapeutics (Antiviral)	RNA dependent RNA polymerase Inhibitor	Diarrhea, Hyperuricemia (elevated uric acid), Reduced neutrophil count, Nausea, Vomiting, abdominal pain	Not Approved
4	Molnupiravir	Chemotherapeutics (Antiviral)	Protease inhibitor	Diarrhea, Nausea, Dizziness	Not Approved
5	Chloroquinine and Hydroxy chloroquine	Chemotherapeutics (Antimalarial)	Lysozomal enzyme Inhibitor	Uncontrolled movements, Deafness, Nausea, Diarrhea, Abdominal cramps, Head ache, Mentalillness, Serious infecton, Skin rashes, Itchiness, Hair loss, Taste loss	Recalled
6	Ivermectin	Chemotherapeutics (Anti parasitic)	Protease inhibitor	Nausea, Vomiting, Diarrhea, Hypotension(low blood pressure), Allergic reactions (itching and hives), Dizziness, Afaxia (problems with balance), Seizures, Coma	Not approved
7	Tocilizunab (Biologic)	Biotherapeutics (Immuno-suppressive)	Interleukin-6 inhibitor	A cough or sore throat, Blocked or runny nose. Headaches or dizziness. Mouth ulcers. High blood pressure. Hypercholesterolaemia (increased cholesterol in the blood)	Approved
8	Infliximab (Biosimilar)	Biotherapeutics (Immuno-suppressive)	Tumor Necrosis is a Factor – alpha (TNF-alpha) inhibitor	Sinus pain, Fever, Cough, Shortness of Breath; High or Low blood pressure, Rash, Itching. Stomach pain	Approved
9	Dexamethasone (Carticosteroid)	Biotherapeutics (Immuno-suppressive)	Human steroidogenic enzyme Inhibitor	Upset stomach. Stomach irritation. Vomiting, Headache, Dizziness Insomnia, Restlessness, Depression.	Approved
10	BioNtech (mRNA vaccine)	Biotherapeutics (Immuno-modulatory)	Proteasome inhibitor	Head ache, Fatigue, Muscle and joint pain, Fever and Chills, pain at the site of Injection	Approved
11	Plasma therapy (Immunoglobulins)	Biotherapeutics (Immuno-modulatory)	Cell proliferation inhibitor	Transfusion related Dyspnea and severe allergic reactions with association bronchospasm	Approved

4.1. Classification of COVID-19 Therapeutics

Drug discovery and development is a complex process that takes decades to develop a branded drug, the reason why most pharmaceutical companies and Research and Development centers develop generic drugs, which are proven to show the efficacy of branded drugs. Based on the structure and nature of the drug classification, the COVID-19 drugs fall into two classes, i.e., Chemotherapeutics and Biotherapeutics (Figure 1). As chemotherapeutic drugs are synthetic chemicals in nature due to their potential reactivity, adverse reactions are mostly expected while using these drugs [29, 30].

On the other hand, biotherapeutics/biosimilars, biologics, and vaccines, derived from natural resources like microorganisms or animals and are generally considered as safe due to their mimicking nature against proteins synthesized in the human body [29, 30]. These products provide cost-effective solutions with minimum adverse effects.

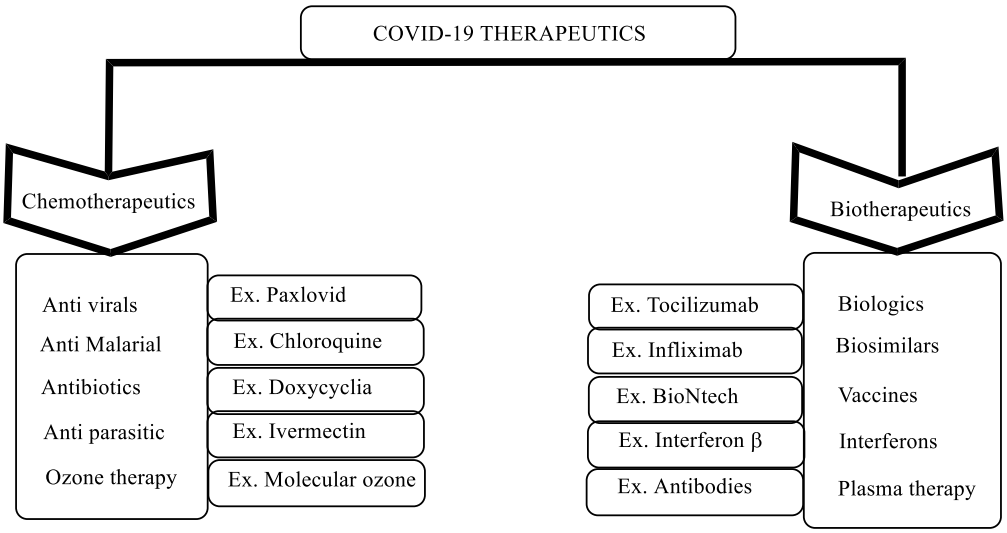

Figure 1. Classification of COVID-19 drugs.

Multiple symptoms are recorded globally for COVID-19 infected patients, so there is a need to use different therapeutics to meet the COVID-19 patient's requirement for better treatment. For example, patients with some strains of COVID-19, it is required to use specific antibiotics such as anti-malarial and anti-inflammatory to get relief from the cold, fever, and pain. So it is a global demand to approve those classes of therapeutics for use in COVID-19 treatment. On 22nd October 2020, US FDA approved the first antiviral drug Remdesivir for the treatment of COVID-19, and it was initially developed to treat Hepatitis-C [31] . However, due to the exigencies of the COVID-19 pandemic, the drug authorities authorized emergency use for treating patients in critical stages. After the approval of Remdesivir®, many therapeutics like antibiotics, hormonal, anti-inflammatory, nutraceutical, etc., were developed and approved. Some are still under the consideration of approval. Considering the extensive use of chemo drugs during API (Active Pharmaceutical Ingredient) manufacturing process, potential impurities, also called related substances, arise from the materials used like raw materials, isomers, intermediates, reagents, solvents, catalysts, etc. Few chemo drugs are

genotoxic and mutagenic, which may alter the DNA sequence and lead to mutations resulting in many life-threatening disorders, including cancer and ulcers [31].

US FDA focused on controlling these GTIs (genotoxic impurities) at the API level. Many methods and techniques were developed from pharmacopeias based on ICH (International Conference on Harmonization) guidelines. In contrast, biotherapeutics were found to be effective with high-quality standards with minimized adverse effects by reduced impurity percentage to meet the global pharmaceutical market demands for better patient care. This review proposes evaluating the effectiveness and drawbacks of chemo and bio-based drug treatments available for COVID-19 [29, 30].

COVID-19 created plenty of opportunities for the pharmaceutical sector in terms of diagnostic, PPE kits, and therapeutics. The pharmaceutical corporations have scaled up their R&D capabilities, production capacities, technology upgradation, and marketing collaboration during the last two years. The rapid recovery of companies to pre-COVID levels, adopting new normals, and adopting preventive measures can slower and minimize the COVID-19 transmission; thereby, COVID-19 therapeutic markets continue to decline further at -44% compound annual growth rate (CAGR). The COVID-19 therapeutics are broadly classified into anti-viral therapies (lopinavir, ritonavir, remdesivir, molnupiravir and Paxlovid), monoclonal antibodies (Lerolimilab, Bamlanivimab+Cetesevimab, Casirivimab+Imdevimab cocktail combinations), cell-based therapies (Mesenchymal stem cells therapy), immunomodulators (prednisone, tocilizumab, methylprednisolone and hydrocortisone) and supplemental therapies (Chloroquine and hydroxychloroquine). The near-term projection for COVID therapeutics is highly contradictory from company to company. The current raising of COVID-19 waves coupled with research in therapeutics, disease awareness, and rising healthcare expenditure will drive the COVID-19 market across the globe (Bloomberg). A group, namely, the Peoples Vaccine Alliance, comprises of 80 low and middle-income (LMI) countries demanding the suspension of intellectual property rights (IPR) for COVID vaccines, tests, and treatment. Another group led by India and South Africa, with the active support of other 100 nations, including the USA and Nobel laureates bidding for IPR weaver, could not make progress due to the blockade of the UK and Germany.

As per the plead from International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the WHO approved seven therapeutic formulations for COVID-19, and the same are produced in 150 manufacturing facilities around the globe [32]. The industry had brought vaccines within 12 months of the declaration of COVID-19 as a pandemic. BioVaxys Technology Corp, Merck, Moderna, Sorrento therapeutics, Pfizer, AstraZeneca, Cipla, Hetero, Dr. Reddy's, Cadila Healthcare, Johnson &Johnson, CanSino, Eli Lilly, Novartis and Glenmark are the leading biotechnology companies offer wide varieties of COVID-19 therapeutics [33]. The Merck and the Pfizer corporations have initiated Voluntary Licensing (VL)/ Sub-licensing model to offer generic therapeutics to the LMIC nations [34]. However, the critics are opposing this model, as it will narrow down the possibility of TRIPS exemption such as compulsory licensing, patent opposition and Bolar provisions. The countries such as Argentina, Brazil, Thailand, Russia, Colombia, Ukraine, Peru, Turkey,

Mexico, and many other countries are excluded from this agreement due to the non-permissibility of generic drugs in their countries due to the statutory provisions. [34]

The price data relating to COVID-19 therapeutics were collected from the top COVID-19 hit countries ever since their introduction into market. The price information published in their national newspapers and official reports are considered. This study has attempted to know the price variations in different countries and their impact on the patients (Table 2). Several drugs of chemo and biological origin are approved, and few are under approval with different activities and different side effects. The above describes all the details about the different drugs for COVID-19 treatment.

Table 2. The prices of anti-viral and monoclonal antibodies in top COVID-19 affected countries.

Nirmatrelvir with Ritonavir	**Remdesivir per vial**	**Molnupiravir**	**Favipiravir/ Course of 122 tabs**	**Hydroxy-chloroquin 200mg (100 tab)**	**Ivermectin (10 tabs)**	**Tocilizumab**	**Casirivimab& Imdevimab**	**Methyl-prednisolone 4mg (10 tabs)**
$529.00	$320.00	$700.00	NAC	$37	$35 (17.5)	$527.00	$2,100.00	$9.00
$18.00	$69.23	$38.46	$20	$9	$5.0	$416.00	$765.38	$0.50
unspecified	NA	$600.00	NAC	$17	$30.0	$500.00	NA	$1.25
$529.00	$390.00	NA	NA	$33	NA	NA	$2,000.00	NA
$530.00	NA	$700.00	NCA	$31	$17.5	$500.00	$2,000.00	NA
$502.50	$390.00	$700.00	NCA	$12	$42.0	NA	$1,500.00	$5.00
$529.00	NA	NA	NA	$37	NA	NA	$2,100.00	NA
NA	$390.00	$700.00	NAC	NA	NA	$500.00	NA	NA
NA	NA	$750.00	$155	$15	$30	NA	$2,730.00	$5.00
NA	$390.00	$20.00	$15	$4	NA	$359.00	NA	NA
$1,000.00	NA	$1,000.00	NAC	$20	$54	$410.00	NA	$5.00

NA - indicates, the prices are not revealed by the public health authorities openly.

4.2. Paxlovid (Nirmatrelvir & Ritonavir)

The Paxlovid (Nirmatrelvir and Ritonavir) is a leading player which can reduce the probability of death rate by 66% in severe COVID patients; hence this drug is an obvious choice for the medical professional in case of severe and high-risk patients (Bloomberg, 2021). US FDA granted EUA for Paxlovid in December 2021 for the COVID-19 treatment. Hence, the US FDA accorded permission to specific pharmaceutical companies to manufacture and market with prior approval from the local regulatory agencies for the quality and efficacy testing to meet the patient's demands. In order to make the drug available in the market, it requires rapid research & development followed by commercial manufacturing until the release of the finished product into the market [35, 36].

The drug maker Pfizer offers Paxlovid by adopting a differential pricing policy based on the nation's economic status, i.e., high-income countries; and low and middle-income

(LMIC) countries. The firm had discussions with 100 low and middle-income (LMIC) countries to sub-license its hallmark drug, Paxlovid, with the support of UN-backed MPP (Medicines Patent Pool) for affordable prices of just below $60 for the entire course (Figure 2) [35, 36]. To bring this humanitarian arrangement into effect, 35 generic manufacturers in 12 countries signed a contract with Pfizer, but this initiative can come into reality from 2023 onwards. Paxlovid is offered to all the top 15 COVID-19 affected countries in the range of $529 to $1000 for developed nations, where the same generic version is manufactured in India and sold for $18, which gives more access to the population. Within 2021-22, Pfizer generated $37 billion and is expected to accrue $22 billion in the current financial year 2022-23 [35, 36].

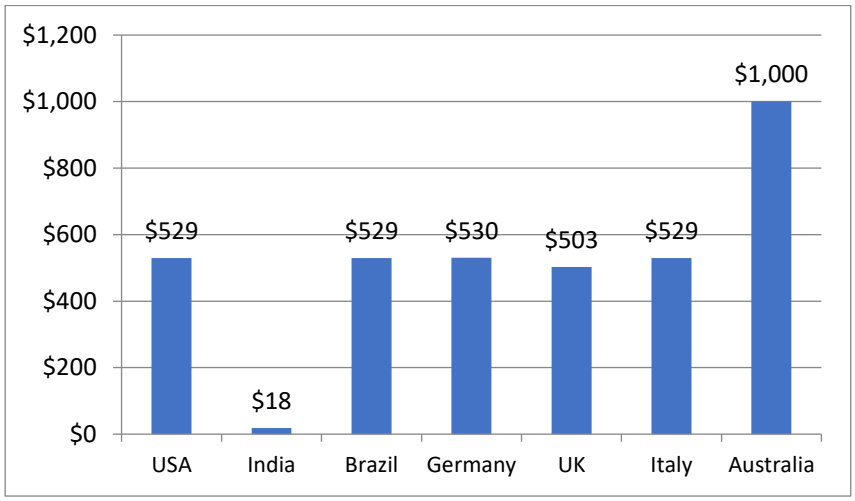

Figure 2. Nirmatrelvir with Ritonavir (Paxlovid) prices in top COVID-19 affected countries.

4.2.1 Chemistry & Pharmacology

Chemically Paxlovid is a combination of two antiviral drugs, Nirmatrelvir and Ritonavir, a co-packaged solid oral investigational medication developed for COVID-19 [37].

4.2.2. Biological activity

Nirmatrelvir is a covalent protease inhibitor that binds directly to the catalytic cysteine residue of the cysteine protease enzyme during translation. In the combination medication Nirmatrelvir+Ritonavir (Paxlovid®), Ritonavir acts to slow down the metabolism of Nirmatrelvir through cytochrome enzyme inhibition, resulting increase of the Nirmatrelvir concentration, thereby enhancing the pharmacokinetics [37].

4.2.3. Adverse effects

As a chemically synthesized drug, Paxlovid® does not have serious side effects. The most common side effects include

- Alteration in the sense of taste

- Diarrhea
- Increased blood pressure
- Muscle aches

4.3 Remdesivir (Veklury)

Remdesivir is a parenteral prodrug medication initially developed to treat Hepatitis-C infection, and later the drug was tested for Ebola and other viral diseases. Due to its broad spectrum of antiviral properties, US FDA & WHO approved under EUA for COVID-19 treatment . However, this drug is mainly used for hospitalized severe COVID-19 infected patients. Remdesivir is widely used in the COVID-19 treatment all over the world [38, 39].

4.3.1. Chemistry & Pharmacology

Chemically Remdesivir is a protide (prodrug of nucleotide) broad-spectrum antiviral therapeutic which can diffuse into the cells. The drug mainly interferes with the action of RNA-dependent RNA polymerase and inhibits the RNA polymerase activity [38, 39].

4.3.2. Adverse effects

The following are the side effects reported for the remdesivir [38, 39].

- Back pain.
- Chest tightness.
- Dark-colored urine.
- Flushing.
- Headache.
- Hives and itching.
- Light-colored stools.
- Nausea and vomiting.

4.3.3. Market status

This drug's patent was awarded to Gilead Corporation initially for treatment of Ebola virus in 2017, but this drug is also used in COVID-19 treatment due to the extended benefits. Remdesivir has not received any recalls from the regulatory agencies except the voluntary recall for a customer complaint of two lots (Remdesivir 100 mg for injection) by the Gilead Sciences Inc. due to glass particulates observed in the product by the customer. The firm investigation confirmed it. The risk involved in such issues results in local irritation and swelling due to the foreign nature of glass particulates. The route of administration of

Remdesivir is parenteral, so the drug directly enters into the bloodstream. If the glass particulates enter the blood vessel, they can travel through different organs and block the blood flow, resulting in stroke and even death. The recall has been completed, and US FDA terminated [38, 39].

The price was offered at $390 per single vial to the USA, Germany, UK, South Korea, and Vietnam. In India, many companies offer the generic version of this medicine at a cheaper price ranging from $40 to $69 (Figure 3). In similar lines to Pfizer's Paxlovid, the generic version of remdesivir was launched within the price range of $390 to 780$ per entire ten days course. The manufacturer Gilead had a tie-up with nine major generic drug makers in Asia. Since the remdesivir is to be administered under medical supervision, the additional hospitalization cost will become an overhead in treatment expenditure [38, 39].

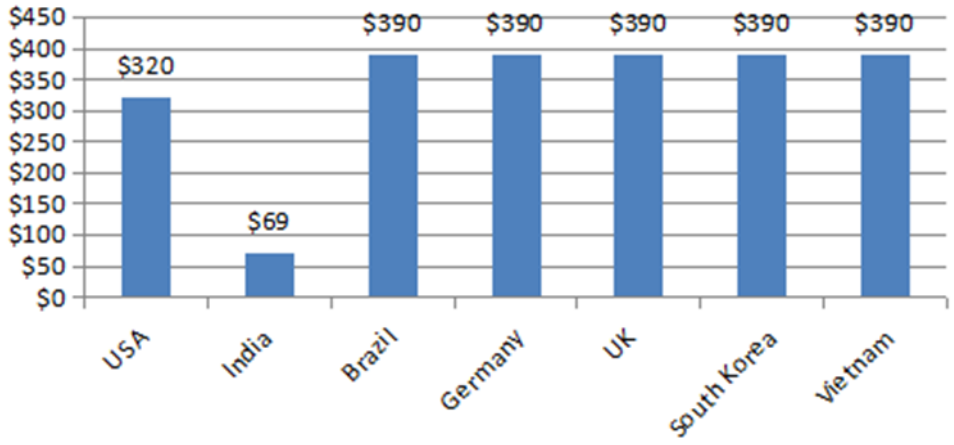

Figure 3. Remdesivir prices/ vial in top COVID-19 affected countries.

4.4. Chloroquine and Hydroxychloroquine

Chloroquine and Hydroxychloroquine are anti-malarial medications used against *Plasmodium vivax*, a parasite that causes malaria. These therapeutics are also used in auto-immune diseases. A combination of these two drugs is used as a treatment for COVID-19 infection, and in fact, neither drug prevents COVID-19 infection. Hydroxychloroquine is a derivative of chloroquine phosphate, which is less toxic than chloroquine. It is used for the treatment of malaria parasites and rheumatoid arthritis. Hydroxychloroquine was approved for medical uses more than 60 years ago. It was used to treat COVID-19 during the initial days of pandemic. It is used as a prophylaxis dosage for health workers and in direct contact with patients suffering from COVID-19. However, the studies revealed that it is effective against COVID-19, and is low effective in preventing COVID-19 transmission, illness, and hospitalization and death events. Therefore, the WHO has not approved hydroxychloroquine for COVID19 treatment [40, 41].

4.4.1. Chemistry & Pharmacology

Both molecules are amino quinoline derivatives that act against malaria, rheumatoid arthritis, and other diseases. Cathepsins are a type of proteases in all animals on the cell membrane. The viral entry into the cell requires the cleavage of spike protein can be accomplished by the cathepsins which are present in the lysosomes. The action of these drugs against cathepsins gives more benefits to the patients of COVID-19 treatment [40, 41].

4.4.2. Adverse effects

Although it is under EUA approval, unlike other medications used in the treatment protocols for COVID-19, hydroxychloroquine has a possible risk of side effects. The clinical research showed the ineffectiveness of these drugs in the treatment of COVID-19. In April 2020, US FDA announced severe heart arrhythmia (rhythm problems) observed in COVID-19 patients treated with hydroxychloroquine. Hydroxychloroquine can exhibit contraindications such as sleep difficulty, hallucinations, paranoia, depression and other problems like kidney injuries and hot rhythm problems [40, 41].

4.4.3. Market Status

As these drugs showed serious side effects in COVID-19 patients, USFDA revoked EUA on 15th June 2020 based on the scientific and clinical data reports. The primary purpose of the revoke is to stop the use of these drugs to minimize the risk of adverse effects specific to the COVID-19 patients [40, 41].

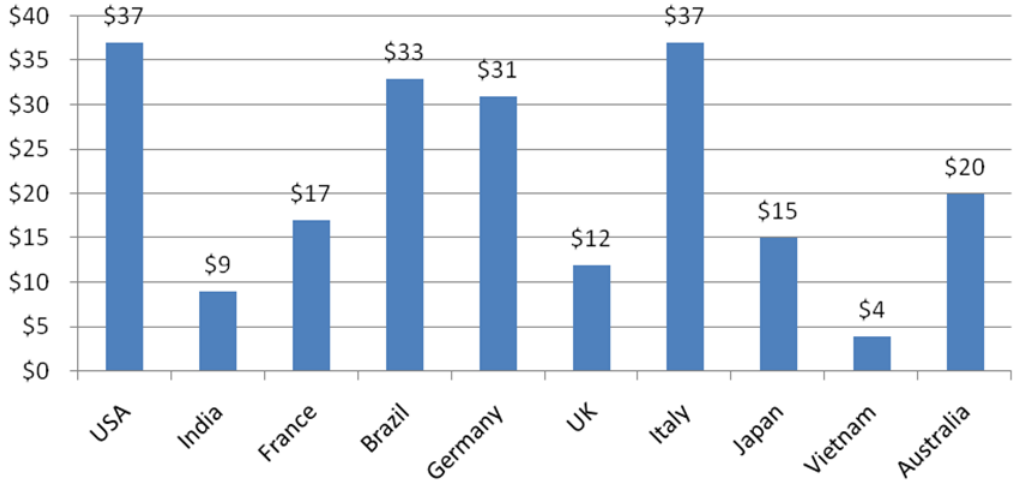

Figure 4. Hydroxychloroquine prices (100 tablets) in top COVID-19 affected countries.

Since hydroxychloroquine failed to show efficacy in trials, the World Health Organization stopped its clinical trials. Since the hydroxychloroquine is an off-patent drug it is available in innovator and generic versions. The innovator version is used in USA, Brazil, Germany and Italy in these countries. Hydroxychloroquine 100 tablets cost $37, $33, $31, $37, whereas the generic version is available in India at $17, UK $12, Japan $15, and

Australia $20, and it is lowest in Vietnam for a meager price of $4 for 100 tablets. During COVID-19 pandemic, non-malaria countries suffered with acute shortage of hydroxychloroquine as it is a prime medication in the treatment of malaria and rheumatic diseases. The hydroxychloroquine is available for sale in almost all countries (Figure 4). Due to the elapsed patent period for this drug, during the first wave of COVID-19, India has played a significant role in exporting hydroxychloroquine to the countries affected severely by COVID-19. Many corporate companies came forward to offer hydroxychloroquine as part of their charity objectives after discontinuing hydroxychloroquine from treatment protocols [42].

4.5. Molnupiravir

The antiviral medication molnupiravir inhibits the RNA viral replication of the infectious viruses in the host cell. The primary purpose of this drug is to treat the influenza virus. Based on the positive results against COVID-19, USFDA granted EUA for molnupiravir to treat COVID-19 patients. This anti-viral drug was developed by Merck Corporation to treat COVID-19. It is the first medication that can be administered orally and taken in isolation treatment. As per the manufacturer's clinical data, Molnupiravir can reduce the probability of hospitalization and death in moderate to severe cases by approximately 50% (Merck, 2021). The patent protection was sought for 20 years; however, the company arranged to reach out the medicines to a larger population at an affordable price [43, 44].

4.5.1. Chemistry & Pharmacology

Like Remdesivir, molnupiravir is also a prodrug of synthetic nucleoside derivative of N-hydroxy cytidine. The drug mainly acts by interfering with the RNA of viruses during viral RNA replication. Molnupiravir can exist in two tautomeric forms one mimics cytidine (nucleoside analogue of cytosine), and another mimics uridine (nucleoside analogue of uracil). Molnupiravir acts by directly attaching to the RNA when the RNA polymerase of the virus tries to copy the host RNA containing molnupiravir, which exists in two tautomeric forms; this causes over mutation of the genetic material, and this effect is known as error catastrophe or lethal mutagenesis [43, 44].

4.5.2. Adverse effects

The common side effects like diarrhea, nausea, and dizziness are reported in the COVID-19 patients. However, if any symptoms of serious allergic reactions are observed, there is a need to seek medical attention [43, 44].

4.5.3. Market status

The antiviral agent molnupiravir is not approved but has been authorized as EUA by US FDA. The approval is purely based on the phase-III clinical trial, and the significant activity of molnupiravir against COVID-19 patients rendered the best marketing strategies. Like Pfizer's Paxlovid, the Molnupiravir drug maker Merck had entered into an agreement

with 105 LMIC nations to supply its Molnupiravir at generic rates (Figure 5). The Molnupiravir prices in all developed nations were in the range of $600 to $1000 per course, which is high in Australia, whereas the same medicine in the generic version is much cheaper in India at $38 and in Vietnam at $20, which is lower than the recommended price for developing countries. France cancelled the order of 50,000 Molnupiravir doses due to the non-conformance of Molnupiravir in reducing hospitalization in high-risk patients by 30% is not demonstrated. The perception of medical and healthcare experts is that the price of Molnupiravir is double that of Remdesivir and 30% higher than the Paxlovid [45].

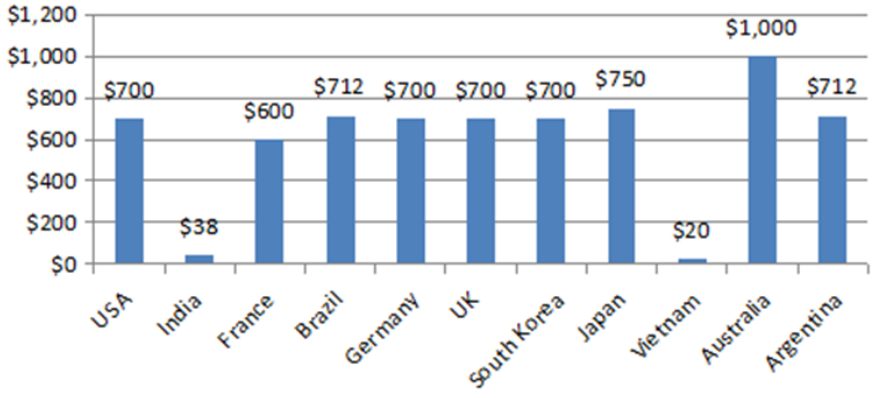

Figure 5. Molnupiravir prices in top COVID-19 affected countries.

4.6. Favipiravir

Favipiravir is an antiviral medication used primarily in the treatment of influenza. US FDA granted permission to favipiravir for COVID-19 treatment under the EUA category [46, 47].

4.6.1. Chemistry & Pharmacology

Favipiravir, a nucleoside analogue, mimics both guanosine (nucleoside of guanine) and adenosine (nucleoside of adenine). It is a selective inhibitor of viral RNA polymerase [46, 47].

4.6.2 Adverse effects

The most common side effects of favipiravir are as follows [46, 47].

- Increased blood uric acid levels
- Diarrhea
- Dizziness
- Elevated Liver Enzymes
- Neutropenia

4.6.3 Market status

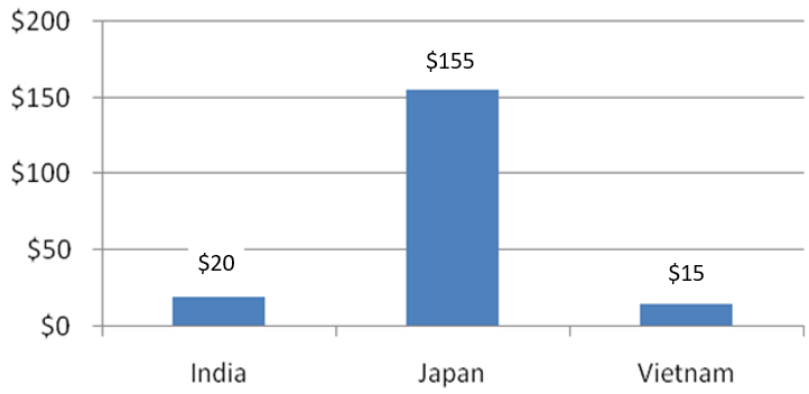

Figure 6. Favipiravir prices (per course) in top COVID-19 affected countries.

This molecule is invented by Fujifilm Toyama chemical and sold under the brand name Avigan. This medicine is efficacy against Ebola virus but unable to demonstrate outcomes in the COVID-19 clinical trials. Except in India, Japan and Vietnam, this drug is basically used for clinical trials. All developed nations have not authorized to use this medicine for commercial use. The prices of favipiravir (Avigan) in Japan is $155, and the same is available in India under the brand name of Fabiflu is below $20 and in Vietnam is $15 (Figure 6) [46, 47].

4.7. Infliximab (Remsima®)

Infliximab is a high molecular weight macro molecular chimeric monoclonal antibody biologic. It is mainly used to treat many auto-immune diseases. The biologic was originally developed in mice as mouse antibodies. However, humans also have some immune reactions to mouse proteins. The mouse monoclonal antibodies were replaced with human antibodies. The US FDA also approves the biosimilars of the biologic. In fact, it is listed in the WHO's list of essential medicines [48].

4.7.1. Structure and activation of Infliximab

The biologic is neither approved nor granted for EUA in treating COVID-19, but the drug is authorized to test on COVID-19 patients in the form of clinical trials. The molecule is in the Phase-III clinical trial, and if it shows efficacy, it would be the future therapeutic option for COVID-19 treatment. Not many side effects are reported for this biologic while used in other treatments [48-50].

4.8. Tocilizumab (Actimera)

When responding to COVID-19, the human body immunologically secretes life-threatening cytokines in the lower respiratory tract. The abnormal release of cytokines (cytokine storming) blocks alluvia, eventually creating acute respiratory distress, leading to

fatality. In light of this biological response to the pathogen, the concept of monoclonal antibody treatment has emerged. Tocilizumab is an immunoglobulin antibody that blocks interleukin-6, used in rheumatoid arthritis to treat the life-threatening cytokine release; thus acute respiratory distress subsided [10, 51]. The drug is patented by Roche Corporation [52].

4.8.1. Chemistry & Pharmacology

Tocilizumab is a humanized monoclonal antibody immunosuppressive drug which targets to Interleukin-6 receptor. The drug is produced by recombinant DNA technology, chemically it is an antibody consisting of 2 heavy chains and 2 light chains with 12 intra-chain, 4 inter-chain disulphide bridges [53, 54].

4.8.2. Adverse effects

Although tocilizumab has some common side effects reported in other infections, there are no adverse effects revealed by the initial research on COVID-19 patients by the researchers [53, 54].

4.8.3. Market status

USFDA granted EUA for tocilizumab to use on COVID-19 hospitalized adults and pediatric patients (2 years and above). This shows that the efficacy of the drug might gain good market and production facilities [55, 56].

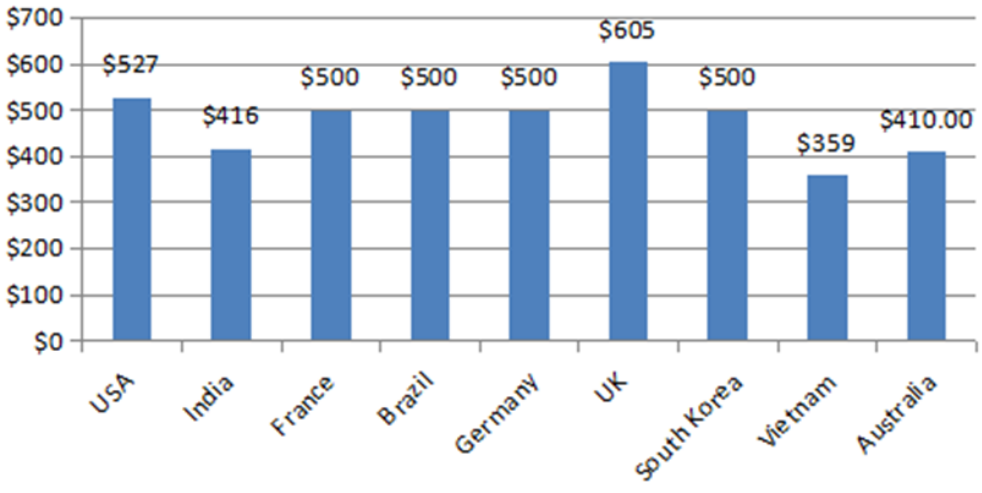

Figure 7. Tocilizumab prices in top COVID-19 affected countries.

The monoclonal drug market continues to dominate in North America, Europe, Asia Pacific, Africa, and the Middle East and Latin American countries. The price of Tocilizumab is close to Paxlovid (Nirmatrelvir and Ritonavir), in the range of $359 to $527 (Figure 7). So far, Tocilizumab is not available in generic form for LMI countries; the lower price version of Tocilizumab is not available in the market; nevertheless, this drug price used to be two to

three times higher than the current price before the COVID-19 pandemic. Due to the higher demand and increased production, bulk procurement of APIs, the manufacturing cost was decreased to $40 but the manufacturer capitalized with 12 times margins due to patent protection. The treatment for Tocilizumab is expensive for LMI countries and patients, but buying this is due to promising results in severe illness patients. Since the drug is to be given along with other immune-suppressant medicines under medical supervision, the cost of hospitalization will have added effect on the patient economic conditions. Hence, the drug maker Roche needs to consider making the drug in a generic version immediately to offer LMI countries [55, 56].

4.9. Casirivimab+Imdevimab (Ronapreve)

4.9.1. Chemistry & Pharmacology

REGN-COV2 is the brand name for Ronapreve, which is a combination drug consisting of two human monoclonal antibodies, namely casirivimab and imdevimab. The combination mainly works against the spike protein of the COVID-19 virus. As a parenteral drug, this combination gives immediate action in the COVID-19 patients who are hospitalized [57, 58].

4.9.2. Adverse effects

From Phase One to Three, there is not even a single death or serious adverse reactions observed with the REGN-COV2, due to the reason the clinical research is still going on for the same [57, 58].

4.9.3. Market status

USFDA limited this combination to the specific variant like Omicron, which is susceptible to this drug. In fact, this combination is approved by the EMA in the European countries to treat the COVID-19 patients and has been issued market authorization for the same. By this date, it is evident that in the future, the use of this combination will bring a huge market demand [57, 58].

Another monoclonal antibodies cocktail demonstrating the promising result is Casirivimab and Imdevimab. This drug is patented by Roche corporation. Out of all the existing therapies, this mAB is expensive; however, quite effective for severe illness patients. The price of Ronapreve ranges from $1500 to $2730 in developed countries, but the same medicine is offered in India for a generic version at $765 (Figure 8). Even though the medicine is lower compared to developed countries, still not accessible to the large populations in LMI countries. Therefore, the generic version must be within the limits of accessibility to reach out to the mass population [57, 58].

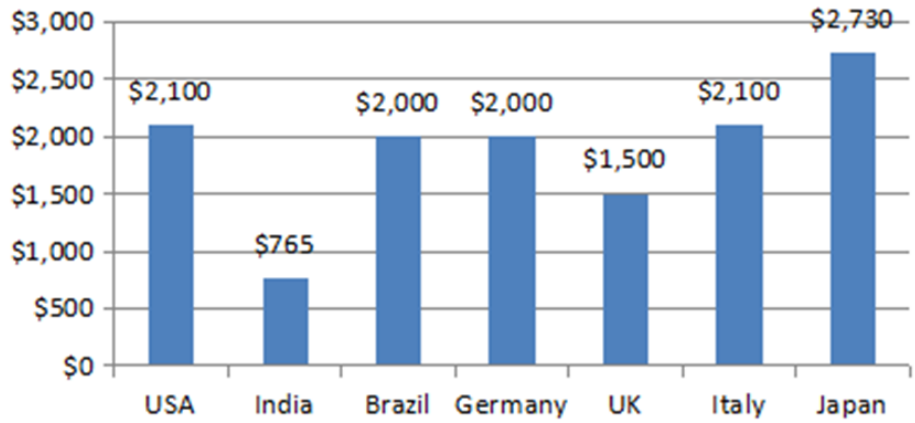

Figure 8. Casirivimab and Imdevimab cocktail prices in top COVID-19 affected countries.

4.10. Ivermectin

Ivermectin was patented under Merck and sold under the brand name Stromectol. It is an anti-parasite medicine and used for veterinary deworming. Due to the misusage, this medicine is highly used in COVID-19 protocols, but it has low and limited outcomes in the pandemic control. The price of branded Ivermectin is in the range of $30 to $54 in patent protection countries. However, the generic version of this medicine is in the range of $5 to $ 75 (Figure 9). The WHO removed this medicine from its treatment protocols upon the detailed studies of its outcomes. Now the price of this medicine is under control due to the decline in the COVID-19 therapeutic consumption, and it is exclusively used for worm related infections [59, 60].

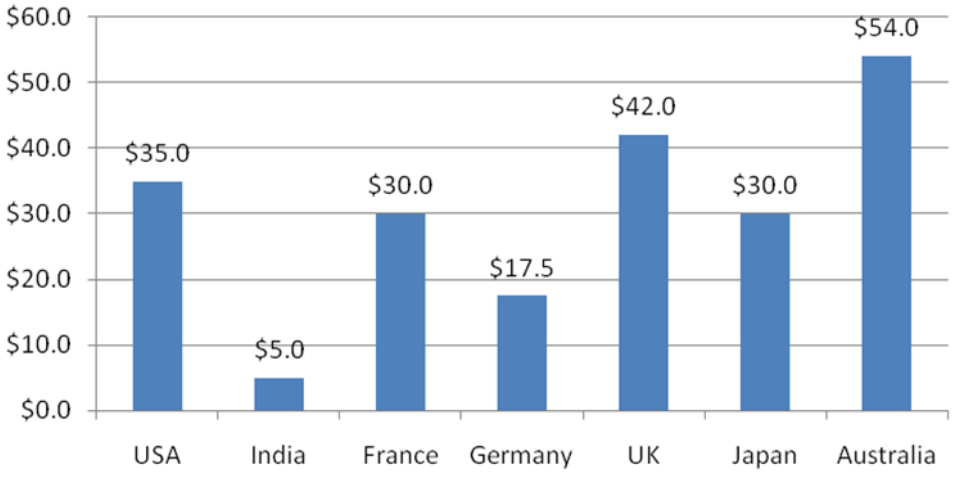

Figure 9. Ivermectin prices (10 tablets) in top COVID-19 affected countries.

4.11. Methylprednisolone

Methylprednisolone is a synthetic glucocorticosteroid which was patented under Pfizer and sold under the brand name Medrol. It is widely used in the health conditions like arthritis, allergies and blood related disorders. It is a proven and effective drug for the

immune related diseases. This is considered for the treatment due to its effectiveness in the treatment of COVID-19. Since the price of Medrol is fairly less, 10 tablets of 4 mg pack is in the range of $5 to $9 in UK, Japan, Australia, and USA. However, the generic version of this drug is available at just below $1 in India and Vietnam, and $1.3 in France (Figure 10). As the medicine is widely available and used around the world, many generic brands exist for this drug. The COVID-19 has given a sudden boost in sales for this product due to its efficacy in treatment [61, 62].

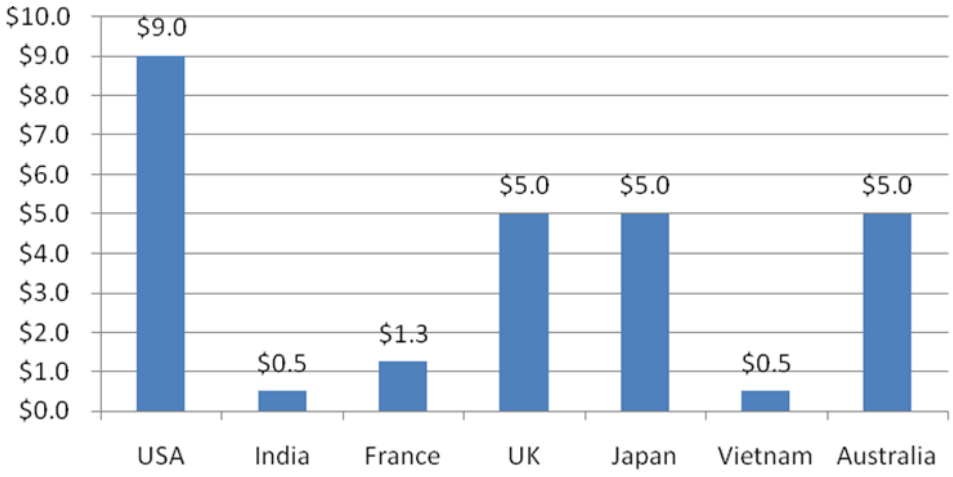

Figure 10. Methylprednisolone (10 tablets) prices in top COVID-19 affected countries.

5. Conclusion

The analysis revealed that the demand for COVID-19 therapeutics is growing as the COVID-19 pandemic has not subsided yet. Pandemic is rising continuously in some or other corners of the world despite the availability of multiple varieties of vaccines. However, the death cases are significantly reduced because of the release of advanced Bio-therapeutics and chemo-therapeutics into the market to treat the disease effectively. These therapeutics are highly expensive and far from ordinary people in LMI countries. The medicines that are to be administered under medical supervision will worsen the financial condition of the patients due to increased hospital expenditure. However, there are positive signs of bringing down these medicine prices to LMI countries by sub-licensing patented medicines to offer them in a generic version under Medicines patent pool. Paxlovid, Molnupiravir, and Remdesivir manufacturers had collaborated with generic manufacturers in South Asia, South America, and Latin American countries around the globe. Therefore, there is a massive demand for therapeutics which can be used in home isolation. The most effective bio-therapeutics, such as monoclonal antibodies, are popular these days, but the costs of these therapeutics are yet to be reduced for LMI countries at the earliest possible in the interest of humanity. The concept of sub-licensing somehow dilutes the compulsory licensing/Bolar provisions, still helping the LMI countries to get medicines at affordable prices. The review outlined important information about the effectiveness and safety of the newly approved COVID-19 medicine, which can help healthcare providers make informed decisions about treatment

options for their patients. This can improve patient outcomes and reduce the burden of the disease on the healthcare system.

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