# Pharmaceutical, biological agents, and vaccines under clinical trials for COVID-19 and roles of pharmacists to combat COVID-19, an update

# Mari Kannan MAHARAJAN<sup>1</sup>, Kingston RAJIAH<sup>2\*</sup>, Bharath POGULA<sup>3</sup>, Sridevi CHIGURUPATI<sup>4</sup>, Sujitha KATRAGADDA<sup>5</sup>

- <sup>1</sup> School of Pharmacy, University of Nottingham Malaysia, Selangor, Malaysia.
- <sup>2</sup> Department of Pharmacy, GITAM School of Pharmacy, GITAM Deem to be University, Hyderabad, India.
- <sup>3</sup> Research and Development, GVB Biopharma, Grass Valley, Oregon, United States of America.
- <sup>4</sup> Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Buraydah, Kingdom of Saudi Arabia.
- <sup>5</sup> Pharmacist, Walgreens, Columbus, Ohio, United States of America
- \* Corresponding Author. E-mail: kingrajiah@gmail.com (K.R.); Tel. +91-9159309257.

Received: 13 February 2022 / Revised: 20 July 2022 / Accepted: 21 July 2022

**ABSTRACT**: Due to the high mortality rate and rapid spread in the early phase of the COVID-19 pandemic, the healthcare system used various treatment options. The pathology associated with COVID-19 includes inflammatory responses which ultimately lead to multi-system organ failure or "cytokines storm". Treating COVID-19 at the initial stage of pandemic has become a challenge as there are no medications that have yet been approved by the FDA or other regulatory agencies. There are many medications have been used by the practitioners to combat the severity of the inflammatory responses. This article summarized the repurposed medications that have received attention during the COVID-19 pandemic and provided an outline of the therapeutic agents, which are under clinical trial that may be helpful to treat COVID-19. This article also emphasizes on pharmacist roles and responsibilities during disasters and pandemics and discussed various vaccines undergoing clinical trials currently.

KEYWORDS: Biological agents; Clinical Trials; Coronavirus; Pharmacist; Therapeutic agents; Vaccines.

#### 1. INTRODUCTION

For the past three years, the world has been suffering from the global pandemic of coronavirus disease 2019 (COVID-19) [1]. Due to the high mortality rate and rapid spread in the initial phase of the COVID-19 pandemic, the health system has deployed various treatment options, and the World Health Organization (WHO) has issued guidelines to control the spread of the disease [2]. Despite all the measures taken, the number of reported COVID-19 cases increased in almost all countries in the early phase of the COVID-19 pandemic. The global mortality rate of COVID-19 is 3.7%, almost three times that of influenza (1%), and the highest number of deaths was documented in the United States of America [2, 3]. The pathology associated with COVID-19 includes inflammatory responses that ultimately lead to multisystem organ failure (MSOF) or a "cytokine storm" [3]. These pathological consequences make COVID-19 a serious infectious disease, as it primarily affects the respiratory tract, followed by multiple organ injury.

Treating COVID-19 was a challenge as there were no defined treatment options approved by the FDA or other regulatory agencies earlier. However, the National Institutes of Health (NIH) developed treatment guidelines for patient care with COVID-19 by the interim guidance by World Health guidance (WHO). During the hour of crisis, there are many pharmaceutical agents have been used to treat COVID-19 based on experts' opinions and scientific evidence. There are a few notable repurposed medications received attention from healthcare professionals. Pharmacists as medication experts play a significant role in the management of patients during the pandemic. In addition to this, the pharmacist is also involved directly in the clinical trials. This article emphasizes the various therapeutic agents used from the pharmacists' point of view. The

How to cite this article: Maharajan MK, Rajiah K, Pogula B, Chigurupati S, Katragadda S. Pharmaceutical, biological agents, and vaccines under clinical trials for COVID-19 and roles of pharmacists to combat COVID-19, an update. J Res Pharm. 2022; 26(6): 1513-1526.

roles and responsibilities of pharmacists in the management of drugs and various vaccines undergoing clinical trials during the COVID-19 pandemic have also been discussed.

# 2. DISCUSSION

# 2.1. Pharmaceutical and biological agents

The National Institutes of Health (NIH) has developed guidelines for patient care management towards COVID-19 by the interim guidance by WHO. The recommendations were based on experts' opinions and scientific evidence. Public health safety depends mainly on a few measures like social distancing, which helps to control the viral spread; this helps indirectly to decrease the surge in cases worldwide and flatten the coronavirus curve. The following are the pharmaceutical agents currently used to treat COVID-19. The list of pharmaceutical and biological agents is given in table 1.

Drug name	Approved indication	Possible mechanism of action	Role in COVID-19	Additional remarks
Anakinra	Rheumatoid Arthritis	Blocks the Interleukin -1 (IL-1) alpha and beta by competitively inhibiting the binding of IL-1 to its receptor.	As the production of inflammatory cytokines is induced by the coronaviruses including IL-1 beta, this mechanism may be beneficial in treating COVID-19 [4]	
Arbidol (Umifenovir)	Influenza and other respiratory viral infections	Targets the S protein/ACE2 interaction and inhibits membrane fusion of the viral envelope to the host cell. [5] It also possesses antioxidant activity that may protect cells through prevention of oxidative damage in mitochondria and inhibition of lipid peroxidation, thus contributing to the compensation of oxidative stress due to the viral disease [6]	In India, approval for the Phase III trial of this drug has been secured by the Central Drug Research Institute (CDRI) for the treatment of COVID-19.	
Baricitinib	Rheumatoid Arthritis	It is an Anti-Janus kinase Inhibitor that Acts through the inhibition of cytokine release, and thus may limit the cytokine storm associated with the complications of COVID- 19 infection.	A randomized controlled clinical trial on Baricitinib combination with Remdesivir has begun. [8]	

Table 1: List of pharmaceutical and biological agents

Camostat	Pancreatitis	Potent serine protease inhibitor. In an animal study, camostat mesylate inhibit the transmembrane protease- serine-2 enzyme's interaction and hence the infectivity of SARS-CoV-2 in inhibited or the function of SARS-Cov-2 is crippled. [9]		Lopinavir alone has
Lopinavir/Ritonavir	An anti-retrovirus protease inhibitor drug combination indicated for HIV infection	The combination blocks the replication of viral genes through an enzyme binding mechanism and prevents proteolysis.	Clinical outcomes are not significant among hospitalized patients with COVID 19.	a short half-life with poor bioavailability. Ritonavir through cytochrome p-450 inhibition acts as a booster by improving the bioavailability and increasing the plasma half-life of lopinavir. [10]
Nitazoxanide	Anti-parasitic drug. Has Broad spectrum antiviral activity against norovirus, parainfluenza, influenza, rotavirus and respiratory syncytial virus	During viral replication, nitazoxanide interferes with the host-regulated pathways rather than virus-specific pathways [11]		
Oseltamivir	Management of uncomplicated, acute influenza infections in adults who are symptomatic for 2 days or less	Inhibits the enzyme neuraminidase within the influenza virus particles, resulting in inhibition of viral replication, possibly by interfering with viral particle assembly and their release from the host cell.	Trails are underway to explore the effectiveness of this drug in treating Covid-19 patients [12]	
Ribavirin	Chronic hepatitis C with compensated liver disease. Respiratory syncytial virus in hospitalized infants and young children.	Probably acting by inhibition of RNA and DNA synthesis, inhibition of RNA polymerase, and interference with the completion of the viral polypeptide coat [13] Acts by inhibiting the		
Lianhuaquingwen	Influenza	replication of SARS-COV- 2 and exerted anti- inflammatory activity in vitro. [14]		

vitro. [14]

Interferons	Enhance the immune system by various mechanisms that include antiviral, antiproliferative, immunomodulatory activities.	Acts by inhibiting viral RNA transcription, protein translation, and post-translational modification [15]	
Tocilizumab	Rheumatoid arthritis	Tocilizumab is a recombinant humanized anti-human interleukin IL-6 receptor monoclonal antibody of the immunoglobulin IgG1. It acts by binding to both soluble and membrane- bound IL-6 receptors and thus has been shown to inhibit IL-6 mediated signaling	Though clinical trials provided evidence that tocilizumab can be included in the treatment of COVID- 19 patients with severe illness, efficacy and safety are still being investigated [16]

## 2.1.1. Anakinra

Anakinra is a non-glycosylated recombinant human Interleukin -1 (IL-1) receptor antagonist, previously approved for, rheumatoid arthritis. It inhibits the action of IL-1 by competitively binding to its receptor. As the production of inflammatory cytokines is induced by the coronaviruses including IL-1 beta, this mechanism may be beneficial in treating COVID-19 [4]. It is contraindicated with asthma or kidney disease. Based on the available evidence it is an option to reduce the mortality, particularly in patients with hyperinflammation.

#### 2.1.2. Arbidol

Arbidol (Umifenovir), is an antiviral drug acting by inhibiting the viral envelope membrane fusion by targeting the viral S protein/human ACE2 receptor interaction [5]. It also possesses antioxidant activity that may protect cells through the prevention of oxidative damage in mitochondria and inhibition of lipid peroxidation, thus contributing to the compensation of oxidative stress due to the viral disease [6]. This drug is used as prophylaxis for, and treatment of influenza infections as well as treatment particularly those with increased serum ferritin or elevated lactate dehydrogenase. It has been widely used in for its benefits over peripheral oxygen saturation and significantly associated with reduced infection in COVID-19 patients.

#### 2.1.3. Baricitinib

This drug is a Janus kinase inhibitor approved for management of rheumatoid arthritis. It acts through the inhibition of cytokine release, and it may thus limit the cytokine storm associated with the complications of COVID-19 infection. Baricitinib was well tolerated without serious adverse effects in patients with moderately severe COVID-19 infection [7]. Also, a randomized controlled clinical trial on baricitinib in combination with remdesivir has been started [8].

#### 2.1.4. Camostat

Camostat is a potent serine protease inhibitor. Physiologically, the transmembrane enzyme proteaseserine-2 interacts between SARS-CoV-2 spike protein and the receptor protein ACE-II that allows the virus to access human cells and infect them. In an animal study, camostat mesylate inhibit the transmembrane protease-serine-2 enzyme's interaction and hence the infectivity of SARS-CoV-2 is inhibited. Or the function of SARS-CoV2 spikes protein is crippled [9].

# 2.1.5. Lopinavir/Ritonavir (LPV/r)

Lopinavir/ritonavir is an anti-retrovirus protease inhibitor drug combination indicated for the management of HIV-1 infection in addition to other antiretroviral drugs. The combination blocks the replication of viral genes through an enzyme binding mechanism and prevents proteolysis. Lopinavir, a protease inhibitor alone has a short half-life with poor bioavailability. Ritonavir through cytochrome p-450 inhibition acts as a booster by improving the bioavailability and increasing the plasma half-life of lopinavir. However, LPV/r clinical outcomes are not significant among hospitalized patients with COVID-19 [10].

#### 2.1.6. Nitazoxanide

Nitazoxanide is an antiparasitic drug, been shown to have broad-spectrum antiviral activity against norovirus, parainfluenza, influenza, rotavirus, and respiratory syncytial virus. During viral replication, nitazoxanide interferes with the host-regulated pathways rather than virus-specific pathways [13]. Nitazoxanide and tizoxanide (nitazoxanide metabolite) showed similar inhibitory activity towards MERS-CoV in-vitro studies [11].

#### 2.1.7. Oseltamivir

Oseltamivir was approved for the management of uncomplicated, acute influenza infections in adults who are symptomatic for 2 days or less. It inhibits the enzyme neuraminidase within the influenza virus particles, resulting in inhibition of viral replication, possibly by interfering with viral particle assembly to get released into the host cell. Trails are underway to explore the effectiveness of this drug in treating Covid-19 patients [12].

#### 2.1.8. Ribavirin

Ribavirin is an antiviral indicated for treating chronic hepatitis C with compensated liver disease, and for the treatment of hospitalized infants and young children infected with the respiratory syncytial virus. It probably acting by inhibition of RNA and DNA synthesis, inhibition of RNA polymerase, and interference with the completion of the viral polypeptide coat. A clinical trial is going on for their combination with interferon [13].

#### 2.1.9. Lianhuaqingwen

Lianhuaqingwen capsule is a Chinese herbal product originally used to treat cold and flu. This compound inhibited the replication of SARS-COV-2 and exerted anti-inflammatory activity in vitro [14].

#### 2.1.10. Interferons

Interferons, comprising three sub-types  $\alpha \beta$  and  $\gamma$  they enhance the immune system by various mechanisms that include antiviral, antiproliferative, immunomodulatory activities. Their antiviral effects are mediated by inhibiting viral RNA transcription, protein translation, and post-translational modification [15].

#### 2.1.11. Tocilizumab

Tocilizumab is a recombinant humanized IL-6 receptor blocking monoclonal antibody of the immunoglobulin IgG1. It acts by binding to both soluble and membrane-bound IL-6 receptors and thus has been shown to inhibit IL-6 mediated signaling. Though clinical trials provided evidence that tocilizumab can be included in the treatment of COVID-19 patients with severe illness, efficacy and safety are still being investigated [16].

#### 2.2. Vaccines

Vaccine platform technologies use a platform-based carrier that can be modulated with antigenic components of target pathogen. There are several platforms under trial, each with different advantages and

drawbacks. One of the foremost difficulties in the development of the COVID-19 vaccine was the presence of undesired immunopotentiation as eosinophilic infiltration or increased infectivity, which lead to infections after immunization with entire virus vaccines or spike protein vaccines [17]. The list of vaccines are given in table 2.

Table 2: List of vaccin	ıes
-------------------------	-----

Platform	Candidate	Sponsor Company /institute	Trial phase	Advantages/ Benefits	Drawbacks/ Risks
	INO-4800	INOVIO	Phase 2		
	bacTRL- Spike	Symvivo	trial [18] Phase 1 [19]		
DNA	GX-19 COVID-	Genexine	Phase2/3 Phase 1/2	Can be used in immunocompromise	No approved DN.
	eVax Adenovirus- based vaccine	Takis Biotech ImmunityBio, NantKest [24]	[20] Pre-clinical	d patients. Has long term stability and oral formulations are possible	vaccines. Ha Variable immur responses
Plasmid DNA	ZyCoV-D [23]	Zydus Cadila	phase 3 clinical trials	possible	
Recombinan t DNA	Recombinan t vaccine	Sanofi, Translate Bio	Pre-clinical [21]		
RNA	mRNA-1273 [24]	Moderna	Phase 3 with 30,000 participant s	No potential for infectious mutagenesis. Has Strong early antiviral	Inflammatory reactions possible Boosting likel necessary to achiev
	BNT162 [25,26,27]	BioNtech	Phase1/2/ 3	responses, both humoral and cell mediated.	robust and lor lasting immunity
	SCB-2019 [29]	GSk, Clover Biopharmaceuticals , Dynavax and Xiamen Innovax	Phase 3		
	NVX- CoV2373 [30]	Novavax	Phase 3		
Protein	UQ-CSL V451	University Queensland and Sanofi/GSK [32] Anhui Zhifei	Phase 1	Strongantibodyresponses.Largestcategory ofcurrentCOVID-19vaccine	Need for adjuvant Potentially lackir correct glycan shiel of native virus
	Adjuvant recombinant vaccine candidate [31]	Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase 3	candidates.	of harive virus
	COVAX-19	Vaxine pvt Ltd [33]	Phase 1		
Gp96 heat shock protein backbone	Gp96-based vaccine [34]	Heat Biologics	Pre- Clinical		
Viral vector (non- replicating)	AZD1222 (Chimpanze e adenovirus vaccine vector)	University of Oxford [35]	Phase 3	Strong antibodies and cellular responses.	Not suitable fo immunocompromise d patients. Variab immunogenicity.
	Ad5-nCoV	CanSino Biologics [36]	Phase 3		minunogenieny.

	A 10/C A DC	T 1 ^			
	Ad26SARS- CoV-2-S [38]	Johnson & Johnson-Janssen Gamaleya research	Phase 1		
	Gam- COVID-Vac [37]	institute, Acellena Contract Drug Research and Development	Phase1/2		
	CoronaVac	Sinovac	Phase 3	Good safety and	Complicated to scale
	COVID-19 vaccine	sinopharm	Phase 3	immunogenicity [39]	up manufacturing.
Virus (inactivated) vaccines	BBIBP-CorV [40]	Beijing Institute of Biological Products	Phase 3	Efficient productivity. Good genetic stability	
	Covaxin	Bharat Biotech; National Institute of Virology	Phase 3 [41]	0	
Inactivated whole virus	PittoCoVacc [42]	University of Pittsburgh	Pre-clinical		
Live attenuated vaccine [43]	Bacillus Calmette- Guerin (BCG) live- attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute	Phase2/3	Low morbidity and mortality rate. Powder form has longer shelf life and stronger stability	Risk of increased severity
Viral vector (replicating) [44]	Recombinan t vaccine	Vaxart	Phase 2	Strong antibody and cellular response	Possible inflammatory adverse effects
	Plant-based adjuvant COVID-19 vaccine candidate [45]	Medicago	Phase 3	Can develop oral vaccines. Efficient syntheses of complex proteins	Requires more time for developing antigen producing lines
Self- replicating RNA and nanoparticle non- viral delivery system	LUNAR- COV19 [46]	Duke-NUS Medical School	Phase 1/2	NA	NA
Novel gene- based	AACOVID [47]	Massachusetts Eye and Ear; University of Pennsylvania	Pre-clinical	NA	NA
Precision	mRNA lipid	·			
Nano Systems' RNA vaccine	nanoparticle (mRNA- LNP)	CanSino Biologics, Precision Nano Systems	Early research	NA	NA
Self- Assembling vaccine	vaccine Halovax [48]	MGH vaccine and immunotherapy center	Pre-clinical	NA	NA

#### 2.2.1. DNA based vaccines

Various vaccines are being proposed and currently under clinical trials, based on DNA platforms. The advantage of the DNA platform is that it can be used in immunocompromised patients. DNA based vaccines possess long-term stability and have the possibility of making oral formulations. However, there are no approved DNA vaccines so far because of their variable immune responses. Inovio pharmaceuticals are developing a vaccine named INO-4800 which is in phase 2 trials [18]. They have reported positive results after experimenting on rhesus macaques that were challenged with SARS CoV-2. These primates developed

durable antibody and T cell responses along with memory T and B cell responses. INO-4800 was also found to inhibit replication of SARS-CoV-2 in mice. Another vaccine, bacTRL-Spike developed by Symvivo is currently being evaluated in the phase 1 trial [19]. This is a bifidobacterial monovalent SARS-CoV-2 DNA oral vaccine candidate. Another vaccine, GX-19, sponsored by Genexine is being tested in South Korea and is currently in Phase 2/3 clinical trial with 190 healthy participants randomized to receive the vaccine or placebo. COVID-eVax by Takis Biotech [20] is in Phase 1/2 trials. Zydus Cadila is researching ZyCoV-D [23], a plasmid DNA vaccine candidate for COVID-19 that targets the viral entry membrane protein of the virus. This vaccine is in phase 3 trials.

# 2.2.2. RNA based vaccines

In virtue of their strong early antiviral responses, both humoral and cell-mediated, in addition to the lack of potential for infectious mutagenesis make them good candidates for vaccine development. However, the disadvantages associated with RNA platform-based vaccines are that they might have inflammatory reactions and need additional boosting to achieve long-lasting immunity. Vaccine named mRNA-1273, sponsored by Moderna [24] is currently in phase III trials with 30,000 participants. During its phase 1 trial, it successfully produces neutralizing antibody titers in 8 participants. It has now been granted fast track designation by FDA. BNT-162 by Pfizer and BioNTech [25], was initially four vaccine candidates- two candidates consisting of nucleoside modified mRNA-based (modRNA) [26], the third one uridine-containing mRNA-based (uRNA) [27], and the fourth candidate is self-amplifying mRNA based (Sanaa) [28]. modRNA has been chosen to move forward in the phase 2/3 trial.

## 2.2.3. Protein-based vaccine

Protein-based subunit vaccines present an antigen to the immune system rather than a complete virus particle, using the pathogen's specific, isolated protein. These vaccines show strong antibody responses and currently form the largest category of COVID-19 vaccine candidates. SCB-2019 is developed by GSK, Clover Biopharmaceuticals, Dynavax, and Xiamen Innovax [34]. This vaccine uses Clover's S-Trimer platform, GSK's AS03 adjuvant, and Dynavax's CpG 1018 adjuvant. Novavax developed NVX-CoV2373 is a perfusion protein nanoparticle vaccine candidate for COVID-19 [30]. Phase 1 positive results showing antibody response at various dose levels have been reported in patients received this vaccine. The Adjuvant recombinant vaccine candidate sponsored by Anhui Zhifei Longcom Biopharmaceutical [31], Institute of Microbiology of the Chinese academy of sciences has reached phase 3 trials. Lead-based protein candidate that is still in the preliminary studies in the pre-clinical phase funded by the University of Queensland and Sanofi/GSK [32]. Covax-19, a monovalent recombinant protein vaccine and Molecular clamp vaccine [33] has entered phase 1 trial. They are sponsored by Vaxine Pvt Ltd and the University of Queensland respectively. The Gp96 - based vaccine [34], which is produced based on the protein platform is being studied in combined sponsorship of Heat biologists and the University of Miami. According to them, the vaccine could expand human-HLA-restricted T-cells against immunomodulant epitopes of SARS-CoV-2 spike protein.

# 2.2.4. Viral vector (non-replicating) based vaccine

There are 4 candidates developed using this platform. AZD1222, developed by the University of Oxford, is a chimpanzee adenovirus vaccine vector. It is currently in phase 2/3 trials [35]. The preliminary phase showed a good safety profile with acceptable antibody response. Ad5-nCoV by CanSino biologics entered phase 3 [36] with a good immunogenic and humoral response seen during phase 1 trials. Gam-COVID-vac [37] by Gamaleya research Institute and Ad26SARS-CoV-2-s [38] by Johnson & Johnson are in phase 1/2 and preclinical studies respectively. These vaccines show strong antibody and cellular responses but are not suitable for immune-compromised patients.

# 2.2.5. Inactivated virus vaccines

These candidates show strong immune responses with efficient productivity and good genetic stability. Four candidates developed using this platform are currently in various stages of trials. CoronaVac by Sinovac is a formalin-inactivated and alum-adjuvanted candidate vaccine. This has entered phase 3 after

the results from the previous trials showed good safety and immunogenicity [39]. COVID-19 vaccine by Sinopharm and BBIBP-CorV [40] by Beijing institute of biological products are in phase1/2 trials. Covaxin, an Indian-based product developed by Bharat biotech and the national institute of virology has entered phase 3 trials [41]. PittoCoVacc, an inactivated whole virus vaccine funded by the University of Pittsburgh is in preclinical studies [42].

# 2.2.6. Live attenuated vaccine

Bacillus Calmette-Guerin (BCG) live attenuated vaccine, is indicated for COVID-19 patients having a higher risk of disease [43]. It is currently in phase 2/3 trials. The advantages of this vaccine may include it has low morbidity and mortality rate; it is formulated as powder so it has a longer shelf and stronger stability. The University of Pittsburgh developed a measles vector vaccine towards COVID-19 is in the preclinical study.

# 2.2.7. Viral vector vaccines

An oral recombinant vaccine developed by Vaxart in collaboration with Emergent Biosolutions and Kindred Bio showed positive preclinical results entered phase 2 trials [44].

# 2.2.8. Plant-based vaccine

Plant-based adjuvant COVID-19 vaccine sponsored by Medicago, GSK is in phase 1 trials. A dose of this vaccine yielded a positive antibody response [45].

# Other vaccines under development

Self-replicating RNA and nanoparticle delivery system platform-based vaccine LUNAR-COV19 is sponsored by a medical school in Singapore. It is in the pre-clinical studies [46]. Recombinant Vesicular stomatitis, a vaccine developed based on Vesicular Stomatitis virus technology is in the preclinical stage and sponsored by Merck and IAVI [47]. AACOVID, a novel gene-based vaccine candidate for COVID-19 is currently being developed by the Massachusetts hospital, together with the University of Pennsylvania. CanSino biologics' mRNA lipid nanoparticle vaccine and Halovax a self-assembling vaccine by MGH vaccine and immunotherapy center are still in early research [48].

# 2.3. Pharmacists' role in COVID-19

# 2.3.1. Community pharmacist

Community pharmacists played a vital role in responding to symptoms, supplying medicines, promote healthy lifestyle. They been regarded as researchers, counselors, and mentors of patients [49]. Community pharmacists are one of the easily, free of charge, accessible healthcare professionals, and this has been shown in earlier emergency preparedness and the response during Ebola and Zika outbreaks. Similarly, community pharmacists are delivering their role towards public health in dealing with this crisis COVID-19. Community pharmacist functioned as substitute to primary care providers in rural areas by providing the COVID-19 medication and preventative supplies (face masks, sanitizer, and disinfectants) where patients are facing shortage of primary care providers [49]. Community pharmacists have offered essential services to confront the COVID-19 health catastrophe by patient education, drug dispensing, psychological support, chronic disease management, vaccination, inhibiting misinformation and pharmaceutical supply chain management. Community pharmacists adapted the technology to minimize direct contact by virtually meeting patients [49]. Community pharmacist succeeded in controlling community transmissions by patient education, social distancing, mask mandate, testing, and vaccination. Community pharmacists reduced the burden on healthcare system by unnecessary hospital visits and for patients by reducing the healthcare expenditure.

# 2.3.2. Hospital pharmacist

Hospital pharmacists played a vital role in medical collaborative team by engaging in treatment and managing COVID-19 infections whilst providing healthcare services to chronic disease patients [50]. Amid

COVID-19 hospital pharmacist responsibilities expanded and became an inherent part of planning and responding to pathogens by partaking in antimicrobial programs, which is of paramount significance during COVID-19. Medication reconciliation and treatment charts reviews became the principal responsibility of hospital pharmacists to fight the drug shortages and to manage the supply chain. There by implementing conservation strategies, choosing drug alternatives aided their battle with COVID-19. Hospital pharmacist developed local therapy protocols to determine the safety and effectiveness of repurposing antiviral drug treatment and antibiotics use in COVID-19 patients. During this catastrophe hospital pharmacists are not only available to treat/prevent the infections but also emotionally supported the patients. Shortage of PPE in most hospitals due to the constrained availability didn't prevent the hospital pharmacist to provide care for their patients even when they are vulnerable to the infections. Testing & vaccination by hospital pharmacist play a vital role in bringing down the number of COVI-19 infections.

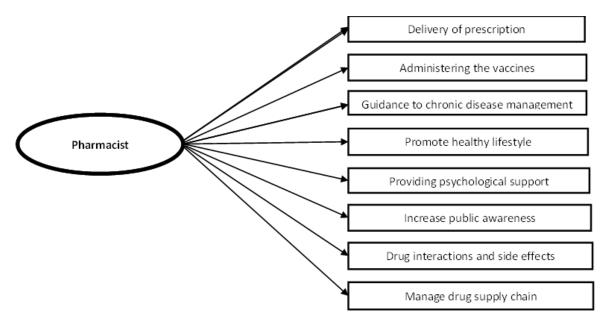
## 2.3.3. Crisis management

Pharmacists play a major role in reducing COVID-19 virus spreading among population by creating awareness among the community and helping them to understand the pandemic situation properly. This pandemic made evident the crucial role of a pharmacist in health care system. Pharmacists educate the community to distinguish the symptoms among common cold, flu, and COVID-19 infections. This helps in the early identification of suspected individuals. Pharmacists provide proper instructions for the selection and safe use of disinfectants, hand hygiene, proper use of masks, and self-protection strategies while being outdoor and at the workplace.

# 2.3.4. Extended role of pharmacists

Pharmacists collaborate with non-governmental organizations (NGOs), health departments, and disaster management teams to provide optimal care for COVID-19 patients [51]. Pharmacists along with the NGO, manage the drug supply cycle. In disaster zones, pharmacists' tasks include but are not limited to dispensing drugs to sick people. They provide pharmaceutical care for patients who underwent surgery, wound dressing, and changing bandages. Not like preceding pandemics coronavirus is obstinate but pharmacists are embracing innovative strategies and working at the forefront of an interdisciplinary team of physicians, nurses, paramedics, and nontechnical staff. Pharmacists play a critical role in facilitating patients and physicians to combat the COVID-19 infection. Pharmacists are not only reliable but also accessible professionals for patients during pandemics. Publication about COVID-19 by pharmacists brought awareness about vaccination, drugs under clinical trials, and their outcomes. Roles of Pharmacists during disasters and pandemics are provided in figure 1.

Figure 1: Roles of Pharmacists during disasters and pandemics



## 4. CONCLUSIONS

A prophylactic strategy is appropriate management for COVID-19 and is critical for reducing mortality and morbidity from the disease. Scientists around the world are working extensively on therapeutic strategies and vaccines for this virus. This update summarizes therapeutic interventions currently in clinical trials and other available treatment options. In addition, the contribution of pharmacists and their expanded role in COVID-19 is presented.

# 5. MATERIALS AND METHODS

A prophylaxis strategy is appropriate management for COVID-19 and is crucial to reducing the Morbidity and mortality of the disease. Scientists around the globe are working comprehensively on therapeutic and preventive strategies for this virus. In this update, the therapeutic interventions under clinical trials and other management options available have been summarized. Along with that, the contribution of pharmacists and their extended roles toward COVID-19 are also presented.

Author contributions: Concept – M.K., B.P.; Design – KR., M.K.; Supervision – KR., M.K.; Resource – B.P., S.C., S.K.; Materials – S.C., S.K.; Data Collection &/or Processing - B.P., S.C., S.K.; Analysis &/or Interpretation - KR., M.K.; Literature Search – B.P., S.C., S.K.; Writing – M.K., B.P., S.C., S.K.; Critical Reviews – KR., M.K.

**Conflict of interest statement:** The authors declared no conflict of interest.

#### REFERENCES

[1] Chen, TM., Rui, J., Wang, QP. et al. A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. Infect. Dis. Poverty. 2020 9, 24. [CrossRef]

[2] Ali I, Alharbi OML. COVID-19: Disease, management, treatment, and social impact. Sci Total Environ. 2020;728:138861. [CrossRef]

[3] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034. [CrossRef]

[4] Kritas SK, Ronconi G, Caraffa A, Gallenga CE, Ross R, Conti P. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. J Biol Regul Homeost Agents. 2020;34(1):9-14.

[5] Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. [CrossRef]

[6] Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-266. [CrossRef]

[7] Cantini F, Niccoli L, Nannini C, et al. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. The Journal of Infection. 2020 Oct;81(4):647-679. [CrossRef]

[8] National Institutes of Health. NIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins. <u>https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins</u> (accessed on 2nd Feb 2022).

[9] Hoffmann M, Hofmann-Winkler H, Smith JC, et al. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. Preprint. bioRxiv. 2020;2020.08.05.237651. [CrossRef]

[10] WHO "Solidarity" clinical trial for COVID-19 treatments. Latest update on treatment arms. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019ncov/solidarity-clinical-trial-for-covid-19-treatments (accessed on 2nd Feb 2022).

[11] Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health. 2016;9(3):227-230. [CrossRef]

[12] Wu R, Wang L, Kuo HD, et al. An Update on Current Therapeutic Drugs Treating COVID-19. Curr Pharmacol Rep. 2020;6(3):56-70. [CrossRef]

[13] National Institutes of Health. IFN Beta-1b and Ribavirin for Covid-19 <u>https://clinicaltrials.gov/ct2/show/NCT04494399</u> (accessed on 2nd Feb 2022).

[14] Runfeng L, Yunlong H, Jicheng H, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2) [published correction appears in Pharmacol Res. 2021 Dec;174:105907]. Pharmacol Res. 2020;156:104761. [CrossRef]

[15] Fensterl V, Chattopadhyay S, Sen GC. No Love Lost Between Viruses and Interferons. Annu Rev Virol. 2015;2(1):549-572. [CrossRef]

[16] Gupta S, Leaf DE. Tocilizumab in COVID-19: some clarity amid controversy. Lancet. 2021 May 1;397(10285):1599-1601. [CrossRef]

[17] Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 Vaccine Pipeline: an Overview [published online ahead of print, 2020 Mar 3]. Curr Trop Med Rep. 2020;1-4. [CrossRef]

[18] National Institutes of Health. Clinical trials-2020. Safety, Immunogenicity, and Efficacy of INO-4800 for COVID-19 in Adults at High Risk of SARS-CoV-2 Exposure <u>https://clinicaltrials.gov/ct2/show/NCT04642638</u> (accessed on 2nd Feb 2022).

[19] National Institutes of Health. Clinical trials-2020. Evaluating the Safety, Tolerability and Immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19 <u>https://clinicaltrials.gov/ct2/show/NCT04334980</u> (accessed on 2nd Feb 2022).

[20] Conforti A, Marra E, Palombo F, et al. COVID-eVax, an electroporated DNA vaccine candidate encoding the SARS-CoV-2 RBD, elicits protective responses in animal models. Mol Ther. 2022;30(1):311-326. [CrossRef]

[21] National Institutes of Health. Clinical trials-2020. Study of Monovalent and Bivalent Recombinant Protein Vaccines Against COVID-19 in Adults 18 Years of Age and Older (VAT00008) <u>https://clinicaltrials.gov/ct2/show/NCT04904549</u> (accessed on 2nd Feb 2022).

[22] National Institutes of Health. Clinical trials-2020. COVID-19 Vaccination Using a 2nd Generation (E1/E2B/E3-Deleted) Adenoviral-COVID-19 in Normal Healthy Volunteers <u>https://clinicaltrials.gov/ct2/show/NCT04591717</u> (accessed on 2nd Feb 2022).

[23] Dey A, Chozhavel Rajanathan TM, Chandra H, et al. Immunogenic potential of DNA vaccine candidate, ZyCoV-D against SARS-CoV-2 in animal models. Vaccine. 2021;39(30):4108-4116. [CrossRef]

[24] National Institutes of Health. Clinical trials-2020. Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis of SARS-CoV-2 Infection (COVID-19) <u>https://clinicaltrials.gov/ct2/show/NCT04283461</u> (accessed on 2nd Feb 2022).

[25] Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med.2020;383(27):2603-2615. [CrossRef]

[26] Granados-Riveron JT, Aquino-Jarquin G. Engineering of the current nucleoside-modified mRNA-LNP vaccines against SARS-CoV-2. Biomed Pharmacother. 2021;142:111953. [CrossRef]

[27] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261-279. [CrossRef]

[28] Maruggi G, Ulmer JB, Rappuoli R, Yu D. Self-amplifying mRNA-Based Vaccine Technology and Its Mode of Action. Curr Top Microbiol Immunol. 2021;10.1007/82\_2021\_233. [CrossRef]

[29] National Institutes of Health. Clinical trials-2020. SCB-2019 as COVID-19 Vaccine <u>https://clinicaltrials.gov/ct2/show/NCT04405908</u> (accessed on 2nd Feb 2022).

[30] National Institutes of Health. Clinical trials-2020. Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS Nanoparticle Vaccine With/Without Matrix-M Adjuvant <u>https://clinicaltrials.gov/ct2/show/NCT04368988</u> (accessed on 2nd Feb 2022).

[31] National Institutes of Health. Clinical trials-2020. A Phase III Clinical Trial to Determine the Safety and Efficacy of ZF2001 for Prevention of COVID-19 <u>https://clinicaltrials.gov/ct2/show/NCT04646590</u> (accessed on 2nd Feb 2022).

[32] Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020;288:198114. [CrossRef]

[33] National Institutes of Health. Clinical trials-2020. Monovalent Recombinant COVID19 Vaccine (COVAX19) <u>https://clinicaltrials.gov/ct2/show/NCT04453852</u> (accessed on 2nd Feb 2022).

[34] Strbo, N, Fisher E, Padula L, O'Neill K. E. Development of a gp96-Ig vaccine for COVID-19. J. Immunol. 2021;206:1.

[35] Falsey AR, Sobieszczyk ME, Hirsch I et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-2360. [CrossRef]

[36] National Institutes of Health. Clinical trials-2020. Phase III Trial of A COVID-19 Vaccine of Adenovirus Vector in Adults 18 Years Old and Above. <u>https://clinicaltrials.gov/ct2/show/NCT04526990</u> (accessed on 2nd Feb 2022).

[37] National Institutes of Health. Clinical trials-2020. An Open Study of the Safety, Tolerability and Immunogenicity of the Drug "Gam-COVID-Vac" Vaccine Against COVID-19. <u>https://clinicaltrials.gov/ct2/show/NCT04436471</u> (accessed on 2nd Feb 2022).

[38] National Institutes of Health. Clinical trials-2020. A Study of Ad26.COV2.S in Adults (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04436276 (accessed on 2nd Feb 2022).

[39] National Institutes of Health. Clinical trials-2020. Clinical Trial of Efficacy and Safety of Sinovac's AdsorbedCOVID-19(Inactivated)VaccineinHealthcareProfessionals(PROFISCOV).https://clinicaltrials.gov/ct2/show/NCT04456595(accessed on 2nd Feb 2022).Safety of Sinovac's Adsorbed

[40] National Institutes of Health. Clinical trials-2020. Efficacy, Immunogenicity and Safety of BBIBP-CorV Vaccine Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. (ECOVA-01). https://clinicaltrials.gov/ct2/show/NCT04984408 (accessed on 2nd Feb 2022).

[50] National Institutes of Health. Clinical trials-2020. An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers. <u>https://clinicaltrials.gov/ct2/show/NCT04641481</u> (accessed on 2nd Feb 2022).

[51] Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav Immun. 2020;87:59-73. [CrossRef]

[52] Chimoyi L, Velen K, Churchyard GJ, Wallis R, Lewis JJ, Charalambous S. An ecological study to evaluate the association of Bacillus Calmette-Guerin (BCG) vaccination on cases of SARS-CoV2 infection and mortality from COVID-19. PLoS One. 2020;15(12):e0243707. [CrossRef]

[53] National Institutes of Health. Clinical trials-2021. A Ph 2 Trial With an Oral Tableted COVID-19 Vaccine. https://clinicaltrials.gov/ct2/show/NCT05067933 (accessed on 2nd Feb 2022).

[54] National Institutes of Health. Clinical trials-2021. Phase 3 Study to Evaluate the Lot Consistency of a Recombinant Coronavirus-Like Particle COVID-19 Vaccine. <u>https://clinicaltrials.gov/ct2/show/NCT05040789</u> (accessed on 2nd Feb 2022).

[55] de Alwis R, Gan ES, Chen S, et al. A single dose of self-transcribing and replicating RNA-based SARS-CoV-2 vaccine produces protective adaptive immunity in mice. Mol Ther. 2021;29(6):1970-1983. [CrossRef]

[56] Kim GN, Choi JA, Wu K, et al. A vesicular stomatitis virus-based prime-boost vaccination strategy induces potent and protective neutralizing antibodies against SARS-CoV-2. PLoS Pathog. 2021;17(12):e1010092. [CrossRef]

[57] Shah SM, Alsaab HO, Rawas-Qalaji MM, Uddin MN. A Review on Current COVID-19 Vaccines and Evaluation of Particulate Vaccine Delivery Systems. Vaccines (Basel). 2021;9(10):1086. [CrossRef]

[58] Bragazzi NL, Mansour M, Bonsignore A, Ciliberti R. The Role of Hospital and Community Pharmacists in the Management of COVID-19: Towards an Expanded Definition of the Roles, Responsibilities, and Duties of the Pharmacist. Pharmacy (Basel). 2020;8(3):140. Published 2020 Aug 7. [CrossRef]

[59] Sami SA, Marma KKS, Chakraborty A, et al. A comprehensive review on global contributions and recognition of pharmacy professionals amidst COVID-19 pandemic: moving from present to future. Futur J Pharm Sci. 2021;7(1):119. [CrossRef]

[60] Goff DA, Ashiru-Oredope D, Cairns KA, et al. Global contributions of pharmacists during the COVID-19 pandemic. J Am Coll Clin Pharm. 2020;3(8):1480-1492. [CrossRef]