International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

A Review on the viral infection caused with SARS-CoV2 and management by medications that are utilized in the therapeutics of COVID-19

Gurpreet Bawa[1*], Navneet Khurana[1], Ayush Singh[2], Smiely[2], Ajay Kumar[2], Nikhil[2]

[1*]*Assistant Professor, Department of Pharmacy, Global Group of Institutes, Amritsar, Punjab, India-143501*
[1*]*Ph.D Scholar, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India-144411.*
[1]*Associate Professor, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India-144411.*
[2]*Student, Department of Pharmacy, Global Group of Institutes, Amritsar, Punjab, India-143501*
**Corresponding Author; Gurpreet Bawa: Assistant Professor, Global Group of Institutes, Department of Pharmacy, Amritsar, Punjab, India-143501 and Ph.D Scholar, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India-144411*

Submitted: 01-12-2021 Revised: 11-12-2021 Accepted: 14-12-2021

ABSTRACT: COVID infection is one of the deadly viral infections across the globe that is generally etiolate by the SARS-CoV-2 infection and spread through the transmission and by the infected person. This infection originated from the bats in Wuhan, Hubei province, China in 2019. Usually, transmission occurs through the infected person to the healthy person via the infected droplets of coughing, sneezing, unnecessary toughing without sanitations. Symptomatology considers several significant symptoms that include pyrexia, pertussis, feeling o discomfort, dyspnea. This disorder shows mild to moderate severity in many patients having comorbidities that further lead to several respiratory syndromes. Few patients are asymptomatic. Common laboratory findings involve normal/ low white cell counts with elevated C-reactive protein (CRP) and PCR. Treatment is essentially supportive; the role of antiviral agents is yet to be established, along with the utilization of several herbal medications such as Tinospora cordifolia, Curcuma longa, Echinacea purpurea, Eugenia caryophyllus, Zingiber Officinale, Capparis moonii. Various allopathic medications are also utilized: anti-viral drugs, and also various immunomodulatory drugs. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome corona virus (MERS-CoV) but has lower fatality. The global impact of this new epidemic is yet uncertain.

KEYWORD: SARS-CoV-2, Medication, MERS-CoV, COVID, herbal, immunopathology, chronic, therapeutics

I. INTRODUCTION

COVID infection 2019 is a pandemic viral issue; began in Wuhan, China, in December 2019 brought about by the original infection SARS-CoV-2[1,2,3]. In this biggest investigation, 10.5% of lethal cases happened in patients with cardiovascular infection and 6% in patients with blood vessel hypertension[3]. Corona Virus for the most part have high danger with the individuals who have managing flu infection, human metapneumovirus, respiratory syncytial infection, and rhinovirus, are endemic and etiolates close around 15% to 30% of yearly pneumonic contaminations. In any case, episodes of intense respiratory pain condition because of novel, exceptionally pathogenic strains—SARS-CoV, MERS-CoV. Thus, SARS-CoV-2 has uncovered the strength and risk of this growing group of microorganisms that have the ability to kill a large number of individuals all throughout the planet if not topographically contained[4]. COVID is profoundly infectious viral ailment brought about by serious intense respiratory condition i.e. SARS-CoV-2, has catastrophically affected the world's socioeconomics bringing about more than 3.8 million passing around the world. Many variations of SARS-CoV-2 have been portrayed over the span of this pandemic, among which a couple are viewed as variations of concern (VOCs) by the WHO, given their effect on worldwide general wellbeing.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

Additionally momentarily gives an outline of the various variations of SARS-CoV-2 and the adequacy of various accessible immunizations for anticipation against Corona virus and its variants. Genomic portrayal has shown that bats and rodents are the plausible quality wellsprings of alphaCoVs and betaCoVs[5].

Actually, avian species appear to address the quality wellsprings of deltaCoVs and gammaCoVs. CoVs have turned into the significant microbes of arising respiratory illness flare-ups. For reasons yet to be clarified, these infections can cross species hindrances and can cause, in people, sickness going from the normal virus to more serious illnesses like MERS and SARS. Until now, seven human HCoVs equipped for tainting people have been distinguished. Portions of the HCoVs were recognized during the 1960s, while others were just identified in the new thousand years. As a rule, gauges propose that 2% of the populace are sound transporters of a CoVs and that these infections are liable for around 5% to 10% of intense respiratory infections[6]. Normal human CoVs: HCoV-OC43, and HCoV-HKU1; HCoV-229E, and HCoV-NL63. These infections can cause normal colds and self-restricting upper respiratory lot diseases in immune competent people. Nonetheless, in immune compromised subjects and the older, lower respiratory parcel contaminations can happen because of this viruses. Other human CoVs: SARS-CoV and MERS-CoV[7].

The genomic correlation between the human SARS-CoV-2 grouping and known creature COVID for sure uncovered high homology (96%) between the SARS-CoV-2 and the betaCoV RaTG13 of Rhinolophus affinis[5].

This review investigated a few potential medications that are utilized in the therapeutics of SARS-CoV-2 syndrome via the management of allopathic anti-viral drugs, anti-malarial drugs; natural herbs; immunomodulatory agents.

II. STRUCTURE OF SARS-COV-2

It is having round wrapped infections including a solitary strand of positive-sense RNA that hushes up looks like with the host mRNA[9]. Morphology of this dangerous infection are club-formed projections from the viral envelope like crown and invigorates with improved glycosylated protein named spike protein. Primary proteins are the envelope, film, and nucleocapsid proteins.

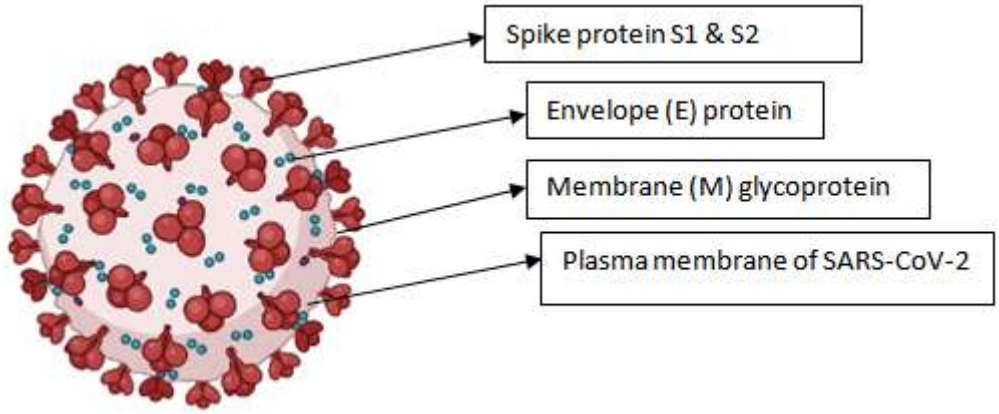

Fig (1): Structure of SARS-CoV-2

Envelope and film are involving two exceptionally covered open perusing outlines that encode 16 nonstructural proteins, including proteases, RNA-subordinate RNA polymerase (prRdRp), RNA helicase, primase, and others, that structure the viral replicase complicated, a stage to engender viral mRNAs.

These nonstructural proteins are altogether expected focuses for treatments, which would in principle neutralize all COVID[10,11,12,13,14]. Rest of the space of this genome includes blended open perusing outlines for the primary proteins, just as various frill proteins for the most part unnecessary for replication in tissue culture however fit for stifling resistant reactions and improving pathogenesis[9,15].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

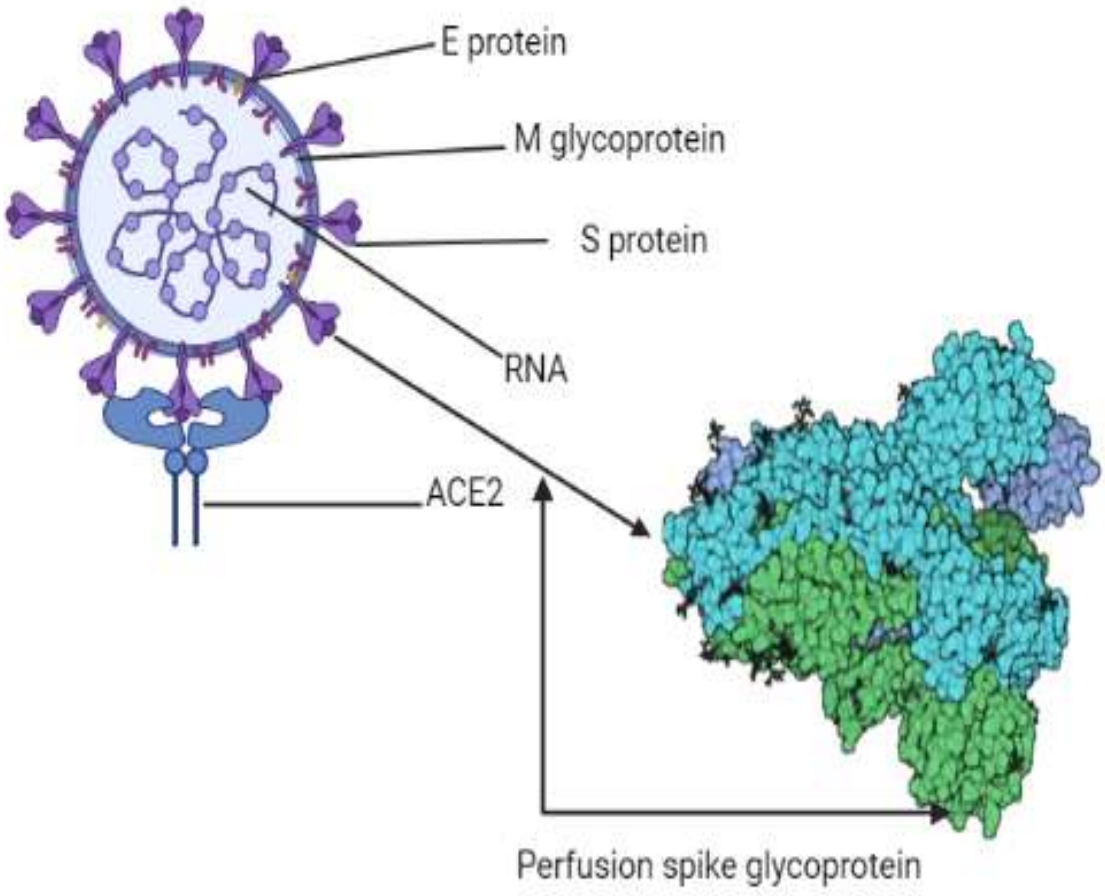

Fig (2) Structure of MERS-CoV; Spike protein adhere with the ACE2, perfusion spike glycoprotein

III. SYMPTOMS

The significant side effects of COVID might show up inside two days to two weeks of period after the openness of this lethal aspiratory disease.

Pre-symptomatic signs might manage pyrexia, pertussis, and sleepiness. Post symptomatic signs might have dysgeusia alongside dyspnea, torment in mycocytes, rhinorrhea, chills, sore throat, cerebral pain, angina, pink eye (conjunctivitis), sickness, and regurgitating, loose bowels, rash. Kids have comparative indications to grown-ups and by and large have gentle sickness.

The seriousness of this issue might have manifestations can go from exceptionally gentle to extreme. Certain individuals might have a couple of indications, and certain individuals might have no manifestations by any stretch of the imagination, likewise called asymptomatic. Certain individuals might encounter demolished indications, for example, deteriorated dyspena and pneumonia, about seven days after side effects start.

IV. ETIOLOGY

Assurance of entire infection cell contamination shows that the infection meddle close around 88% grouping so it can check with two bat-determined serious intense respiratory conditions like Covids, yet is more far off from the extreme intense respiratory disorder COVID. On 11 February 2020, the Covid Study Gathering of the Worldwide Advisory group on Scientific classification of Infections at last elaborate it as serious intense respiratory disorder COVID-2 that for the most part dependent on phylogeny, scientific categorization and set up training[16]. It has been sent to people from contaminated creature, with resulting spread by means of human-to-human transmission[17]. Age is the most significant and impressive factor to decide the disease from this infection. Individuals managing

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

genuine CNS illness like Constant cardiovascular breakdown, cardiomyopathy, malignancy, chronic obstructive pneumonic sickness (COPD) , Type 1 or type 2 diabetes, obesity, high BP, Smoking, Persistent kidney infection, inherited blood infection that generally reduce the amount of O_2 in the body, Debilitated resistant framework from strong organ transfers, Pregnancy, Asthma, cystic fibrosis or aspiratory fibrosis, hepatic disease, dementia, hereditary confusion like Down disorder , debilitated safe framework from bone marrow relocate, HIV, neurological conditions are having high danger of this contamination and less opportunities for the therapy .

V. PROGNOSIS

The guess of corona virus is generally reliant upon different variables that incorporate the patient's age, the seriousness of ailment at show, previous conditions, how rapidly treatment can be carried out, and reaction to treatment. As recently depicted, the WHO's present gauge of the worldwide case casualty rate for corona virus is 2.2%. In any case, the case casualty rate is influenced by variables like age, fundamental prior conditions, and seriousness of disease. Results from an European multicenter forthcoming partner concentrate on that included 4000 fundamentally sick patients with corona virus revealed a 90-day mortality of 31%, with higher mortality noted in old, diabetic, corpulent, and serious ARDS patients[18].

VI. CORONA VIRUS STATISTICS

This pandemic spread across the globe with the positive cases more than 242,125,591 and passing rate 4,924,573 alongside restoring rate more than 219,433,726. This insights is till mid of October 2021. Every one of the landmasses are managing pandemic. USA has generally number of Corona virus cases till date now, followed by India , Brazil , UK , Russia , Turkey , France, Iran and others . Most elevated death rates are coming from the USA, Brazil , India , Mexico, Russia, Peru, Indonesia and others. Europe has In excess of 6 Cr. positive cases with 12 lakh death rate and 5.6 Cr individuals are recuperated from this viral contamination. Asia, has in excess of 78,099,774 positive cases with recuperation rate more than 75,052,541 and death rate 1,151,453. Rely on the epidemiological update by the WHO, four SARS-CoV-2 infection variation have been seen till the underlying of this pandemic. Alpha (B.1.1.7): first variation of concern portrayed in the Unified Realm (UK) in late December 2020, Beta (B.1.351): first revealed in South Africa in December 2020, Gamma (P.1) first detailed in Brazil toward the beginning of January 2021, Delta (B.1.617.2): first announced in Quite a while in December 2020[19].

VII. INFECTION EXAMINATION OF SARS-COV-2

Full-genome sequencing and phylogenic ID uncover that this disease etiolates the issue Covid is the β type of Corona virus as the SARS contamination. The Middle East respiratory condition (MERS) disease is even more by implication related[20,21]. Bat are the critical wellspring of this viral defilement and RNA progression is close to the bat Corona virus . Along these lines, Covid contamination might be imparted clearly from bats[22] .segment of this sickness is same as the SARS-CoV, the angiotensin-changing over substance 2 (ACE2)[23]. Nidovirales are the solicitation for their viral family , infers duplication of viral sickness with the use of settled game plan of dispatch RNA (mRNA). This viral infection subfamily has commonly four genera: alpha, beta, gamma, and delta COVID. HCoV are portrayed in two genera: alpha COVID (HCoV-229E and HCoV-NL63) and beta COVID (HCoV-HKU1, HCoV-OC43, Center East respiratory issue Corona virus, the super exceptional respiratory condition Corona virus), and SARS-CoV-2[24,25]. Production of this viral genome is involved medium-sized wrapped positive-deserted RNA diseases that is considered as greatest viral RNA genomes that dealing with the length of 27 to 32 Kb[26,27]. Cell wall of host cell remained with glycoprotein spikes. Duplication occur in the host cytoplasm wherein RNA polymerase predicaments to a pioneer progression and leaves then, further follow at the various regions that permit for the actuation of a settled plan of mRNA particles with typical 3' ends.The genome encodes four or five fundamental proteins, S, M, N, HE, and E. HCoV-229E, HCoV-NL63, and the SARS Corona virus have four characteristics that encode the S, M, N, and E proteins, independently, while HCoV-OC43 and HCoV-HKU1 also contain a fifth quality that encodes the HE protein[28] . The spike (S) protein projects through the viral envelope and constructions the brand name spikes in the Corona virus "crown" and glycosylated, probable designs a homotrimer, and intervenes receptor limiting and blend with the host cell layer. Guideline antigens that start killing neutralizing specialist, similarly as

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

huge focal points of cell destructive WBC are on the S protein[29]. Layer protein has fundamental impact in the viral get-together[30]. The hemagglutinin-esterase glycoprotein (HE), moiety generally hold quick to the neuraminic destructive on the host cell surface: found in the betacorona virus es, HCoV-OC43 and HKU1[31]. Little envelope protein leaves its C end inside the envelope and a while later bends around and projects its N end inside. Though, in the SARS-CoV, the Envelope protein close by M and N are required for authentic get-together and libration of the disease[32].

VIII. IMMUNOPATHOLOGY

SARS-CoV-2 has a tropism for ACE2-conveying epithelial cells of the lungs area, people with continuous COVID have signs of basic hyper inflammation.

Clinical exploration community revelations of raised IL2, IL7, IL6, granulocyte-macrophage state animating variable , interferon gamma-actuated protein 10 (IP10), monocyte chemo attractant protein 1 , macrophage provocative protein 1alpha (MIP1alpha), and cancer rot factor (TNFα) illustrative of cytokine release condition (CRS) suggest an essential immunopathology. people with Covid and intense respiratory difficulty condition (ARDS) have traditional serum biomarkers of CRS, including raised C-open protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin. Basic exacerbation brings about vasodilation, allowing red hot lymphocytic and monocytic intrusion of the lung and the heart. In particular, pathogenic GM-CSF-emitting Immune system microorganisms were shown to relate with the enlistment of blazing IL-6-discharging monocytes and genuine lung pathology in people with Covid 19[33].
Lymphocytic infiltrates have similarly been represented at posthumous[34,35].

IX. REVERSE GENETICS SYSTEM FOR CORONA VIRUS

Several reverse genetics systems available for Corona Viruses.

Table 1: Reverse genetics system for Corona virus

Reverse genetics of corona virus				
Virus	**Targeted recombinations**	**Full length Cdna**		
		In vitro ligations	**Bacterial artificial chromosomes vector**	**Vaccinia virus**
Transmissible gastroenteritis virus	274	362	2	310
severe acute respiratory syndrome corona virus		363		
Murine corona virus	155, 156	364		58
Infectious bronchitis virus		361		36
Feline infectious peritonitis	125			310

Initiative, full-length cDNA clones were hard to growth due to enhancing of the genome of the COVID-19 . Furthermore, first turn around hereditary qualities framework accessible for COVID was designated recombination, that was created for Murine Covid (155, 166, 208) and afterward for Contagious gastroenteritis infection (274) and Cat Irresistible Peritonitis Infection (125).

X. CLINICAL INDICATIONS

All matured individuals get contamination from one individuals to another nearby contact through transmission. Kids and youths under 18 years shows under 2% of the affirmed Corona virus cases[36]. Different examinations seen that the tainted youngsters are asymptomatic or experience gentle side effects during the Corona virus

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

pandemic[37], 11% require hospitalization. In an associate of 100 youngsters conceded in the crisis in Italy second rate pyrexia (54%), pertussis (44%) and anorexia (23%) were seen. Constant issue was inspected in 1–2% of the cases[38]. The normal clinical elements of Corona virus pneumonia in grown-ups incorporate fever, dry hack, sore throat, migraine, weariness, myalgia and windedness[39,40]. The danger of death relies upon age, hidden comorbidities and seriousness of the infection, expanding up to 49% in basically sick patients[41]. Epidemiologic information from China show that autonomous old enough, men are at more serious danger for the advancement of extreme Corona virus contrasted and ladies[42]. Relieving rate was found in the second or third week from side effect beginning. The middle term of hospitalization in people who restored was 10 days. Aspiratory district, cardiovascular area, renal, hepatic, neurological framework influences most[43].

XI. PATHOGENESIS OF COVID-19 DISEASE

SARS-CoV-2 cling to the cell film of the epithelial layer of the buccal cavity, bodily fluid layers of the conjunctiva or the otic trench. ACE, still up in the air on various human cells including type II alveolar cells , oral, esophageal, ileal epithelial cells, smooth muscles of heart, proximal tubule cells of the kidneys just as urothelial cells of the bladder[8] that is accepted to relocate the disguise of SARS-CoV2 .

The spike protein of this genome of infection breaks by a cell organic impetus for example furin at the S1/S2 site. Because of this breakdown , which is crucial for the addition of Corona virus genome into the aspiratory locale[44].

Incitement of spike protein is for the most part solidified by transmembrane protease, serine 2 which is an organic impetus and further stick to the Pro 2 receptors to embed into the objective cell. This genome of SARS-CoV-2 is homologous in nature with the SARS-CoV and might have comparable skipe protein structure. Both these varieties of Covid embed into the host cell , yet SARS-CoV-2 ties Expert 2 receptors with ten times higher liking[45].

Viral duplication of this hereditary succession of the tragetted cell, downregulation of Expert 2 alienates the cleavage of angiotensin II into angiotensin . Unsettling influence in Expert 2/angiotensin hub explains the overall therapeutics of Corona virus, like hypokalemia, vasoconstriction [46] and development of aspiratory disorders[47].

Additionally, this viability of Expert 2 articulation in the gastrointestinal, CNS, genitourinary, endocrine (pancreas) and genitourinary (testis) frameworks is exceptionally higher than that in the transcendent objective of the infection, the respiratory framework[8].

Some of the examinations exhibit that the occurrences of the SARS-CoV-2 in certain organs is profoundly powerful with Pro 2 receptors[48]. Consequently, there is no relationship between's the infection infectivity and the degree of ACE 2 articulation.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

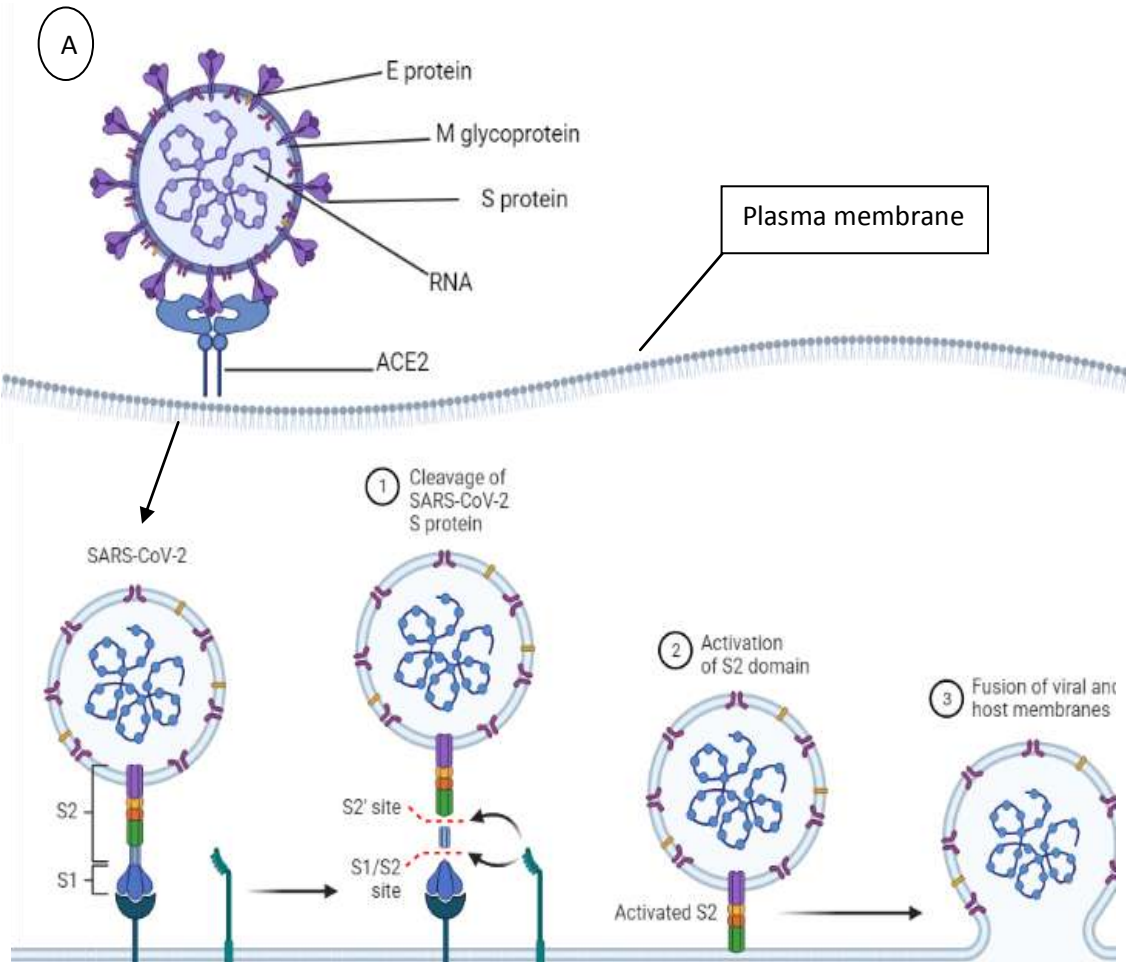

Fig (2): Entry of viral infection etiolates by the SARS-CoV-2 infection; (A) Entry of MERS-CoV through the plasma through in the immune system that leads to cleavage of SARS-CoV-2 (S)-protein via the stimulation of S2 domain and then it leads to the fusion of viral and host membrane.

XII. TRANSMISSION

Examinations elaboration achieved that this viral disease communicates through the contaminated individuals by means of sniffling, hacking , hand shaking and through respiratory drops[49,50,51]. This bodily fluid emission transmission when a contaminated individual interact with solid individual inside 1 m . Thus, solid individual have high viability to collaborate with infection however naso-pulmonary district, mouth or oral depression, conjunctiva. Drop transmission may likewise happen through fomite in the quick climate around the contaminated individual[52]. This is considered as immediate with infection. One more method of transmission is through the aberrant contact with tainted patient by means of contact with surfaces in the quick climate , objects used by the contaminated individual.

Airborne transmission is unique in relation to drop transmission and it considered to the occurrence of microorganism inside bead cores, which are by and large viewed as particles <5µm in measurement, closes from the dissipation of bigger drops or exist inside dust particles. They might stay noticeable all around for extensive stretches of time and be communicated to others over distances more prominent than 1 m. With regards to corona virus, airborne transmission might be conceivable in explicit conditions and settings in which works that create vapor sprayers are performed. No faecal−oral transmission is happen.

XIII. INSUSCEPTIBLE REACTION AFTER VIRAL CONTAMINATION

From different examinations, individuals who are managing this infection, exceptionally influence the pneumonic locale however in certain

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

patients with specific comorbidities, the clinical side effects may be more terrible. Method of contamination is human to human transmission. The interferon and adequacy might have duplication of this disease and enlistment of the versatile insusceptible reaction. This clarifies the inborn insusceptible framework working in COVID19. Many cases managing this infection, have improved pinnacle of IgM in nine days after illness beginning and relocated to IgG in the second week [53]. In any case, barely any cases this arising danger is known as cytokine discharge disorder or a cytokine storm. This condition occurs after contamination with some flu infections [54]. A review gave proof to recommend that a subgroup of patients with extreme Corona virus may have cytokine discharge condition that prompts demise[55]. It very well may be start with the site of disease that is the choreographer of cytokine intensification during contamination, essentially in respiratory epithelial cells. At whatever point infection enter the host cell replication happen inside these cells and subsequently, by and large influence different cells including to the alveolar macrophages. Apoptosis happen through an insusceptible reaction by means of contaminated cell.

Along these lines, safe result animates pro inflammatory cytokines. then, at that point, these cytokines lead to the enlistment of fiery cells, activity finishes up in insusceptible cell penetration and tissue check, this block lead to regenerative cycle, that etiolates with ongoing translates in organs and their cytokines can enter the dissemination lead to cytokine storm. Subsequently, this further prompts multi organ harm[56]. Upgraded IL-2, IL-7, granulocyte-province invigorating variable, IFN-c, inducible protein (IP)- 10, monocyte chemo attractant protein (MCP)- 1, macrophage provocative protein (MIP) 1-α, and growth rot factor (TNF)- α can be portrayed as the cytokine storm[57]. There are upgrading phases of some pro inflammatory cytokines. Lymphopenia and cytokine tempest might assume an imperative part in the pathogenesis of Corona virus.

This cytokine tempest might turn into a starter activity of viral sepsis and irritation instigated aspiratory locale check .this activity further created different entanglement including pneumonitis, intense respiratory trouble condition, respiratory disappointment, multi organ disappointment, and conceivably passing[53].

XIV. COMPLICATIONS

It include pneumonia, aspiratory disorders, a few organs harm, septic shock, CVS, atrial fibrillations, aggravation on myocardial dividers of heart, apoplexy, venous thromboembolism, hepatic compound disappointment[58,59,60,61]. CNS related confusions include epilepsy, stroke, irritation of the mind, and loss of engine nerve physiology[62,63]. Pediatric multisystem incendiary disorder might happen in kids, lethal[64,65]. Amazingly uncommon , In extremely uncommon cases, gentle changes In the cerebrum or gentle chane in the physiology of mind may be happen , and it tends to be considered in the people who have been determined to have corona virus and have a modified mental status[66]. According to the Places for Infectious prevention and Avoidance , it upgrades the odds of genuine sickness from COVID in pregnant ladies, on the grounds that pregnant lady with this SARS CoV-2 diseases having the development of aspiratory disorders and obstetric confusions that could possibly prompt unexpected labor , premature delivery and intrauterine development limitation[67]. Mycosis like Aspergillosis, Candidiasis from Candida albicans, Cryptococcosis and Mucormycosis (Black mycosis) have been found in patients restoring from Corona virus[68,69].

XV. ALLOPATHIC MEDICATIONS UTILIZIED IN THE THERAPEUTICS OF SARS-COV-2

For the strong treatment, inception is to ensure adequate confinement to stop spread for other reached people, cases and medical care laborers. According to the circumstances, tainted patients should be holed up at home according to the specialists' recommendation. Affirmed patients can be cohorted in a similar ward. Genuine patients ought to be conceded to Concentrated Basic Unit quickly. bed rest and palliative treatment required during treatment, providing sufficient calorie and water utilization, supporting water-electrolyte equilibrium and homeostasis, examining indispensable signs and oxygen immersion, keeping up with aviation route unhindered and enhancing oxygen when required[68,69]. The standard methodology is proceeding with hydration, nourishment and overseeing fever and hack. Patient having pyrexia above 38.5°C with perceptible pain, substantial cooling or antipyretic medication treatment would be given. Medications that incorporate are PCM orally, 10–15 mg/kg, 4-6 times/day.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

i. Oseltamivir

Use of oseltamivir, ought to be avoided confirmed patients[68]. In hypoxic people, oxygen treatment through nasal prongs, facial covering, high stream nasal cannula or non-obtrusive ventilation might be required. Mechanical ventilation and surprisingly extra physical film oxygen treatment may be viewed as fundamental [68]. Antiviral Treatment broadly acknowledged remedial choice for Corona virus illness that by and large incorporates ribavirin, lopinavir-ritonavir, have been attempted rely upon the narrative information with HIV, SARS and MERS contamination treatments [68,70].

ii. Lopinavir-Ritonavir

This mix has seen that a proficient impact on the serious intense respiratory disorder Covid contamination in vitro and some action against MERS-CoV in creatures [71,72]. In a review, incorporating five cases treated with lopinavir-ritonavir, three cases recuperated and two cases declined; four instances of them had gastrointestinal secondary effects. Lopinavir/ritonavir mix has been at present attempted in the treatment of grown-up SARS-CoV-2 patients with pneumonia, however its viability and wellbeing hold back to be characterized [72].

iii. Ribavirin

In a past control study in SARS, cases treated with lopinavir-ritonavir with ribavirin had end when contrasted with the cases used ribavirin just[73]. Remdesivir is another nucleotide simple that has impacts against SARS-CoV-2 in vitro and connected Covids including SARS and MERS-CoV, both in vitro and in creature contemplates[74]. Many randomized clinical preliminaries are progressing to survey the steady usage of remdesivir viability in humble or serious Corona virus contamination and any clinical impacts of remdesivir on Corona virus stay as of late unidentified. Use of remdesivir, a wide range hostile to RNA drug previous used for Ebola in Corona virus determination[75].

iv. Chloroquine and Hydroxychloroquine

They hamper SARSCoV-2 duplication in vitro, despite the fact that hydroxychloroquine show to have a more strong adequacy considering Corona virus viral disease[68,76,77].

v. Molnupiravir

It is an orally antiviral medication in Phase III trials, that inhibits the replication of certain RNA viruses, and is used to treat COVID-19 in those infected by SARS-CoV-2[78]. Molnupiravir is a prodrug of the synthetic nucleoside derivative N4-hydroxy cytidine and exerts its antiviral action through introduction of copying errors during viral RNA replication[79,80]. It increases the frequency of viral RNA mutations and impairs SARS-CoV-2 replication in animal models and in humans. Molnupiravir inhibits viral reproduction by promoting widespread mutations in the replication of viral RNA by RNA-directed RNA polymerase[81]. It is metabolized into a ribonucleoside analog that resembles cytidine, β-D-N 4-Hydroxycytidine 5′-triphosphate (also called EIDD-1931 5′-triphosphate or NHC-TP)[82,83,84].

XVI. MANAEMENT OF NATURAL HERBS THAT ARE UTILIZED IN THE THERAPEUTICS OF SARS-COV-2

Preventive and restorative specialists have not been created, prescribed for the prologue to endure, natural drugs remains best and used in this administration by different patient in the worldwide level .different home grown normal medications are there for the treatment, the executives or avoidance of this problem. These natural medications may improve the invulnerability and cut off best to enhance in the treatment of Corona virus patients. Different natural medications that are used in the administration of Corona virus issue are: Purple Coneflower (Echinacea purpurea) , zebrawood , clove (Eugenia caryophyllus), cinnamon , dark pepper, long pepper (Piper nigrum), turmeric (Curcuma longa), ginger (Zingiber officinale) , Capparis moonii, Tinospora cordifolia, liqourice,

a. Purple Coneflower/ Echinacea purpurea

Purple coneflower or Echinacea purpurea is famous home grown medication in light of its high adequacy against viral contaminations. This spice can be administrated as concentrates, colors, teas, and splashes. This spice can be used for pneumonic contaminations[85,86]. This spice includes bioactive compound like chicoric acids and caffeic acids, alkylamides, and polysaccharides [87]. This utilization of this home grown concentrate used in the administration of viral disease. Interestingly, regardless of whether it has either mitigating or immune stimulatory impacts stay far from being obviously true. Concentrate from spice considered appearance best enemy of viral viability in the administration of infections with a film through direct virucidal movement. In light of this review, since the human COVID is an

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

encompassed infection, it could be a promising objective for the impact of E. purpurea that can prompt a treatment for Corona virus [85].

b. Tinospora cordifolia

Tinospora cordifolia and its plausible job in the treatment of Corona virus has arisen as the world's most perilous pandemic danger since its December 2019. Settling the issue for this dangerous infection has turned into a major test for the analysts and clinical experts. The best ways of forestalling COVID19 disease are breaking the chain of contamination, helping the body's insusceptible framework, recognizing early and fitting preventive clinical consideration for the contamination[86]. In viral respiratory contaminations, a few phytomedicinal plants help to assemble the resistant framework. T. cordifolia is one of the conventional therapeutic plants utilized as tonic and vitaliser to improve the body's normal opposition diuretic[87]. T. cordifolia stem and entire spices have exhibited immunomodulatory movement and henceforth proposed for the wide range antivirals and protease inhibitors[88]. It has been shown that the T. cordifolia fluid concentrate initiates macrophages which structure the primary line of guard against microbes that attack the living framework[89]. Corona virus goes into a host cell by restricting to ACE2 (Angiotensin Changing over Compound 2) by means of its spike protein receptor-restricting space (RBD). On the off chance that this connection could be disturbed, infection increase could be stayed away from, along these lines altogether decreasing the disease rate. The phytochemical compound, "tinocodiside" has the movement of which is known to tie to the complex ACE2-RBD and subsequently, can debilitate the section of the infection[90,91]. They might restore lung wellbeing by lessening oxidative pressure and upgrading endothelial brokenness[92]. The more grounded docking among ligands and viral targets was uncovered in the investigation of atomic docking with the most un-restricting energy. In this way, it was accounted for that phytoconstituent, cordifolin separated from giloy evoked the most un-restricting energy to show antiviral action[93]. Likewise, the consequences of the reenactment additionally exhibited that berberine can frame 3-chemotrypsin-like protease (3CLpro) docked complex with better security and could go about as a superior CoV-2 protein inhibitor contrasted with different inhibitors. Since berberine is inacceptable restricting communication mode with less restricting energy and more prominent non-reinforced collaboration limit, in this manner it set up a solid office to address possible inhibitors in observing the job of the 3CLpro protein just as additional better control against viral replication[94]. Sub-atomic docking discoveries showed that tinocordiside displayed restricting fondness as anticipated to go about as likely SARS-CoV-2 ((Extreme Intense Respiratory Condition) Covid 2) primary Proteases (Mpro) inhibitor. Such phytoconstituents not simply to repress the transmission and engendering of viral protein into the host cell inside the human body. Moreover, they are additionally more secure to repurpose against Corona virus with no harmfulness[95].

c. Curcuma longa

The fiery course of Corona virus is complicated and multifactorial. Patients with the cytokine storm, featuring the requirement for mitigating treatment to reduce the hyperactivation of the resistant reaction, which actuates this cytokine storm. Zeroing in on the mitigating activity of curcumin, patients with corona virus. In the exploration bunch researched the balance of favorable to fiery cytokines by nanocurcumin. Patients showed high mRNA articulation and discharge of cytokines, IL-1β, IL-6, TNF-α, and IL-18, however showed a huge decrease in IL-6 and IL-1β after treatment with nanocurcumin[96]. Accordingly, investigating the modulatory systems of nanocurcumin, the scientists showed that the quantity of Th17 cells, quality articulation, and serum Th17-interceded factors level (IL-17, IL-21, IL-23, and GM-CSF) were essentially diminished in the two phases of the sickness in the gathering of patients with Corona virus treated with nanocurcumin[97]. In spite of the fast logical advancement in regards to the pathophysiology of Corona virus, the atomic factor-kappa B (NF-κB) pathway is straightforwardly associated with this incendiary interaction and can animate the creation of favorable to provocative cytokines when enacted. Late discoveries prompted concerns in regards to the overstimulation of the NF-κB pathway and its likely commitment to the development of cytokine storms. Studies have shown that NF-κB can be actuated straight by SARS-CoV-2 from Cost like receptors (TLRs) and RAAS framework parts[98]. In such circumstances, the SARS-CoV envelope (E) and nucleocapsid (N) proteins were demonstrated to be straightforwardly identified with NF-κB initiation [99]. Thus, when this protein was erased in a hereditarily changed infection, a decrease in NF-κB actuation was noticed[100]. NF-κB is idle in the cell cytoplasm due

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

to its relationship with the IκB protein complex. Curcumin acts by hindering the phosphorylation of IκB through repressing movement and the resulting enactment of NF-Kb[101,102,103] that is attributable to NF-κB hindrance, there is a decrease in the creation of fiery cytokines, for example, IL-1α, IL-6, and TNF-α [104,105,106]. Viral diseases normally actuate inflammasomes. SARS-CoV has been displayed to communicate somewhere around three proteins that initiate the NLRP3-type inflammasome (Gesture , LRR-, and pyrin area containing protein 3): envelope protein (E), Open Perusing Casing 3a (ORF3a) and these two invigorate NF-κB flagging in this manner advancing the arrival of favorable to fiery cytokines and Open Perusing Edge 8b (ORF8b)[107,108,109].

The amino corrosive succession of protein E is 94.7% moderated in SARS-CoV and SARS-CoV-2, demonstrating the chance of inflammasome initiation in patients with Corona virus. A new report exhibited that dynamic caspase-1 (Casp1p20), IL-1β, IL-18, IL-6, and lactate dehydrogenase (LDH) were expanded in the serum of patients with Corona virus, and that Casp1p20 and IL-18 are items gotten from inflammasomes.

The specialists likewise found dynamic inflammasome NLRP3 in fringe blood mononuclear cells (PBMCs) and in the tissues of perished patients at dissection. The degrees of IL-18 and Casp1p20 were higher in patients who had extreme illness, showing a more awful guess[110]. Accordingly, the guideline of NF-κB by curcumin represses the development of inflammasomes, explicitly NLRP3, diminishing the emission of IL-1β and IL-18[111]. Curcumin at low dosages was found to stifle the mTORC1-Raptor communication, prompting restraint of the mTORC1 complex. Curcumin additionally advanced interference of the mTORC2-Rictor connection at higher portions, in this manner hindering mTORC2[112,113,114].

d. Cinchona

Cinchona succirubra have valuable benefits that heal pyrexia that was discovered by Jesuit missionaries[115]. C. succirubra have several bioactive compound i.e. quinine alkaloids also considered as chloroquine analogue [116]. Nowadays, quinine sulphate has become one of the most wanted drugs in the society for COVID-19 treatment. So, people looked for quinine-containing drugs competitively. Quinine acts as an antiviral agent and function as an immunomodulator in a disease caused by a SARS-CoV-2. Further explanation will also discuss the potentially harmful effects of quinine in individuals with or without COVID-19.

e. Java turmeric

Curcuma xanthorrhiza Roxb is a home grown plant that is generally utilized in Southeast Asian nations come under the family; Zingiberaceae and genus; Curcuma. This plant is native to Indonesia, Thailand, Philippines, Sri Lanka, and Malaysia. It likewise has been utilized as a food added substance to upgrade the kind of food[117]. This plant is utilized to treat a few illnesses[118,119], treated against microbes, mitigating, cell reinforcement, antihyperglycemic, treat BP, antiplatelet, nephroprotective, anticancer, and supplemental specialist for systemic lupus erythematosus (SLE)[120,121,122]. C. xanthorrhiza is a dried rhizome and contains curcuminoids (1%–2%), unpredictable oil (3%–12%), xanthorrhizol (44.5%), and camphor (1.39%).

The presence of xanthorrhizol is explicit and can recognize this plant from C. longa[123,124]. Major bioactive compound of this plant is xanthorrhizol and possess discharge of pro inflammatory cytokines, for example, IL-6 and TNF-α. This restraint cycle is the consequence of hindered inducible nitric oxide synthase (iNOS) and diminished creation of nitric oxide (NO)[125,126,127].

Hence, shows immunosuppressant activity that might be utilized in the therapeutics of COVID-19 in view of its capacity to hinder pro inflammatory cytokines. Patients with COVID-19 are defenseless to CRS. Nonetheless, the organization of xanthorrhizol should be done cautiously and with thought in light of the fact that as of now, no review has been directed with xanthorrhizol in COVID-19. Utilizing xanthorrhizol for treatment and avoidance in COVID-19 actually requires more assessment, particularly in the clinical preliminary setting.

XVII. ROLE OF IMMUNOMODULATORY AGENTS THAT ARE UTILIZED IN THE THERAPEUTICS OF SARS-COV-2

a) Corticosteroids

Serious corona virus is related with irritation related lung injury driven by the arrival of cytokines described by a height in provocative markers. During the pandemic's initial course, glucocorticoids' viability in patients with Corona virus was not all around depicted. The Randomized Assessment of Corona virus Treatment (Recuperation) preliminary, which included hospitalized patients with clinically suspected or lab affirmed SARS-CoV-2 who were haphazardly

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

appointed to got dexamethasone (n=2104) or common consideration (n=4321), showed that the utilization of dexamethasone brought about lower 28-day mortality in patients who were on obtrusive mechanical ventilation or oxygen support however not in patients who were not getting any respiratory support[123]. Based on the aftereffects of this milestone preliminary, dexamethasone is presently viewed as the norm of care either alone or in blend with remdesivir dependent on the seriousness of ailment in hospitalized patients who require supplemental oxygen or non-intrusive or intrusive mechanical ventilation.

b) Interferon-β-1a (IFN- β-1a)

Interferons are cytokines that are fundamental in mounting a resistant reaction to a viral disease, and SARS-CoV-2 stifles its release in vitro[124]. However, past experience with IFN-β-1a in intense respiratory trouble disorder (ARDS) has not benefited[125]. Results from a little randomized, twofold visually impaired, fake treatment controlled preliminary showed the utilization of breathed in IFN-β-1a had more noteworthy chances of clinical improvement and recuperation contrasted with fake treatment[126]. Another little randomized clinical preliminary showed that the clinical reaction utilizing breathed in IFN-β-1a was not essentially unique in relation to the benchmark group. The creators revealed when utilized early, this specialist brought about a more limited length of hospitalization stay and diminished 28-day death rate. Nonetheless, four patients who kicked the bucket in the treatment bunch prior to finishing treatment were prohibited, accordingly making the understanding of these outcomes troublesome[125]. Currently, there is no information accessible with respect to the adequacy of interferon β-1a on the four SARS-CoV-2 VOCs Alpha (B.1.1.7), Beta (B.1.351), Gamma(P1), and Delta (B.1.617.2). Given the deficient and modest quantity of information in regards to this present specialist's utilization and the overall potential for harmfulness, this treatment isn't prescribed to treat corona virus contamination.

c) Interleukin (IL)- 1 antagonist

Anakinra is an interleukin-1 receptor adversary that is FDA supported to treat rheumatoid joint inflammation. Its off-mark use in extreme corona virus was evaluated in a little case-control concentrate being investigated dependent on the reasoning that the serious corona virus is driven by cytokine creation, including interleukin (I.L.)- 1β. This preliminary uncovered that of the 52 patients who got anakinra and 44 patients who got standard of care, anakinra diminished the requirement for intrusive mechanical ventilation and mortality in patients with extreme Corona virus 19. There is no information accessible in regards to the viability of interleukin-1 receptor enemies on the three new SARS-CoV-2 variations (B.1.1.7; B.1.351, and P.1). Given the inadequate information in regards to this treatment dependent on case series just, this isn't presently prescribed to treat corona virus disease.

d) Hostile to IL-6 receptor Monoclonal Antibodies

Interleukin-6 (IL-6) is a pro inflammatory cytokine that is viewed as the critical driver of the hyper inflammatory state related with corona virus. Focusing on this cytokine with an IL-6 receptor inhibitor could dial back the course of aggravation dependent on case reports that showed good results in patients with extreme Corona virus[127,128]. The FDA approved three distinct kinds of IL-6 receptor inhibitors for different rheumatological conditions (Tocilizumab, Sarilumab) and an uncommon problem called Castleman's disorder i.e. overgrowth of cell in the lymph nodes (Siltuximab).

e) Tocilizumab

It is an enemy of interleukin-6 receptor alpha receptor monoclonal neutralizer that has been shown for different rheumatological sicknesses. The information in regards to the utilization of this specialist is blended. A randomized control preliminary including 438 hospitalized patients with serious corona virus pneumonia, among which 294 were randomized to get tocilizumab and 144 to fake treatment, showed that tocilizumab didn't convert into a huge improvement in clinical status or lower the 28-day mortality contrasted with fake treatment[129]. Results from one more randomized, twofold visually impaired fake treatment controlled preliminary including patients with affirmed extreme Corona virus that elaborate 243 patients randomized to get tocilizumab or fake treatment showed that the utilization of tocilizumab was not powerful in forestalling intubation or demise rate[130]. The REMAP-CAP and Recuperation preliminaries (not yet distributed), two enormous randomized controlled preliminaries, showed a mortality advantage in patients displaying fast respiratory decompensation[131].

f) Sarilumab and Siltuximab

They are IL-6 receptor bad guys that may conceivably similarly affect the hyper inflammatory state related with corona virus as tocilizumab. As of now, there no realized

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

distributed clinical preliminaries supporting the utilization of siltuximab in serious corona virus. Then again, a 60-day randomized, twofold visually impaired fake treatment control global stage 3 preliminary that assessed the clinical adequacy, mortality, and wellbeing of sarilumab in 431 patients didn't show any critical improvement in clinical status or mortality rate[132]. Another randomized, twofold visually impaired fake treatment controlled review on sarilumab's clinical viability and security in grown-up patients hospitalized with Corona virus is right now ongoing[133].

g) Baricitinib

It is an oral particular inhibitor of Janus kinase (JAK) 1 and JAK 2 at present showed for moderate to seriously dynamic rheumatoid arthritis patients. It was viewed as an expected treatment for Corona virus dependent on its inhibitory impact on SARS-CoV-2 endocytosis in vitro and on the intracellular flagging pathway of cytokines that cause the late-beginning hyper inflammatory express those outcomes in extreme ailment [134,135,136]. This double inhibitory impact makes it a promising restorative medication against all phases of corona virus. A multicenter observational, review investigation of 113 hospitalized patients with Corona virus pneumonia who got baricitinib joined with lopinavir/ritonavir (baricitinib arm, n=113) or hydroxyl chloroquine and lopinavir-ritonavir (control arm, n=78) revealed critical improvement in clinical indications and 2-week death rate in the baricitinib arm contrasted and the control arm. Results from the ACTT-2 preliminary, a twofold visually impaired, randomized fake treatment controlled preliminary assessing baricitinib in addition to remdesivir in hospitalized grown-up patients with Corona virus, detailed that the blend treatment of baricitinib in addition to remdesivir was better than remdesivir treatment alone in decreasing recuperation time as well as speeding up clinical improvement in hospitalized patients with Corona virus, especially who were getting high stream oxygen supplementation or noninvasive ventilation. Baricitinib, in mix with remdesivir, has been supported for clinical use in hospitalized patients with Corona virus under a EUA gave by the FDA. The viability of baricitinib alone or in blend with remdesivir has not been assessed in the SARS-CoV-2 variations, and there is restricted information on the utilization of baricitinib with dexamethasone[137].

h) Ruxolitinib

It is one more oral specific inhibitor of JAK 1 and 2 that is shown for myelo proliferative problems, polycythemia vera, and steroid-safe GVHD. Like baricitinib, it has been conjectured to inhibitorily affect cytokines' intracellular flagging pathway, making it a possible treatment against corona virus. Results from a little planned multicenter randomized controlled stage 2 preliminary assessing the viability and security of ruxolitinib revealed no measurable contrast than the norm of care. Be that as it may, the vast majority of the patients showed critical chest C.T. improvement and quicker recuperation from lymphopenia[138]. A huge randomized, twofold visually impaired, fake treatment controlled multicenter trial is progressing to survey ruxolitinib's adequacy and security in patients with serious Corona virus[139].

i) Tofacitinib

It is one more oral particular inhibitor of JAK 1 and JAK3 that is shown for moderate to serious RA, psoriatic joint inflammation, and moderate to extreme ulcerative colitis. Given its inhibitory impact on the fiery course, it was estimated that its utilization could enhance the viral irritation intervened lung injury in patients with serious Corona virus. Results from a little randomized controlled preliminary that assessed the adequacy including 289 patients who were randomized to get tofacitinib or fake treatment showed that tofacitinib prompted a lower hazard of respiratory disappointment or demise.

j) Bruton's tyrosine kinase inhibitors

It involves acalabrutinib, ibrutinib, rilzabrutinib are tyrosine kinase inhibitors that control macrophage flagging and actuation at present FDA supported for some hematologic malignancies. It is recommended that macrophage initiation happens during the hyperinflammatory safe reaction seen in extreme Corona virus. Results from a little off-name investigation of 19 hospitalized patients with serious Corona virus who got acalabrutinib featured the likely clinical advantage of BTK hindrance[140]. Clinical preliminaries are in progress to approve the genuine adequacy of these medications in extreme Corona virus disease.

XVIII. CONCLUSION

From this review, conclusion finds that SARS CoV-2 is a viral variant of COVID-19 infection that directly infects the pulmonary regions which is transmitted through person to person via infected contact. These also ensure that

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 741-761 www.ijprajournal.com ISSN: 2249-7781

COVID-19 outbreak has challenged almost all sectors due to the spread of the disease at an alarming rate across the globe. Notably, COVID-19 is an RNA virus that poses a threat to public health. Ideally, the rapid spread of the ailment calls for strong investigation and isolation protocols to avert additional spread. After these infections get entered in the immune might damage the immune responses in a prolonged period time. People who are already suffering from this disorder having very high chances of getting this infection (diabetic patient, nephropathical patients, neurological suffer, CVS, Onco- patients, Asthma, Alcoholic hepatic ailment). This infection can be treated by natural herbs that are easily available like curcumin, purple coneflower, ginger, java turmeric, cinchona utilized for corona pyrexia management .these herbs found best for the therapeutics of this disorder. Along with these herbs some of the immunomodulatory agent allopathic medications are also utilized in the diagnosis of these SARS-CoV-2 infections. Several herbs found best in view of viral infections, and to possess anti-allergic/anti-inflammatory activities, need to be tested against COVID-19. Indian Traditional Medicines have a wide potential i.e. The AYUSH ministry, Govt. of India has issued several advisories from time to time, considering the strength and evidence of these systems of medicines and making considerable efforts to encourage researchers to explore herbal products for COVID-19. Furthermore, growth of lead molecule against SARS-CoV-2 and COVID-19, the herbal drug, manufacturers, and the national and global research organizations should develop necessary strategies for furtherance of preclinical and clinical research on these promising therapeutic leads.

REFRENCES

[1]. Zhu N; Zhang D; Wang W; Li X; Yang B; Song J; Zhao X; Huang B; Shi W; and Lu R.,2020, “A novel corona virus from patients with pneumonia in China” N Engl J Med:727–733.

[2]. World Health Organization. Corona virus disease (COVID-2019) situation reports. Accessed March 21(2020).

[3]. The Novel Corona virus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel corona virus diseases (COVID- 19) China, CDC Wkly(2020):113 –122.

[4]. De Wit E; van Doremalen N; Falzarano D; and Munster VJ.,2016, “Recent insights into emerging corona virus es” SARS and MERS. Nat Rev Microbiol. 14:8:523–534.

[5]. Chan JF; To KK; Tse H; Jin DY; and Yuen KY.,2013, Interspecies transmission and emergence of novel viruses. lessons from bats and birds. Trends Microbiol. 10:544-55.

[6]. Lei J; Kusov Y; and Hilgenfeld R; 2018, Nsp3 of corona virus es, Structures and functions of a large multi-domain protein, Antiviral Res.149:2018:58-74.

[7]. Chan JF; Kok KH; Zhu Z; Chu H; To KK; Yuan S; and Yuen KY.,2020, Genomic characterization of the 2019 novel human-pathogenic corona virus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect, 9(1):221-236.

[8]. Zou X; Chen K; Zou J; Han P; Hao J; and Han Z., 2020, Single-cell RNA-seq data analysis on the receptor ACE 2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection.185–192

[9]. Fehr AR; and Perlman S., 2020, An overview of their replication and pathogenesis. Corona virus es: Methods MolBiol .1282:1–23.

[10]. Hoffmann M; Kleine-Weber H; and Schroeder S.,2020, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is blocked by a clinically proven protease inhibitor, Cell 181(2):271–280

[11]. Lan J; Ge J; and Yu J., 2020, Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor Nature.

[12]. E, Lescure F-X; Yazdanpanah Y; Mentre F; and Peiffer-Smadja.,2020, N Type 1 interferons as a potential treatment against COVID-19 Sallard AntiviralRes 178 :104791.

[13]. Totura AL; and Bavari S.,2020, Broad-spectrum corona virus antiviral drug discovery Expert Opin Drug Discov. 14:4:397–412

[14]. Sheahan TP; Sims AC;
and Zhou S.,2020, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple corona virus es in mice, SciTransl Med.

[15]. Zhao Lu R; and Li X J.,2020, Genomic characterization and epidemiology of 2019 novel corona virus : implications for virus

origins and receptor binding, Lancet, 395;10224:565–574.

[16]. Lu R; Zhao X; Li J; Niu P; Yang B; Wu H; Wang W; Song H; Huang B; and Zhu N., 2020. Genomic characterisation and epidemiology of 2019 novel corona virus : Implications for virus origins and receptor binding, Lancet. **395**:565–574.

[17]. Lai C.C; Shih T.P; Ko W.C; Tang H.J; Hsueh P.R.,2020, Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): The epidemic and the challenges. Int. J. Antimicrob. Agents, **55**:105924.

[18]. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021 Jan;47(1):60-73.

[19]. Worldometer ; COVID-19 CORONA VIRUS PANDEMIC ; Last updated: October 19, 2021, 16:30 GMT.

[20]. Zhu N; Zhang D; and Wang W.,2020, A Novel Corona virus from Patients with Pneumonia in China, 2019. N Engl J Med 382:727.

[21]. Lu R; Zhao X; and Li J.,2020, Genomic characterisation and epidemiology of 2019 novel corona virus : implications for virus origins and receptor binding. Lancet, 395:565.

[22]. Perlman S. Another Decade, Another Corona virus . N Engl J Med 2020; 382:760.

[23]. Zhou P; Yang XL; and Wang XG.,2020, A pneumonia outbreak associated with a new corona virus of probable bat origin, Nature 579:270.

[24]. Chan JF; Lau SK; and To KK.,2020, Middle East respiratory syndrome corona virus : another zoonotic betacorona virus causing SARS-like disease, ClinMicrobiol Rev 28:465.

[25]. International Committee on Taxonomy of Viruses.2015.

[26]. McIntosh K; Dees JH; and Becker WB.,1967, Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl AcadSci U S A 57:933.

[27]. Knipe DM; Howley PM; and Cohen JI.,2013, Virology, 6th ed, Lippincott Williams & Wilkins, a Wolters Kluwer business, Masters PS, Perlman S. Coronaviridae. Philadelphia Vol 2:825.

[28]. Richman DD; Whitley RJ; Hayden FG; McIntosh K; and Peiris JSM.,2009. In: Clinical Virology, 3rd ed, Corona virus es. ASM Press, Washington, DC.1155.

[29]. Enjuanes L; Smerdou C; and Castilla J.,1995,Development of protection against corona virus induced diseases, A review. AdvExp Med Biol.380:197.

[30]. Masters PS; Kuo L; and Ye R.,2006, Genetic and molecular biological analysis of protein-protein interactions in corona virus assembly. AdvExp Med Biol.581:163.

[31]. W Bredenbeek PJ; and Noten AF.,1988, Sequence of mouse hepatitis virus A59 mRNA 2: indications for RNA recombination between corona virus es and influenza C virus. Luytjes Virology.166:415.

[32]. Siu YL; Teoh KT; and Lo J.,2008, The M, E and N structural proteins of the severe acute respiratory syndrome corona virus are required for efficient assembly, trafficking, and release of virus-like particles. J Virol.82:11318.

[33]. Eketunde AO; Mellacheruvu SP; and Oreoluwa P Cureus., Cureus.,2020,"A Review of Postmortem Findings in Patients With COVID-19".

[34]. Zhang C; Wu Z; Li JW; Zhao H; and Wang GQ. "Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality", International Journal of Antimicrobial Agents.2020.

[35]. Gómez-Rial J; Rivero-Calle I; Salas A; and Martinón-Torres F., (2020), "Role of Monocytes/Macrophages in Covid-19 Pathogenesis: Implications for Therapy". Infection and Drug Resistance. **13**: 2485–2493.

[36]. Dong Y; Mo X; and Hu Y.,2020, Epidemiology of COVID-19 among children in China, Pediatrics 145(6), e20200702:(2020).

[37]. Bialek S; and Gierke R.,2020, Corona virus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb. Mortal. Wkly Rep. 69(14);2020:422–426

[38]. Parri N; Lenge M; and Buonsenso D.,2020, Children with Covid-19 in pediatric emergency departments in Italy. N. Engl. J. Med. 383.187–190.

[39]. Wang D; Hu B; and Hu C.,2020, Clinical characteristics of 138 hospitalized patients with 2019 novel corona virus –infected pneumonia in Wuhan, China, JAMA 323(11):1061–1069
[40]. Chen N; Zhou M; Dong X.,2020, Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study, Lancet 395(10223):507–513.
[41]. Characteristics of and important lessons from the Corona virus Disease 2019 (COVID-19) outbreak in China, Wu Z, McGoogan JM. JAMA 323(13), (2020):1239.
[42]. Jin J-M; Bai P; He W.,2020, Gender differences in patients with Covid-19: focus on severity and mortality. Front. Public Health. 8:152.
[43]. Zhou F; Yu T; Du R.,2020, Clinical course and risk factors for mortality of adult in patients with Covid-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062.
[44]. Hoffmann M; Kleine-Weber H; Pohlmann S.,2020, A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells, Mol. Cell. 78(4):779–784
[45]. Wrapp D; Wang N; and Corbett KS.,2020, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367(6483):1260–1263
[46]. Gheblawi M; Wang K; and Viveiros A.,2020, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE 2. Circ. Res. 126(10):1456–1474
[47]. Pal R; Bhansali A.,2020, COVID-19, diabetes mellitus and ACE 2: the conundrum. Diabetes Res. Clin. Pract. 162.
[48]. Zhang S; Wang X; and Zhang H.,2020, The absence of corona virus in expressed prostatic secretion in COVID-19 patients in Wuhan city. Reprod. Toxicol. 96:90–94
[49]. Shenzhen; Liu J; Liao X; Qian S.,2020, Community transmission of severe acute respiratory syndrome corona virus 2, Emerg Infect Dis.
[50]. Chan J; Yuan S; and Kok K., 2020, A familial cluster of pneumonia associated with the 2019 novel corona virus indicating person-to-person transmission: a study of a family cluster.
[51]. Li Q; Guan X; Wu P.,2020, Early transmission dynamics in Wuhan, China, of novel corona virus -infected pneumonia. N Engl J Med.
[52]. Ong SW; Tan YK; Chia PY; Lee TH; Ng OT; Wong MS.,2020, Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) from a symptomatic patient, JAMA.
[53]. E Prompetchara; C Ketloy; T Palaga.,2020, Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asi Pac J All Imm. 38(1),1–9.
[54]. Q Liu; Y-h; Zhou; Z-q Yang.,2020, The cytokine storm of severe influenza and development of immunomodulatory therapy: Cell Mol Immunol.13(1), 3–10.
[55]. P Mehta; D F Mcauley; M Brown; E Sanchez; R S Tattersall; J J Manson.,2020, COVID-19: consider cytokine storm syndromes and imm: the Lancet. 395, 10229:1033-1034.
[56]. Hui DS; I Azhar E; Madani TA; Ntoumi F; Kock R; Dar O., The continuing 2019-nCoV epidemic threat of novel corona virus es to global health - The latest 2019 novel corona virus outbreak in Wuhan, China"International Journal of Infectious Diseases.264–266.
[57]. Murthy S; Gomersall CD; Fowler RA JAMA.,2020. Care for Critically Ill Patients With COVID-19. **323** (15):1499-1500.
[58]. StatPearls; Cascella M; Rajnik M; Cuomo A; Dulebohn SC; Di Napoli R.,2020. Features, Evaluation and Treatment Corona virus (COVID-19)". Treasure Island (FL): StatPearls Publishing. PMID 32150360. Retrieved 18 March .
[59]. Heymann DL; Shindo N.,2020 (WHO Scientific and Technical Advisory Group for Infectious Hazards), "COVID-19: what is next for public health?". Lancet. **395** (10224):542–545.
[60]. "Neurological complications of corona virus and COVID-19". Revista de Neurología, Carod-Artal FJ **70** (9): 311–322. doi:10.33588/rn.7009.2020179. PMID 32329044 :(2020).

[61]. Toscano G; Palmerini F; Ravaglia S; Ruiz L; Invernizzi P; Cuzzoni MG.,2020, "Guillain-Barré Syndrome Associated with SARS-CoV-2". The New England Journal of Medicine. 382 (26):2574–2576.
[62]. "Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19". World Health Organization (WHO). 15 May 2020. Retrieved 20 May 2020.
[63]. HAN Archive – 00432. U.S. Centers for Disease Control and Prevention (CDC) (Report). 15 May 2020. Retrieved 20 May 2020.
[64]. Poyiadji N; Shahin G; Noujaim D; Stone M; Patel S; Griffith B.,2020. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features". Radiology. 296 (2): E119–E120.
[65]. Córdoba-Vives S; Peñaranda G.,2020, "COVID-19 y Embarazo". Medical Journal of Costa Rica :629.
[66]. Das S; Dhar S.,2021. "Mucormycosis Following COVID-19 Infections: an Insight", The Indian Journal of Surgery:1–2.
[67]. . Baruah C; Devi P; Deka B; Sharma DK.,2021. "Mucormycosis and Aspergillosis have been Linked to Covid-19-Related Fungal Infections in India". Advancements in Case Studies. **3** (1). 10.31031/AICS.2021.03.000555.
[68]. Shen K; Yang Y; Wang T; Zhao D; Jiang Y; Jin R.,2020. Diagnosis, treatment, and prevention of 2019 novel corona virus infection in children: experts' consensus statement. World J Pediatr. Feb 7.
[69]. Ahn DG; Shin HJ; Kim MH; Lee S; Kim HS; Myoung J.,2020. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Corona virus Disease, (COVID-19). J MicrobiolBiotechnol 30(3):313–24.
[70]. Shen C; Wang Z; Zhao F; Yang Y; Li J; Yuan J.,2020. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma:Mar 27.
[71]. Dong X; Cao YY; Lu XX; Zhang JJ; Du H; Yan YQ.,2020, Eleven Faces of Corona virus Disease 2019. Allergy.
[72]. Chan JF; Yao Y; Yeung ML; Deng W; Bao L; Jia L.,2015. Treatment with Lopinavir/Ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset, J Infect Dis. 212(12):1904–13.
[73]. Lim J; Jeon S; Shin HY; Kim MJ; Seong YM; Lee WJ.,2020, Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci. 35(6):79.
[74]. Guo YR; Cao QD; Hong ZS; Tan YY; Chen SD; Jin HJ.,2020, The origin, transmission and clinical therapies on corona virus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 7(1):11.
[75]. Wang M; Cao R; Zhang L; Yang X; Liu J; Xu M.,2020, Remdesivir and chloroquine effectively inhibit the recently emerged novel corona virus (2019-nCoV) in vitro.Cell Res. 30(3):269.
[76]. Cao YC; Deng QX; Dai SX.,2020, Remdesivir for severe acute respiratory syndrome corona virus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis. 101647.
[77]. Yao X; Ye F; Zhang M; Cui C; Huang B; Niu P.,2020, In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Clin Infect Dis.
[78]. Product approval Molnupiravir. Medicines and Healthcare products Regulatory Agency (MHRA). 4 November 2021.
[79]. Toots M; Yoon JJ; Cox RM; Hart M; Sticher ZM; Makhsous N.,2019,Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. Sci Transl Med. **11**,515.
[80]. Toots M; Yoon JJ; Hart M; Natchus MG; Painter GR; Plemper RK.,2020, Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model. Transl Res. **218**:16–28.
[81]. Lowe D.,2021. Molnupiravir Mutations.
[82]. Ainter WP; Holman W; Bush JA; Almazedi F; Malik H; Eraut NC.,2021, Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimic Age Chemo. **65** (5)
[83]. Amara A; Penchala SD; Else L; Hale C; FitzGerald R; Walker L.,2021, The

development and validation of a novel LC-MS/MS method for the simultaneous quantification of Molnupiravir and its metabolite ß-d-N4-hydroxycytidine in human plasma and saliva. J Pharma Biomed Anal. **206**,114356.

[84]. Mole B., 2021. Meet molnupiravir, Merck's Thor-inspired pill that hammers COVID". Ars Technica.

[85]. Sharma S; A Anderson; R Schoop and JB Hudson.,2020, Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract. M. Antivir Res. 83(2):165–170.

[86]. J Hudson; S Vimalanathan.,2011, Pharmaceuticals, Echinacea-a source of potent antivirals for respiratory virus infections.4(7),1019–1031.

[87]. J Barnes; L A Anderson; S Gibbons; J D Phillipson.,2005, Echinaceaspecies (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties. J Pharma Pharmacol. 57(8),929–954.

[88]. B Vellingiri; K Jayaramayya; M Iyer; A Narayanasamy; V Govindasamy; B Giridharan; K Rajagopalan.,2020, COVID-19: A promising cure for the global panic. Sci Total Env. 725,138277.

[89]. B T Chand Mittal.,2020, Global Care through Ayurveda in Pandemic of COVID-19. Int J Health Sci Res. 10,165-172.

[90]. Rastogi D N; Pandey; RH Singh.,2020, COVID-19 Pandemic: A pragmatic plan for Ayurveda Intervention, S J Ayur Integrative med.1-4.

[91]. S Sachan; K Dhama; SK Latheef; H Abdul Samad; AK Mariappan; P Munuswamy; RK Singh.,2019, Immunomodulatory Potential of Tinosporacordifolia and CpG ODN (TLR21 Agonist against the Very Virulent, Infectious Bursal Disease Virus in SPF Chicks, Vaccines.

[92]. R Gayatri; S Lavanya; M Hussain; J Veslin., The New Pandemic Covid-19: Treatment Options and Developments, Asian Journal of Biology, :1-13.

[93]. DS Rajput.,2020 .Evolution, Ayurveda, immunity, and preventive aspects for emerging infectious diseases such as COVID19, DS, International Journal of Research in Pharmaceutical Sciences, 11 :86-93.

[94]. M Dimri; VS Rajwar; L Kush.,2020. Rasayana Drugs Promise Better Anti-Covid-19 Medications, Asian Journal of Pharmaceutical Research and Development:148- 149.

[95]. RC Mishra; R Kumari; S Yadav; JP Yadav.,2020. Antiviral potential of phytoligands against chymotrypsin-like protease of COVID- 19 virus using molecular docking studies: An optimistic approach:1-15.

[96]. P Chowdhury.,2020. Insilico investigation of phytoconstituents from Indian medicinal herb Tinosporacordifolia (giloy) against SARS-CoV2 (COVID-19) by molecular dynamics approach, Journal of Biomolecular Structure and Dynamics:1-18 .

[97]. P Shree; P Mishra; C Selvaraj; SK Singh; R Chaube; N Garg; YB Tripathi.,2020 Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants – Withaniasomnifera (Ashwagandha), Tinosporacordifolia (Giloy) and Ocimum sanctum (Tulsi) – a molecular docking study, Journal of Biomol Structure and Dynamics:1-14.

[98]. Valizadeh; H Abdolmohammadi-vahid; S Danshina; S ZiyaGencer; M Ammari; A Sadeghi.,2020. A Nano-curcumin Therapy, a Promising Method in Modulating Inflammatory Cytokines in COVID-19 Patients. Int. Immunopharma.

[99]. Tahmasebi S; El-Esawi; M A Mahmoud; Z H Timoshin; A Valizadeh; H Roshangar L.,2020 Immunomodulatory Effects of Nanocurcumin on Th17 Cell Responses in Mild and Severe COVID-19 Patients. J. Cel. Physiol. 236:5325–5338.

[100]. Mahmudpour M; Roozbeh J; Keshavarz M; Farrokhi S; Nabipour I.,2020 COVID-19 Cytokine Storm: The Anger of Inflammation.SSSS

[101]. Liao Q.-J; Ye L.-B; Timani K A; Zeng Y.-C; She Y.-L; Ye L.,2005, Activation of NF-kappaB by the Full-Length Nucleocapsid Protein of the SARS Corona virus . ActaBiochim. Biophys. Sinica. 37,607–612.

[102]. DeDiego M L; Nieto-Torres J L; Regla-Nava J A; Jimenez-Guardeno J M; Fernandez-Delgado R; Fett C.,2014. Inhibition of NF- B-Mediated Inflammation

in Severe Acute Respiratory Syndrome Corona virus -Infected Mice Increases Survival, J. Virol. 88,913–924.

[103]. Karunaweera N; Raju R; Gyengesi E; Münch G.,2015, Plant Polyphenols as Inhibitors of NF-Îob Induced Cytokine Productionâ€"a Potential Anti-inflammatory Treatment for Alzheimer's Disease. Front. Mol. Neurosci. 8, 1–5.

[104]. Wang Y; Tang Q; Duan P; Yang L.,2018, Curcumin as a Therapeutic Agent for Blocking NF-Kb Activation in Ulcerative Colitis. Immunopharmacol Immunotoxicol. 40,476–482.

[105]. Cheemanapalli S; Chinthakunta N; Shaikh N M; Shivaranjani V; Pamuru R R; Chitta S K.,2019. Comparative Binding Studies of Curcumin and Tangeretin on Up-Stream Elements of NF-kB Cascade: a Combined Molecular Docking Approach.. Netw. Model. Anal. Health Inform. Bio informa. 8,1–11.

[106]. Rahardjo B; Widjajanto E; Sujuti H; Keman K.,2014, Curcumin Decreased Level of Proinflammatory Cytokines in Monocyte Cultures Exposed to Preeclamptic Plasma by Affecting the Transcription Factors NF-Kb and PPAR-γ. Biomarkers Genomic. 105–115.

[107]. Ma T; Guo C J; Zhao X; Wu L; Sun S X; Jin Q H.,2015, The Effect of Curcumin on NF-Kb Expression in Rat with Lumbar Intervertebral Disc Degeneration. Eur. Rev. Med. Pharmacol. Sci. 19,1305–1314.

[108]. Yadav R; Jee B; Awasth S K.,2015, Curcumin Suppresses the Production of Pro-inflammatory Cytokine Interleukin-18 in Lipopolysaccharide Stimulated Murine Macrophage-like Cells, Ind. J. Clin. Biochem. 30:109–112.

[109]. Nieto-Torres J L; Verdiá-Báguena C; Jimenez-Guardeño J M; Regla-Nava J A; Castaño-Rodriguez C; Fernandez-Delgado R.,2015. Severe Acute Respiratory Syndrome Corona virus E Protein Transports Calcium Ions and Activates the NLRP3 Inflammasome, Virol. 485,330–339.

[110]. Chen I Y; Moriyama M; Chang M F; Ichinohe T.,2019, Severe Acute Respiratory Syndrome Corona virus Viroporin 3a Activates the NLRP3 Inflammasome. Front. Microbiol. 10,1–9.

[111]. Shi C S; Nabar N R; Huang N N; Kehrl J H.,2019, SARS-corona virus Open Reading Frame-8b Triggers Intracellular Stress Pathways and Activates NLRP3 Inflammasomes. Cell Death Discov.

[112]. Rodrigues T S; de Sá K S G; Ishimoto A Y; Becerra A; Oliveira S; Almeida L.,2021, Inflammasomes Are Activated in Response to SARS-CoV-2 Infection and Are Associated with COVID-19 Severity in Patients. J. Exp. Med. 218.

[113]. Yin H; Guo Q; Li X; Tang T; Li C; Wang H.,2018, Curcumin Suppresses IL-1β Secretion and Prevents Inflammation through Inhibition of the NLRP3 Inflammasome. J Immunol. 200, :2835–2846.

[114]. Beevers C S; Chen L; Liu L; Luo Y; Webster N J G; Huang S.,2009, Curcumin Disrupts the Mammalian Target of Rapamycin-Raptor Complex, Cancer Res. 69, 1000–1008.

[115]. Beevers C S; Li F; Liu L; Huang S.,2006, Curcumin Inhibits the Mammalian Target of Rapamycin-Mediated Signaling Pathways in Cancer Cells. Int. J. Cancer. 119, 757–764.

[116]. Johnson S M; Gulhati P; Arrieta I; Wang X; Uchida T; Gao T.,2009, Curcumin Inhibits Proliferation of Colorectal Carcinoma by Modulating Akt/mTOR Signaling, Anticancer Res. 29,:3185–3190.

[117]. C Maldonado; C J Barnes; C Cornett.,2017, “Phylogeny predicts the quantity of antimalarial alkaloids within the iconic yellow Cinchona bark (Rubiaceae: Cinchona calisaya). Frontiers in Plant Science. 8:1–16.

[118]. E Abolghasemi; S H Moosa-Kazemi; M Davoudi; A Reisi; M T Satvat.,2012, Comparative study of chloroquine and quinine on malaria rodents and their effects on the mouse testis. Asi Paci J Trop Biomed. 2(4), 311–314.

[119]. S F Vesely; M Nallappan; T T Tee.,2015, Xanthorrhizol: a review of its pharmacological activities and anticancer properties. Can Cell Int. 15;100,1–15.

[120]. C Singgih Wahono; C DiahSetyorini; H Kalim; N Nurdiana; K Handono.,2017, Effect of Curcuma xanthorrhiza supplementation on systemic lupus erythematosus patients with hypovitamin D which were given vitamin D_3 towards disease activity (SLEDAI), IL-6, and TGF-β1 serum Int J Rheumatol.8.

[121]. M B Kim; C Kim; Y Song; J K Hwang.,2014, Antihyperglycemic and anti-inflammatory effects of standardized Curcuma xanthorrhiza Roxb. extract and its active compound xanthorrhizol in high-fat diet-induced obese mice. Evi Bas Comp Alt Med.10.

[122]. S D'alessandro; D Scaccabarozzi; L Signorini.,2020, The use of antimalarial drugs against viral infection. Microorg. 8(85),1–26.

[123]. N Ismail; A H Lope Pihie; M Nallapan.,2005, Xanthorrhizol induces apoptosis via the up-regulation of Bax and p53 in HeLa cells. Antican Res. 25,2221–2228.

[124]. E Van Galen; B Kroes.,2014, Assessment report on Curcuma xanthorrhiza Roxb. (C. xanthorrhiza D. Dietrich), rhizome. Eur Med Age. 44,1–22.

[125]. C S Lim; D Q Jin; H Mok.,2005, Antioxidant and antiinflammatory activities of xanthorrhizol in hippocampal neurons and primary cultured microglia. J Neurosci Res. 82(6),831–838.

[126]. E Van Galen; B Kroes.,2014, Assessment report on Curcuma xanthorrhiza Roxb. (C. xanthorrhiza D. Dietrich), rhizome. Eur Med Age. 44,1–22.

[127]. Horby P; Lim WS; Emberson JR; Mafham M; Bell JL; Linsell L; Staplin N; Brightling C; Ustianowski A; Elmahi E; Prudon B; Green C; Felton T; Chadwick D; Rege K; Fegan C; Chappell LC; Faust SN; Jaki T; Jeffery K; Montgomery A; Rowan K; Juszczak E; Baillie JK; Haynes R; Landray MJ.,2021, RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 25;384(8),693-704.

[128]. Yuen CK; Lam JY; Wong WM; Mak LF; Wang X; Chu H; Cai JP; Jin DY; To KK; Chan JF; Yuen KY; Kok KH.,2019, SARS-CoV-2 nsp13, nsp14, nsp15 and orf6 function as potent interferon antagonists. Emerg Microbes Infect, 2;9(1),1418-1428.

[129]. Ranieri VM; Pettilä V; Karvonen MK; Jalkanen J; Nightingale P; Brealey D; Mancebo J; Ferrer R; Mercat A; Patroniti N; Quintel M; Vincent JL; Okkonen M; Meziani F; Bellani G; MacCallum N; Creteur J; Kluge S; Artigas-Raventos A; Maksimow M; Piippo I; Elima K; Jalkanen S; Jalkanen M; Bellingan G.,2020, INTEREST Study Group. Effect of Intravenous Interferon β-1a on Death and Days Free from Mechanical Ventilation among Patients with Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 323(8),725-733.

[130]. Monk PD; Marsden RJ; Tear VJ; Brookes J; Batten TN; Mankowski M; Gabbay FJ; Davies DE; Holgate ST; Ho LP; Clark T; Djukanovic R; Wilkinson TMA.,2021, Inhaled Interferon Beta COVID-19 Study Group. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med ;9(2),196-206.

[131]. E Rahmani H; Khalili H; Hajiabdolbaghi M; Salehi M; Abbasian L; Kazemzadeh H; Yekaninejad MS.,2020, A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19. Davoudi-Monfared Antimicrob Agents Chemother. 64,9.

[132]. Huet T; Beaussier H; Voisin O; Jouveshomme S; Dauriat G; Lazareth I; Sacco E; Naccache JM; Bézie Y; Laplanche S; Le Berre A; Le Pavec J; Salmeron S; Emmerich J; Mourad JJ; Chatellier G; Hayem G.,2020, Anakinra for severe forms of COVID-19: a cohort study, Lancet Rheumatol. 2,7.

[133]. Lescure FX; Honda H; Fowler RA; Lazar JS; Shi G; Wung P; Patel N; Hagino O.,2021, Sarilumab COVID-19 Global Study Group. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 9(5),522-532.

[134]. Cellina M; Orsi M; Bombaci F; Sala M; Marino P; Oliva G.,2020, Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab. Diagn Interv Imaging. 101(5),323-324.

[135]. Michot JM; Albiges L; Chaput N; Saada V; Pommeret F; Griscelli F; Balleyguier C; Besse B; Marabelle A; Netzer F; Merad M; Robert C; Barlesi F; Gachot B; Stoclin A.,2020, Tocilizumab, an anti-IL-6 receptor

antibody, to treat COVID-19-related respiratory failure. Ann Oncol. 7,961-964.

[136]. Rosas IO; Bräu N; Waters M; Go RC; Hunter BD; Bhagani S; Skiest D; Aziz MS; Cooper N; Douglas IS; Savic S; Youngstein T; Del Sorbo L; CubilloGracian A; De La Zerda DJ; Ustianowski A; Bao M; Dimonaco S; Graham E; Matharu B; Spotswood H; Tsai L; Malhotra A.,2021, Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 384(16),1503-1516.

[137]. Stebbing J; Phelan A; Griffin I; Tucker C; Oechsle O; Smith D; Richardson P.,2020, COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 20(4),400-402.

[138]. Stone JH; Frigault MJ; Serling-Boyd NJ; Fernandes AD; Harvey L; Foulkes AS; Horick NK; Healy BC; Shah R; Bensaci AM; Woolley AE; Nikiforow S; Lin N; Sagar M; Schrager H; Huckins DS; Axelrod M; Pincus MD; Fleisher J; Sacks CA; Dougan M; North CM; Halvorsen YD; Thurber TK; Dagher Z; Scherer A; Wallwork RS; Kim AY; Schoenfeld S; Sen P; Neilan TG; Perugino CA; Unizony SH; Collier DS; Matza MA; Yinh JM; Bowman KA; Meyerowitz E; Zafar A; Drobni ZD; Bolster MB; Kohler M; D'Silva KM; Dau J; Lockwood MM; Cubbison C; Weber BN; Mansour MK.,2020, BACC Bay Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. Tocilizumab Trial Investigators. N Engl J Med. 383(24),2333-2344.

[139]. Kalil AC; Patterson TF; Mehta AK; Tomashek KM; Wolfe CR; Ghazaryan V; Marconi VC; Ruiz-Palacios GM; Hsieh L; Kline S; Tapson V; Iovine NM; Jain MK; Sweeney DA; El Sahly HM; Branche AR; Regalado Pineda J; Lye DC; Sandkovsky U; Luetkemeyer AF; Cohen SH; Finberg RW; Jackson PEH; Taiwo B; Paules CI; Arguinchona H; Erdmann N; Ahuja N; Frank M; Oh MD; Kim ES; Tan SY; Mularski RA; Nielsen H; Ponce PO; Taylor BS; Larson L; Rouphael NG; Saklawi Y; Cantos VD; Ko ER; Engemann JJ; Amin AN; Watanabe M; Billings J; Elie MC; Davey RT; Burgess TH; Ferreira J; Green M; Makowski M; Cardoso A; de Bono S; Bonnett T; Proschan M; Deye GA; Dempsey W; Nayak SU; Dodd LE; Beigel JH.,2021, ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 384(9),795-807.

[140]. Gordon AC; Mouncey PR; Al-Beidh F; Rowan KM; Nichol AD; Arabi YM; Annane D; Beane A; van Bentum-Puijk W; Berry LR; Bhimani Z; Bonten MJM; Bradbury CA; Brunkhorst FM; Buzgau A; Cheng AC; Detry MA; Duffy EJ; Estcourt LJ; Fitzgerald M; Goossens H; Haniffa R; Higgins AM; Hills TE; Horvat CM; Lamontagne F; Lawler PR; Leavis HL; Linstrum KM; Litton E; Lorenzi E; Marshall JC; Mayr FB; McAuley DF; McGlothlin A; McGuinness SP; McVerry BJ; Montgomery SK; Morpeth SC; Murthy S; Orr K; Parke RL; Parker JC; Patanwala AE; Pettilä V; Rademaker E; Santos MS; Saunders CT; Seymour CW; Shankar-Hari M; Sligl WI; Turgeon AF; Turner AM; van de Veerdonk FL; Zarychanski R; Green C; Lewis RJ; Angus DC; McArthur CJ; Berry S; Webb SA; Derde LPG.,2021. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. REMAP-CAP Investigators. N Engl J Med. 22;384(16),1491-1502.