



A REVIEW ON USE OF AZITHROMYCIN AND DOXYCYCLINE IN COVID-19 TREATMENT

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ABSTRACT

A novel corona virus SARS-CoV-2 has led to an outbreak of the highly infectious pan demic COVID-19 complicated viral pneumonia. Patients with risk factors frequently develop secondary infections where the role of appropriate antibiotics is mandatory. However, the efforts of drug repurposing lead to recognizing the role of certain antibiotics beyond the management of infection. The current review provided the detailed antiviral, immunomodulatory effect, unique pharmacokinetic profile of two antibiotics namely azithromycin and doxycycline. It summarizes current clinical trials and concerns regarding safety issues of these drugs.

Azithromycin has excellent lung tissue penetration, broad antibacterial effectiveness, and potential antiviral activity against COVID-19. In limited clinical trials, it also showed efficacy when paired with other antiviral medications, however many clinicians are concerned about cardiovascular risk in susceptible patients. Doxycycline plays an important role in the treatment of pneumonia. It has a number of advantages, including cardiac safety, easy access to lung tissue, antiviral potential, and immunomodulation effects through a variety of routes. The pharmacological characteristics of these medicines raise the possibility of additional research into their use in the treatment of COVID-19.

COVID-19 infection, which has no renowned cures or treatments, has wreaked havoc on humanity and has gone beyond precedent. Currently, the only therapeutic option for controlling COVID-19 symptoms and associated co-infections in order to reduce mortality is to repurpose existing medications. Antimicrobials such as anti-parasitic, antiviral, and antibiotics are being evaluated at various levels. Topics covered include: Doxycycline, a broad-spectrum antibiotic with antiviral and anti-inflammatory effects, was recently repurposed for COVID-19 treatment after extensive research in clinical trials, either alone or in combination with other medications. The potential therapeutic applications of Doxycycline in COVID-19 treatment, or its potential negative consequences in terms of antimicrobial resistance conferred by repurposing the antibiotic, are discussed in the review. Background Azithromycin's antibacterial, anti-inflammatory, and antiviral characteristics suggest that it could be used to treat COVID-19. There are no randomise data in mild-to-moderate disease. We wanted to see if azithromycin may help people with mild-to-moderate infections avoid hospitalisation. COVID-19. Covid is 19 years old. As the sickness becomes more bad by the day, more variables will emerge. 100 percent corid-19 There isn't one. Today's researchers are located all around the world. In 2020, the World Health Organization declared an outbreak. are attempting This mixture can be used to some extent as a solution to this (AZI) and (DOXY).

Keywords: Azithromycin, Covid-19, Doxycycline, SARS-CoV-2, Omicron, Nongonococcal urethritis, Epidemic, Delta.

INTRODUCTION

A novel coronavirus is a type of coronavirus that has never been seen before. Coronavirus Disease (COVID-19 / Covid-19) is a disease caused by Novel Coronavirus, which was initially discovered in Wuhan, China. Corona is CO, virus is VI, and disease is D. '2019 Novel Coronavirus,' or '2019-nCoV1,' was the previous name for the disease. The COVID-19/Covid-19 virus is a novel virus linked to Severe Acute Respiratory Syndrome (SARS) (SARS). Coughing or sneezing of an infected individual, direct contact with inhaled particles / droplets, or contacting a virus-contaminated surface are all ways for the virus to spread. The COVID-19 / Covid-19 virus only lasts a few hours on the surface before being killed by a basic disinfectant.

Fever, cough, shortness of breath, and other symptoms may occur. Pneumonia or shortness of breath are more dangerous symptoms, and in acute but uncommon situations, death can result. COVID-19 / Covid-19 has symptoms that are comparable to the flu (influenza) or a regular cold, which is more likely. As a result, it's critical to test to see if it's working. COVID-19 / CO It's vital to understand that there are simple measures to avoid this, such as frequent hand washing and taking precautions when breathing (cover your mouth and nose by bending the tissue or elbow when coughing or sneezing, and place the tissue in a closed dustbin after use.) Toss it out. We don't know much about how it affects children because it's a novel virus. Although anyone can become infected with this virus, there have been fewer occurrences of COVID-19 thus far.

There is currently little evidence on whether a pregnant woman can spread the virus to her baby when pregnant or what effect it may have on her kid. This is still being researched. Take the appropriate steps to avoid exposing pregnant women to this virus, and get medical attention if you develop symptoms such as fever, cough, or shortness of breath.

Statistics (On 20/01/2022)

Table No 1: Global and Indian statistic of Covid-19 and Omicron variant.

Sr. No.	Region	Covid-19 positive cases	Covid 19 deaths	Omicron Positive cases	Omicron deaths
1)	Global	26.9cr	52.9L	4.44mil	7.27K
2)	India	3.47cr	4.74L	1.79L	3.33K

➤ What Is a Variant?

When an infected human cell assembles new coronaviruses, it occasionally makes tiny copying errors called mutations. Scientists can track mutations as they are passed down through a lineage, a branch of the coronavirus family tree. A group of coronaviruses that share the same inherited set of distinctive mutations is called a variant.

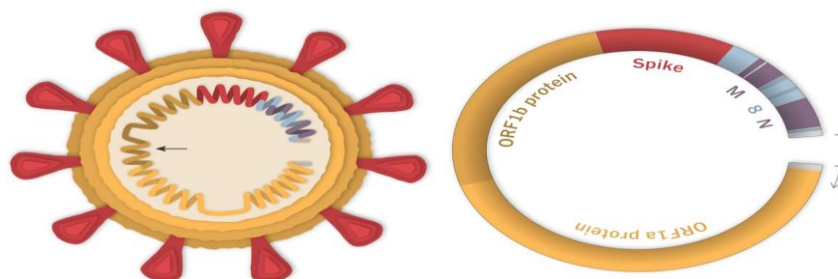


Image 01 coronaviruse mutations.

➤ **AVAILABLE TREATMENT-**

There is currently no cure for covid-19 that is 100 percent certain. The sickness is worsening by the day, and the new Omicron version has piqued the world's interest.

• **Remdisivir** and

• **favipiravir** are two antiviral drugs.

✓ **Treatments and medicines currently available in the market-**

➤ **Remdesivir** Dose of injection – 100 mg (concentrated solution)

The cost of Ramdesivir Injection is quite high. On covid-19, this is regarded as a viable option. It was widely utilised in the first wave (Covid-19), however it had a low cure rate. Due to a scarcity of this injection, it has not yet reached the general public. The average person cannot afford this medicine due to its high cost. Some patients had the effect, but not all.

➤ **Side effects of Remdisivir-**

Recently, there have been multiple occurrences of SARS Covid-2 where the medicine Remdisivir has been mislabeled. It has a direct impact on the health of the population. It also has some major negative effects.

Remdesivir has a number of side effects. Nausea, vomiting, perspiration, dizziness, and acne are all symptoms of being cold or shivering. Increased or decreased heart rate, swelling of the face.

➤ **remdesivir banned in india-**

Remdesivir is not recommended for patients hospitalised with Covid-19, regardless of how critically ill they are, according to the WHO Guideline Development Group (GDG) panel of worldwide experts, because there is presently no evidence that it improves mortality or reduces the requirement for ventilation. The suggestion is based on a recent data evaluation that compares the effects of several Covid-19 medication therapies. It contains data from four international randomised studies involving nearly 7,000 Covid-19 patients who were hospitalised. The WHO GDG expert panel, which includes experts from around the world and four patients who have had Covid-19, concluded that Remdesivir had no meaningful effect on mortality or other important patient outcomes, such as the need for mechanical ventilation or time to clinical improvement, after thoroughly reviewing the evidence. The WHO has decided to remove Remdesivir from the pre-qualification list as a result of all of these unfavourable recommendations, "added Dr. Swaminathan. Results from previous interim studies.

➤ **Favipiravir-**

antiviral treatment The duration of shedding and the severity of the effector immune response are likely to decrease in the early stages of infection; however, due to higher levels of early SARS-CoV-2 replication, there may be a limited influence on viral area under the curve (AUC). As a result, it was projected that the only way to minimise viral AUC is to start taking antivirals as soon as possible, possibly before the onset of symptoms and before the peak viral load. This backs up the notion of hitting hard and hitting fast. Adults should take 1800 mg orally twice day on the first day, then 800 mg orally twice daily on the second day. Favipiravir is a type of antiviral medication.

to treat influenza, and it could be used to treat other viral illnesses as well. Incrise has no recovery rate.

• The majority of side effects are minor and will go away as your body adjusts to the medication. Fabiflu's most common negative effects.

• Increased uric acid in the blood

• Diarrhea

• Lower white blood cell count (neutrophils)

• Higher liver enzymes

➤ **Tosilizumab-**

Tosilizumab-treated patients required mechanical breathing in 33 (18%) cases. New infections were carefully observed in the Tosilizumab group compared to the standard therapy group. Out of 179 patients treated with Tosilizumab, 24 (13%) had new infections, compared to 14 in the standard therapy group (4 percent). Routine care was provided to 365 patients. Patients treated with usual treatment died 20% of the time, while patients treated with tocilizumab died 7% of the time.

➤ **Side effect of tosilizumab-**

The following are the most common side effects:

-a painful throat or cough, a clogged or runny nose.

-dizziness or headaches -mouth ulcers.

-blood pressure that is too high.

-Hypercholesterolemia is a condition in which a person's cholesterol levels are abnormally high (increased cholesterol in the blood).

-allergic symptoms, such as aching muscles, shortness of breath, tightness in the chest, wheezing, and a high temperature.

-increased weight or swollen ankles.

-skin rashes, infections, or itching -abdominal pain or stomach irritation.

-In patients with rheumatoid arthritis, tocilizumab has been proven to increase the risk of infection.

➤ **Herbal medications-**

Chinese herbal medications were also evaluated as an alternate option for COVID-19 prophylaxis in high-risk populations based on historical records and anecdotal evidence of SARS and H1N1 pdm09 prevention. However, there is no clinical evidence that these medicines are effective in preventing this new viral illness. 57,58 Some traditional Chinese medicine was frequently used during the COVID-19 outbreak in China, and the six most commonly used are listed here. Astragali Radix (Huangqi), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikovia Radix (Fangfeng), Atractylodis Macrocephalae Rhizoma (Baizhu), Lonicerae Japonicae Flos (Baizhu), Lonicerae Japonicae Flos (Baizhu), Lonicerae Japonicae Flos (Baizhu), Lonicerae Japonicae Flos (Baizhu).

Fructus forsythiae and Fructus forsythiae (Lianqiao). To confirm the possible preventive impact of Chinese medicine, however, large-scale clinical trials should be done.

➤ **Nongonococcal urethritis-**

Nongonococcal urethritis, or NGU, is urethral inflammation caused by nongonococcal bacteria. Having unprotected sex with an infected person is the main cause of NGU. However, there are nonsexual causes of NGU, such as UTIs. Talk to your doctor if you develop signs of NGU, such as discharge from the penis or pain while peeing.

Chlamydia trachomatis, Mycoplasma genitalium, and Neisseria gonorrhoeae produce nongonococcal urethritis (NGU), which is one of the most frequent sexually transmitted illnesses. NGU's pathogen, Mycoplasma, can cling to the genitourinary tract's surface, causing an epithelial infection. The incidence of NGU has increased in recent years as a result of changes in people's lifestyles and sexual behaviours, and the predominant clinical manifestation is urethritis, which has a serious impact on people's quality of life and health.

Patients with NGU are currently treated with azithromycin (a broad-spectrum antibiotic) as a monotherapy. A macrolide antibiotic called azithromycin is used to treat infections caused by Gram-positive aerobic bacteria like Staphylococcus aureus. However, numerous organisms have acquired resistance to azithromycin as a result of its broad clinical use in recent years. Azithromycin also has a number of side effects. As a result, while it has an influence on NGU, it still has some limitations.

Doxycycline is a broad-spectrum antibiotic based on the tetracycline family that has a high fat solubility. Doxycycline inhibits the replication of bacterial protein DNA and hinders protein synthesis in pathogenic bacteria via binding to the nucleosome 30S component. Doxycycline has a higher tolerance, a longer half-life, and a stronger antibacterial action than tetracycline, according to previous study. However, due to the

widespread use of antibiotics in recent years, common pathogenic bacteria have developed antibiotic resistance, resulting in ineffective antibiotic monotherapy treatment. A prior study found that Ureaplasma urealyticum and Mycoplasma hominis were both very susceptible to doxycycline and were not resistant to it. Multiple antibiotics are also more effective than monotherapy, according to previous research. NGU treatment. As a result, the efficacy of azithromycin and doxycycline combination therapy for the treatment of NGU was assessed in this study.

Clinical efficacy in the two groups (n, %).

Table no.02: Comparison of symptom relief time and medication time in two groups

Efficacy	Azithromycin group (n=46)	Combination group (n=52)	χ^2 test	P-value
Healing achieved	14 (30.43)	28 (39.02)		
Markedly effective	10 (21.74)	16 (31.71)		
Improvement achieved	16 (34.78)	6 (17.07)		
Ineffective	6 (2.22)	2 (12.20)		
Total effective rate	24 (52.17)	44 (84.62)	12.09	<0.001

➤ DOXYCYCLINE:

Doxycycline is a broad-spectrum antibiotic that is generated synthetically from oxytetracycline Label. This antibiotic is a second-generation tetracycline, which means it is less harmful than first-generation antibiotics. Depending on the findings of antibiotic susceptibility testing, doxycycline can be used to treat a wide spectrum of bacterial illnesses. Antibiotic of the broad-spectrum tetracycline class used to treat infections caused by bacteria and parasites, such as pneumonia, acne, chlamydia infection, and lyme disease. Despite the lack of evidence from clinical trials to support its treatment, doxycycline is frequently used in the community to treat COVID-19 respiratory symptoms. The goal of this study was to see how effective doxycycline was at treating suspected COVID-19 in the community among persons who were at high risk of negative outcomes. Doxycycline is a broad-spectrum antibacterial drug that is still an affordable option for treating community-acquired respiratory infections and urinary tract infections. Despite these clinical findings, doxycycline use has dropped in recent years.

- **molecular weight:** 444.4 g/mol
- **Bioavailability:** 100%
- **Excretion:** mainly feces, 40% urine
- **Protein binding:** 80-90%
- **Elimination half-life:** 18-22 hrs.
- **Melting point:** 201°C
- **Solubility:** 630mg/L (at-25)
- **pH:** 2.16 (acidic)

Mechanism of action-

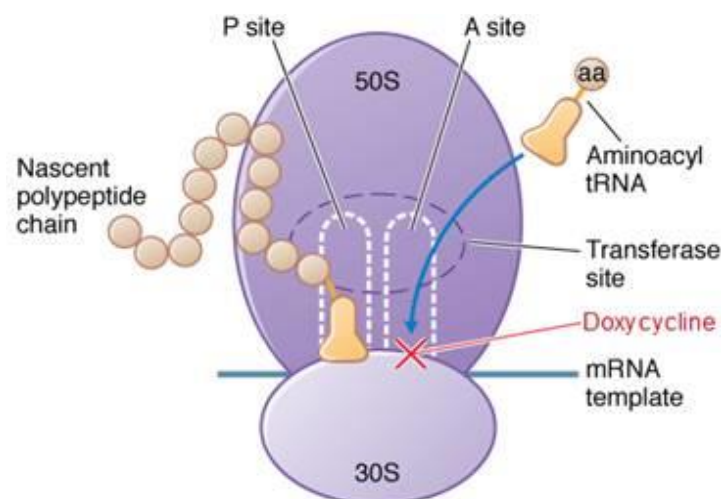


Image 02 Mechanism of action-doxycycline

STRUCTURAL FORMULA

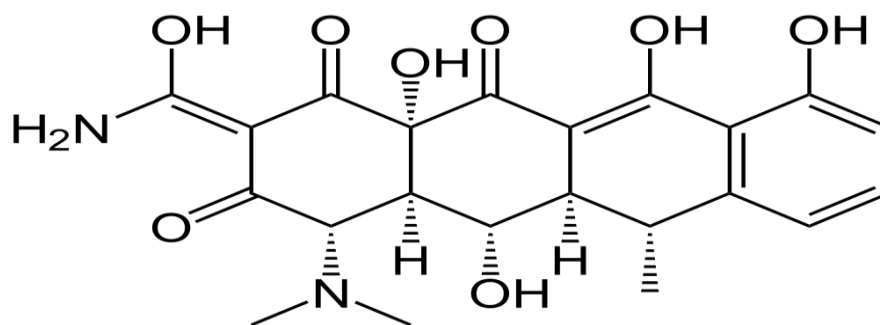
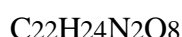


Figure 1: Structure of doxycycline

➤ **Molecular formula:**➤ **AZITHROMYCIN:**

In other viral infections, azithromycin usage was linked to a reduction in mortality and ventilation days. These characteristics may be useful throughout the COVID-19. However, there is a scarcity of evidence of its use, and it is of poor quality. Antibiotic azithromycin is a kind of antibiotic. It's commonly used to treat chest infections like pneumonia, nose and throat infections like sinusitis, skin infections, Lyme disease, and some sexually transmitted infections. Azithromycin belongs to the macrolide antibiotics family of drugs. It works by preventing bacteria from growing. Colds, flu, and other viral diseases will not respond to antibiotics like azithromycin. Azithromycin is a synthetic macrolide antibiotic with antibacterial, anti-inflammatory, and antiviral effects that can be taken orally. It was identified as a viable candidate medication to be repurposed for the treatment of COVID-19 by in silico and in vitro screens in early 2020. Macrolides, particularly azithromycin, have traditionally been used to treat infections.

In vitro, azithromycin exhibits antiviral action against a wide range of human viruses, including the human rhinovirus, Zika virus, enteroviruses, Ebola virus, SARS-CoV, and SARS CoVid-2, and has been found to inhibit viral reproduction. a worldwide issue The disease has symptoms that are similar to viral pneumonia, and genetic analysis of lower respiratory tract samples from early infected patients revealed that they were infected with the novel coronavirus 2019-nCoV, later dubbed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19). The disease spread quickly throughout China, infecting a number of other countries. The World Health Organization (WHO) proclaimed the outbreak on March 12, 2020.

The macrolide antibiotic azithromycin (AZM) has been found to be effective in avoiding severe respiratory infections in people with viral pneumonia. In vitro research have been conducted. It has been shown to be effective against the Zika and Ebola viruses, and it has a high affinity for the binding interaction site of the SARS-CoV-2 spike protein and angiotensin-converting enzyme (ACE2), which is a critical human cell receptor for the SARS-CoV-2 virus. It is thought that blocking this interaction could prevent infection. COVID-19 has been declared a global pandemic. Other organ systems, including as the gastrointestinal, neurological, and haematopoietic systems, have been shown to be significantly affected by this virus, in addition to the primary respiratory system. The macrolide antibiotic azithromycin (AZM) has been found to be effective in avoiding severe respiratory infections in people with viral pneumonia. It is active against the Zika and Ebola viruses in vitro, and it has a high affinity for the binding interaction site of the SARS-CoV-2 spike protein and angiotensin-converting enzyme 2 (ACE2), which is the critical human cell receptor for the SARS-CoV-2 virus, and it is thought that blocking this interaction could prevent infection. Patients' core

body temperature, respiration rate, heart rate, and peripheral capillary oxygen saturation (SpO₂) were all measured on a daily basis. Daily electrocardiogram (ECG) examinations were also performed to track the progression of heart rate corrected QT (QTc) interval prolongation, which would have halted therapy with (AZI) and HCQ. For the correction of the QT interval in cases of general and/or pulmonary deterioration. The medication methylprednisolone was prescribed. When the patients' SpO₂ levels stabilised at 92 percent, they were discharged.

Macrolide antibiotics, such as azithromycin, clarithromycin, and erythromycin, are widely available and their safety is well established. In addition to antibacterial properties, they are known to have immunomodulatory activity, decreasing production of pro-inflammatory cytokines and inhibiting neutrophil activation. They are widely used both in bacterial pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to their immunomodulatory effects. Furthermore, azithromycin has antiviral activity in vitro against a variety of viruses and has been shown to inhibit SARS-CoV-2 replication in Vero cells and human epithelial cells at concentrations (50 percent effective concentration 2.12 M) comparable to those found in lung tissue with a daily dose of 500 mg.

- **Synonyms:** Zithromax, Azro
- **Molecular weight:** 749.0
- **Physical state:** Solid
- **Colour:** Amorphous solid
- **melting point:** 126°C
- **boiling point:** 717 °C
- **Elimination half-life:** 68 hrs
- **pH:** 6.0-7.2
- **Bioavailability:** 37%
- **protein binding:** 12% at 0.5 mg/l

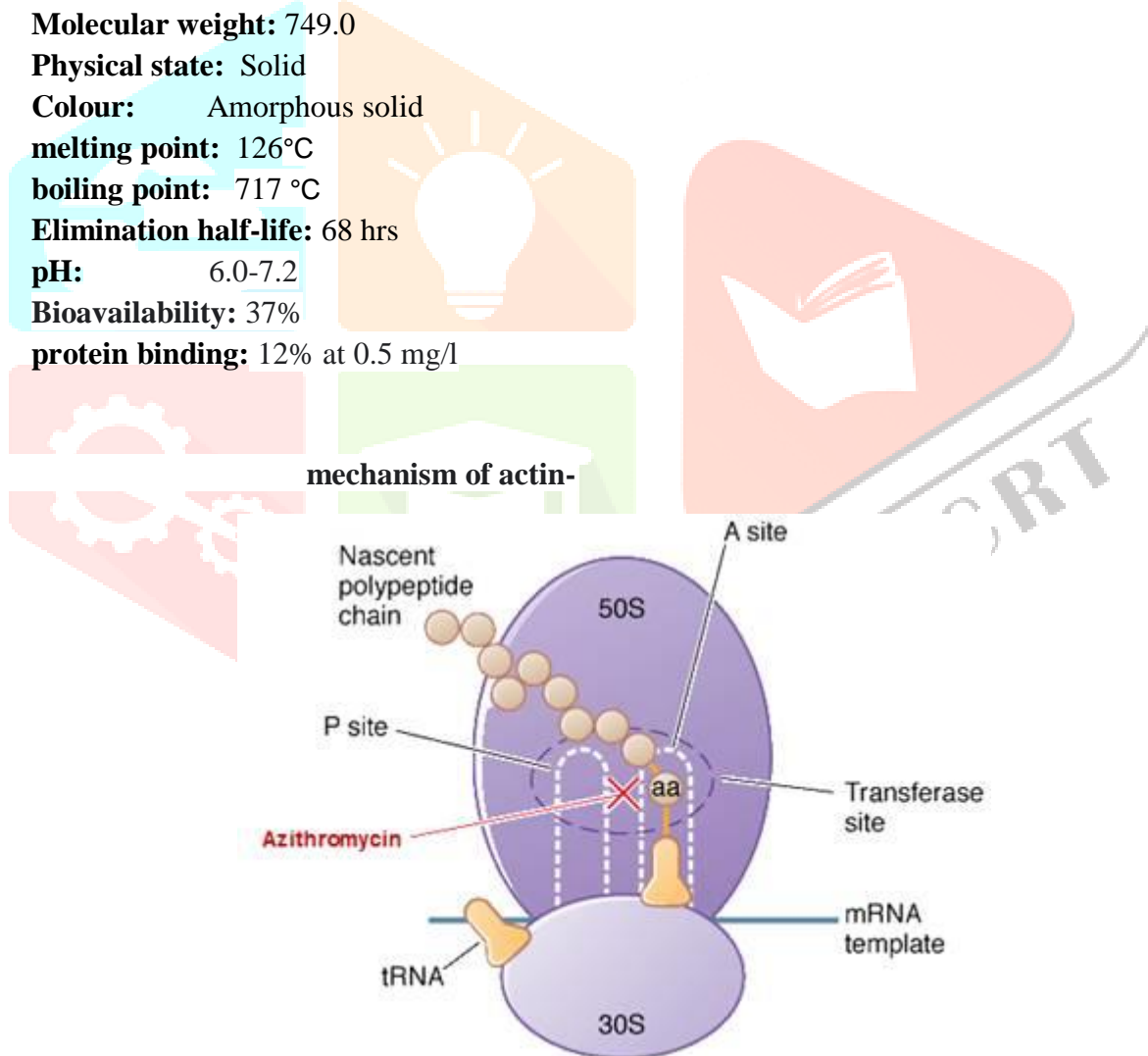
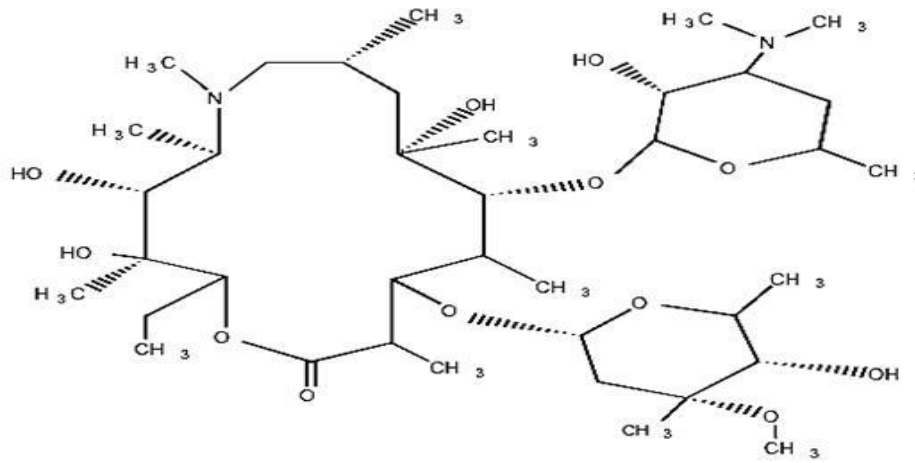
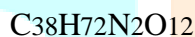


image 03 mechanism of action- azithromycin

STRUCTURAL FORMULA:**AZITHROMYCIN****Figure 2: Structure of Azithromycin**➤ **molecular formula:**➤ **DOXYCYCLINE AND AZITHROMYCIN**

- The best treatment for covid-19 is a combination of doxycycline and azithromycin.
- Non-gonococcal urethritis treated with doxycycline and azithromycin (NGU).

The most prevalent sexually transmitted disease caused by Chlamydia or Mycoplasma is non-gonococcal urethritis (NGU). The purpose of this study is to look at the clinical efficacy of azithromycin in combination with doxycycline in patients with NGU, as well as the effect on interleukin-6 levels in the blood (IL-6). A total of 98 individuals with non-gonococcal urethritis were considered for the study, with 46 being assigned to the azithromycin group (treatment with azithromycin alone) and the rest to the combination group (treatment with azithromycin and doxycycline). The health of the patients was measured, and comparisons between the two groups were conducted. Patients in the combination group had considerably superior treatment efficacy than those in the azithromycin group, with significant differences in time to symptom relief, drug duration, recurrence rate within one year after withdrawal, and serum IL-6 levels. People in the azithromycin group had a lower rate. The standard of excellence

The occurrence of adverse reactions between the two groups. Azithromycin with doxycycline has been shown to be more effective than azithromycin monotherapy for NGU.

- The ideal combination of doxycycline and azithromycin is Pneumonia and cough are two of the most common symptoms of pneumonia.

Doxycycline is a second-generation tetracycline antibiotic, similar to azithromycin. Covid-19 is a medication cocktail that combines two medicines.

- The best doxycycline and azithromycin combo is Pneumonia is characterised by two symptoms: cough and pneumonia.

Doxycycline, like azithromycin, is a second-generation tetracycline antibiotic. Covid-19 is a drug cocktail made up of two different medications.

• The optimal azithromycin and doxycycline combination is Cough and pneumonia are the two symptoms that define pneumonia.

- Doxycycline is a second-generation tetracycline antibiotic, similar to azithromycin. Covid-19 is a medicine cocktail that combines two drugs.
 - ✓ Azithromycin treatment for 3 days (500mg)
 - ✓ 7-day doxycycline (100/200) course.
 - ✓ Non-gonococcal urethritis mix with dox and azi.
 - ✓ Dox + Azi produces a more powerful result than Dox alone.

➤ CONCLUSION:

Treatment-

DOXY- In light of these prospective benefits, we recommend combining doxycycline (potentially) or minocycline with hydroxychloroquine or other promising antiviral COVID-19 therapies, particularly in elderly people with various health problems, including heart disease. According to recent evidence-based clinical practise guidelines, doxycycline is frequently recommended as part of an experimental treatment for atypical bacterial pneumonia or community-acquired pneumonia. As a result, a large retrospective study assessing illness severity, co-infection, mortality, length of hospitalisation, and the requirement for harsh ventilation in Covid-19-infected patients who have had doxycycline-based or other tetracycline-based therapy should be beneficial. - Antibiotic regimens based on empirical data.

Furthermore, COVID-19 patients should be recognised at the time of presentation, regardless of disease severity, in placebo-controlled randomised clinical trials (treatment arm, antiviral (i.e., remdesivir) with doxycycline versus control arm, antiviral plus placebo). Clinical improvement (delay), respiratory closure, mechanical ventilation (duration and extubation), virological clearance, and length of hospital stay should all be considered primary end points in addition to death.

AZI- Azithromycin is a macrolide antibiotic that is often used to treat bacterial infections of the respiratory tract. Nonetheless, various studies have indicated that the medication has a variety of pharmacological effects. The immunomodulatory qualities of azithromycin are thought to be one of its most important characteristics, leading to its use in the treatment of inflammatory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Additionally, azithromycin may have direct inhibitory effects on viral load and replication, or it may have indirect inhibitory effects linked to the production of antiviral genes. Currently, coronavirus disease 2019 (COVID-19) is a global emergency that is caused by coronavirus 2 (severe acute respiratory syndrome coronavirus) (SARS-CoV-2). Acute respiratory distress syndrome (ARDS), which is linked to cytokine release and hyper inflammation, is one of the primary causes of death in COVID-19 patients with critical illness conditions. The purpose of this paper is to explore azithromycin's immunomodulatory and antiviral capabilities, as well as its possible clinical applications in COVID-19 patients.

COVID-19 can be treated using antibacterial and antiviral drugs to slow down the disease's course and consequences. Future research is needed to identify specific targets that impede SARS-life COV-2's cycle, preventing replication, and that, if administered early enough, could prevent COVID-19's typical complications. Patients treated with plasma and hyperimmune immunoglobulins showed clinical and survival improvements. Inflammation drugs (especially anti-IL6, anti-IL1, and Janus kinase inhibitors) are promising prospects for treating COVID-19 in its advanced phases. Clinical trials are under way to validate safety and efficacy, as well as to define the COVID-19 stage at which these medicines provide the most benefit in terms of disease regression.

Focus Azi+Doxy-

- ✓ Both drugs are more effective in the treatment of covid-19, pneumonia, and nongonococcal urethritis.
- ✓ Future Prospects Benefits of Azi + Doxy - Combining doxy and azi is more advantageous.

This is because when the two medications are taken together, they work better. At the same time, both medications have different effects. However, both medications lengthen the time and duration of the action. Separately using both medications will take some time. You will save time by taking both pills simultaneously, and the medicine will have a greater effect than if you took them separately.

Azithromycin and doxycycline are both affordable and widely available antibiotics. nongonococcal urethritis.

➤ References:

- 1) Ahmed S, Ali A, Mai a. asattar , Shahid karim", Kutbi d", Aljohani h, duaa bakhshwin", Mohammed a", huda m. alkreaty. Review article pharmacological basis for the potential role of azithromycin and doxycycline in, management of covid-19, Arabian journal of chemistry (2021) 14, 102983, 2-8.
- 2) Yendrapalli U, Hassoun a, Green J, jonathan edwardsd ,effects of cardiac toxicity of combination therapy with hydroxychloroquine and azithromycin in covid-19 patients,journal of infection and public health. (2021) 14,1668-1670.
- 3) Sekhavati e, Jafari f b.c, Seyedalinalaghi s, Jamalimoghadamshahkalie s, Sadr s, Tabarestani m, Pirhayati m, etc L,safety and effectiveness of azithromycin in patients with covid-19: an open-label randomised trial. international journal of antimicrobial agents (2020) 56, 106143.
- 4) Zhongming lu.1. Hou m , Dandan li., Cheng J. Deng h. and Yan j. experimental and therapeutic medicine spandidos publications exp ther med, 2020 out: 20(4): 3887-3894 published online 2020 aug 19. doi: 10.3892/etm.2020.9125 pmcid: pmc7468211,1-3,6,9
- 5) Tóthf m f, Sotgia f, Lisanti p.m doxycycline, azithromycin and vitamin c (dav): a potent combination therapy for targeting mitochondria and eradicating cancer stem cells (cscs) aging 2019, vol. 11, no. 8 received: february 13, 2019 accepted: april 3, 2019 published: april 14, 2019.,2202-2206,2212
- 6) René L m ", Hernándezb.c. p.m, Yvonne n. floresc.de. patricia o", Christian ronal sancho-hernándezk. Etc L. effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast, and acetylsalicylic acid to prevent hospitalization and death among ambulatory covid-19 cases in tlaxcala, Mexico, international journal of infectious diseases 105 (2021)598-605, .599-600
- 7) Narendrakumar l, Lype. j and Thomas s expert review of anti-infective therapy. review: potential effectiveness and adverse implications of repurposing doxycycline in covid-19 treatment. expert review of anti-infective therapy 2021, vol 19, no. 8, (1001-1008),1001-1004
- 8) Mohammed a t, Chowdhury m , Rezaul k md, hahbaz m, Jahirul i. "a comparative study on ivermectin-doxycycline and hydroxychloroquine azithromycin therapy on covid19 patients". ejmo research article hubei university of chinese medicinesee discussions, stats, and author profiles for this publication at.,64,68
- 9) Schinks t,Cureton L, -Knight l, Wang a.Cane j, Barber v s,Black j, Dutton s j, Melhorn j, Jabeen m, etc L.azithromycin versus standard care in patients with mild-to moderate covid-19 (atomic2): an open-label, randomised trial. respiratory vol 9 october 2021.9:1130-40 published online july 9, 2021 respiratory on sept 2, 2021.1130-1132,1138
- 10) Peyriere h*,Makinson, Marchandin h and Reynes j, doxycycline in the management of sexually transmitted infections. journal of antimicrobial chemotherapy 2018; 73: 553-563 doi:10.1093/jac/dkx420 advance access publication 22 november 2017.553-560

11) Raval p.j, .Joshi p, in applications of nanocomposite materials in drug delivery, 2018. development of injectable in situ gelling systems of doxycycline hyclate for controlled drug delivery system. doxycycline can be formally viewed as the result of transferring the c6 hydroxyl group of tetracycline to c5. from: synthesis of essential drugs, 2006.1-2

12) B. teh', m. . Grayson, P. d. r. Johnson, and .p. g. p. Charles doxycycline vs. macrolides in combination therapy for treatment of community acquired pneumonia. clinical microbiology and infection 2011 european society of clinical microbiology and infectious diseases original submission: 17 october 2011; revised submission: 7 december 2011; accepted: 19 december 2011 editor: g. pappas article published online: 29 december 2011 research note infection diseases doxycycline macrolides in combination therapy for treatment of community acquired pneumonia.01

13) Navarro-TriviÃ±o, FJ; PÃ©rez-LÃ³pez, I; RuÃ­z-Villaverde, R (2020). *Doxycycline, an Antibiotic or an Anti-Inflammatory Agent? The Most Common Uses in Dermatology. Actas Dermo-SifiliogrÃ¡ficas (English Edition)*, (), S1578219020301980-. doi:10.1016/j.adengl.2019.12.014 received 19 june 2019; accepted 18 december 2019 available online 8 august 2020.562-564

14) 2214-2509/© 2020 the authors. published by elsevier ltd. this is an open access article under the cc by-nc-nd license. doxycycline as a potential partner of covid-19 therapie.idcases 21 (2020) 00861.1,2

15) Nobuaki m a,* , Katayama m a, Shigenari n b.

triple therapy with hydroxychloroquine, azithromycin, and ciclesonide for covid-19 pneumonia journal of microbiology, immunology and infection (2021) 54, 109-112.

received 13 may 2020; received in revised form 24 august 2020; accepted 9 september 2020 available online 5 october 2020. 111

16) Aballero j* and Rello j., combination antibiotic therapy for community-acquired pneumonia annals of intensive care a springer open journal caballero and rellor annals of intensive care 2011, 1:48 .1,2,5

17) Uddin m,a Mohammed t, ,a, Metersky m,, Anzueto a, carlos a alvarez, and eric m. Mortensen, effectiveness of beta-lactam plus doxycycline for patients hospitalized with community-acquired pneumonia clinical infectious diseases doxycycline and mortality in pneumonia •received 22 may 2021; editorial decision 16 september 2021; published online 9 november.1-2,4,6

18) Manhart, L. E.; Gillespie, C. W.; Lowens, M. S.; Khosropour, C. M.; Colombara, D. V.; Golden, M. R.; Hakhu, N. R.; Thomas, K. K.; Hughes, J. P.; Jensen, N. L.; Totten, P. A. (2013). *Standard Treatment Regimens for Nongonococcal Urethritis Have Similar but Declining Cure Rates: A Randomized Controlled Trial. Clinical Infectious Diseases*, 56(7), 934–942. doi:10.1093/cid/cis1022 . 936,940

19) Kong, F. Y. S.; Tabrizi, S. N.; Law, M.; Vodstrcil, L. A.; Chen, M.; Fairley, C. K.; Guy, R.; Bradshaw, C.; Hocking, J. S. (2014). *Azithromycin Versus Doxycycline for the Treatment of Genital Chlamydia Infection: A Meta-analysis of Randomized Controlled Trials. Clinical Infectious Diseases*, 59(2), 193–205. doi:10.1093/cid/ciu220.

20) Joshi, Shashank; Parkar, Jalil; Ansari, Abdul; Vora, Agam; Talwar, Deepak; Tiwaskar, Mangesh; Patil, Saiprasad; Barkate, Hanmant (2020). *Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases*, (), S1201971220322736-. doi:10.1016/j.ijid.2020.10.069

21) Jean, Shio-Shin; Lee, Ping-Ing; Hsueh, Po-Ren (2020). *Treatment options for COVID-19: The reality and challenges. Journal of Microbiology, Immunology and Infection*, (), S1684118220300943-. doi:10.1016/j.jmii.2020.03.034