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Analysis of Selected Proteins and Natural Antibiotic Compounds in the Treatment of Tuberculosis: An In-Silico Apprroach

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ABSTRACT: Tuberculosis is an old infectious disease .Potentially fatal, tuberculosis or "TB" is caused by the bacterium Mycobacterium tuberculosis ,which mainly affects the lungs of the human body. Tuberculosis is highly infectious but the bacterium does not make everyone it infects sick, up to one-third of the world's population currently carries the bacterium without showing symptoms.It's spread when a active TB disease carrying person coughs or sneezes and someone else inhales the expelled droplets of TB bacteria. It has two subtypes – latent TB and active TB.In the latent TB the bacteria remain in an inactive state but later it can become active, and in active TB the bacteria do cause symptoms and can get transmitted to others.TB shows symptoms like – cough, fever ,chest pain, weightloss, chills, night sweats and etc.TB can get diagnosed by blood test, chest X-ray, sputum test, mantaux test ,also knownas the Mantoux screening test, tuberculin sensitivity tes t, Pirquet test, or PPD test for purified protein derivative.Many drugs have been widely used against tuberculosis in chemotherapy such as-Streptomycin, Rifampicin, Kanamycin, Cycloserine. There are many antibiotic and natural compounds (Quinolones, Nitroimidasoles , Thiophenes, Sulfonamides , Benzimidazoles) and proteins (like amyloid A , transthyretin and Beta lactamase) which are effective in treating TB .These can be further used in the making of suitable drug or therapeutic medicine for the treatment of Tuberculosis.

KEYWORDS: Mycobacterium Tuberculosis, montoux screening test, pirquet test, Quinolones, Nitroimidasoles , Thiophenes, Sulfonamides , Benzimidazoles, amyloid A , transthyretin ,Beta lactamase

I. INTRODUCTION

Tuberculosis is an infectious disease which affects the lungs but sometimes it can also affect other organs of the body.It is mainly caused by Mycobacterium Tuberculosis. TB also known as : Phthisis and Phthisis pulmonalis. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections do not have symptoms, About one in ten infections eventually progresses to critical stages of TB disease which, if left untreated, kills more than 50% of those so infected.[1]

1.TYPES OF TUBERCULOSIS-

a.)Latent Tuberculosis:

In the latent TB the bacteria remain in an inactive state but later it can become active. The person with latent TB doesn't experience any symptoms. They also aren't contagious. Still, they will have a positive result from TB blood and skin tests. Latent TB can turn into active TB in 5-10% of people. This risk is higher for those patients who are having weakened immune system due to any other disease , medications or an underlying condition.

b.)Active Tuberculosis:

Active TB, sometimes called TB disease, causes symptoms and is contagious. The symptoms of active TB vary depending on whether it's pulmonary or extrapulmonary.If the TB germs are in the lungs or voicebox, the person may spread TB to other people by coughing, sneezing, talking, or singing.There are further subtypes of active TB disease[2].

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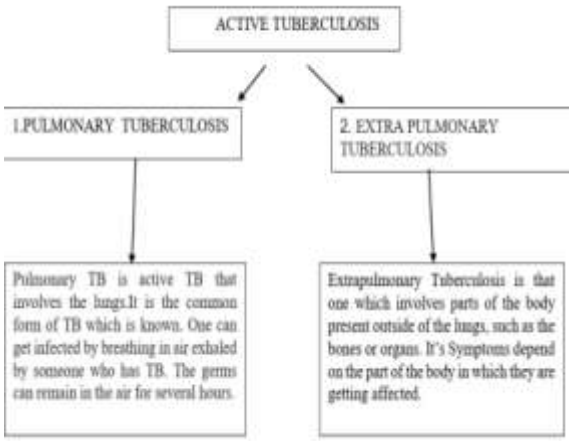

Fig1: Types of Active Tuberculosis

2.SYMPTOMS AND CAUSES-

The symptoms are mostly common in active pulmonary TB but in case of Extrapulmonary Tuberculosis (i.e. TB lymphadenitis, Skeletal TB, Miliary TB ,Genitourinary TB, Liver TB ,Gastrointestinal TB, TB peritonitis) the symptoms may vary depending upon the part of the body and organ it's infecting.

- Common symptoms of Tuberculosis are-
- Unexplained weight loss
- Loss of appetite
- Fever
- Chills
- Fatigue
- Night sweats

3.TREATMENT AND DIAGNOSIS

Tuberculosis is one of the world's leading causes of morbidity and mortality. A complete medical history and clinical examination, as well as radiological, microbiological, immunological, molecular biology, and histological tests, are used to diagnose a patient with tuberculosis.Significant developments have recently been made in these sectors, resulting in significant improvements in the accuracy and speed of tuberculosis diagnosis. New technologies allow for a more accurate identification of latently infected people who are at risk of developing active tuberculosis, as well as a faster diagnosis of active tuberculosis in patients[3].

a.)Blood Test-

Interferon gamma release assays (IGRAs) evaluate the immune system's reaction to TB antigens, which trigger the immune system to produce antibodies. The FDA has given its approval to two tests. They can be used instead of or in addition to a tuberculosis skin test.Theperson won't need to come back once he had his blood test. If it's a negative TB skin test or if patient had the BCG vaccine, they can assist. If the blood test comes back positive, the person has been infected with tuberculosis germs. Other tests will be performed to determine whether the TB is active.[4]

b.)Chest X-ray –

A chest X-ray (CXR) is a quick imaging tool for detecting lung abnormalities.

CXR is used to diagnose problems with the airways, ribs, lungs, heart& ddiaphrag.CXR has lon g been one of the most common methods for detecti on tuberculosis (TB), particularly pulmonary TB.

CXR has a high sensitivity for pulmonary tuberculosis, making it a useful tool for identifying TB as a differential Diagnosis for patients, especially when the Xray is reviewed to look for any abnormalities that are compatible with Tuberculosis. CXR, on the other hand, has a low specificity. Although some CXR abnormalities are specific to p ulmonary tuberculosis (for example, cavities)many CXR
abnormalities that are consistent with pulmonary tu berculosis are also observed
in a variety of other lung illnesses
and thus diagnostic of TB as well as other pathologi es.
Furthermore, there is significant intra-observer and inter-observer heterogeneity in CXR reading. TB diagnosis based solely on CXR results in both overdiagnosis and underdiagnosis.[5][6]

c.)Sputum test-

Nucleic acid amplification assays are another name for rapid sputum diagnostics (NAATs). A sputum culture is one of the most effective approa ches to diagnose tuberculosis. A sputum

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Culture is a test used to identify microorganism that can cause infection(such as tuberculosis Bacterium)A sample of sputum is mixed with a che mical that encourges bacteria growth.

d.)Mantoux test-

The Mantoux test, also known as the Pirquet test or the PPD test for pure protein derivative, is a skin test used to diagnose tuberculosis. The purpose of this test's reading is to determine whether or not there is any induration (localised swelling). It's used to see if a person's immune system has produced a response to the bacteria that causes tuberculosis.The testing is driven by the fact that the bacteria that causes tuberculosis, Mycobacterium Tuberculosis, caused a delayed hypersensitivity skin reaction to the pirquet test to particular bacterial components.

Although a negative Tb Mantoux test result does not necessarily imply that a person is free of tuberculosis, it is a good indicator.This is due to the fact that when a person is exposed to the bacteria, the PPD test can take anywhere from two to twelve weeks to become positive[7].

4.ANTI-TUBERCULOSISCHEMOTHERAPY –

Techniques which are used for controlling TB like (BCG) vaccine and chemotherapy ,etc seems to be less effective, thus anti-tubercular (anti-TB) medication treatment becomes the sole alternative. The goals of treatment are to ensure cure without relapse, to prevent death, to obstruct transmission, and to prevent medication resistance from developing.

Treatment with a mix of medications over a long period of time is required[8].

Being the most important target The replication of M. Tuberculosis in pulmonary cavities most closely resembles optimal aerobic growth in vitro, and the effectiveness of frontline drugs in treating acute TB is manifested in rapid bacillary clearance within the first two months of chemotherapy.The most significant drawback of current therapy is the frontline anti-TB medications' reliance on actively multiplying cells for action.Drug efficacies in vivo have been blamed on suboptimal antibiotic penetration, host environmental heterogeneity, and changed bacterial physiology and metabolic activities within such settings[9].

Multidrug-resistant tuberculosis requires second-line medicines that are less efficacious and have a poor tolerability profile. In order to avoid resilient tuberculosis, each case of tuberculosis must be adequately treated, and patient compliance must improve.[10]

5. ANTI- TUBERCULOSIS DRUGS-

For the treatment of tuberculosis over twenty medicines have been created.

Anti-tuberculosis medications are used in various combinations depending on the situation. Some anti-TB medications are only used in the first line of treatment for new patients who are unlikely to develop resistance to any of the TB drugs.

Other TB medications, referred to as second-line treatments, are solely used to treat drug-resistant TB.There are several novel TB medications on the market presently, but most are still being tested. Anti-TB medications, often known as TB medicine, are typically used to treat active TB or TB sickness. When TB medications are used to treat latent TB, there is an exception to this rule.A single tuberculosis medicine should never be used on its own. TB medications, or TB treatment, must always be used in combination. If only one TB medicine is used, resistance to that drug may develop. This indicates that the drug will not function and that the patient will not be free of tuberculosis.[11]

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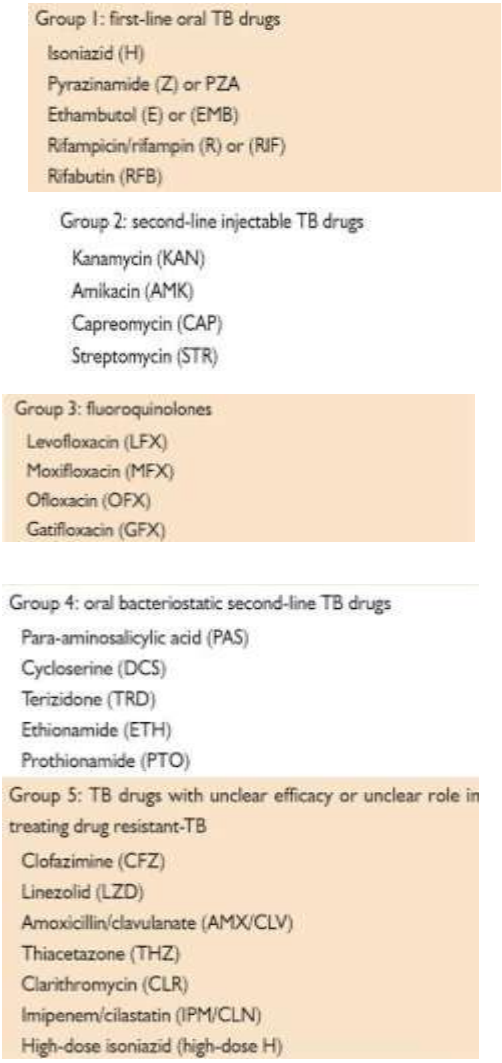

Fig.2 first and second line drugs based on the WHO classification [12]

- First line anti TB drugs- High antitubercular efficacy as well as low toxicity- routinely used.For example: Isoniazid (H),Rifampin®, Pyrazinamide (Z) ,Ethambutol€ , Streptomycin (S).

- Second line anti TB drugs- Low antitubercular efficacy as well as high toxicity – Cycloserine, Kanamycin ,Amikacin ,ciprofloxacin.

II. NATURAL COMPOUNDS AND ANTIBIOTIC COMPOUNDS-

1. quinolones- Quinolones are antibiotics with far more serious consequences than were previously known when they were approved by the FDA. Fluoroquinolones, such as ciprofloxacin (Cipro), lomefloxacin (Maxaquin), norfloxacin (Noroxin), ofloxacin (Floxin), moxifloxacin (Avelox), and levofloxacin (Levofloxacin), are the most widely used quinolones (Levaquin).The first three can be taken as pills, while the last two can be injected or implanted. Different fluoroquinolones differ slightly in ways that benefit or harm some patients.Quinolones stop bacterial DNA replication by blocking the ligase domain of bacterial DNA gyrase (topoisomerase II); a few even stop topoisomerase IV from working.[13]
2. Nitroimidasoles- These are the group of drugs, work by killing the bacteria which is causing the infection.Metronidazole (Metrocream, Metrogel, Metrogel-Vaginal, Metrolotion, Flagyl) is a low-cost antibiotic of nitroimidasole group that's used to treat bacterial and protozoal infections.
3. Thiophenes- Thiophenes are prepared commercially from butane or butene and sulfur

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or sulfur dioxide. There are certain thiophene derivatives occur as plant pigments and other natural products.Friedel-Crafts alkylation of diarylcarbinols followed by integration of amino alkyl chains yielded a new series of thiophene containing triarylmethane derivatives. These were tested against the H37R strain of Mycobacterium TB [14].

4. Sulfonamides- Sulfonamide antibiotics function by interfering with the creation of dihydrofolic acid, a type of folic acid used by bacteria and human cells to make proteins.Examples of sulfonamidesinclude:Sulfamethoxazole/trimeth oprim ,Sulfasalazine l,Sulfisoxazole[15].The combination of sulfamethoxazole (sulfonamide) and trimethoprim (diaminopyrimidine) (co-trimoxazole) has been studied as a possible treatment for drug-resistant tuberculosis[16].
5. benzimidazoles-This bicyclic molecule is made up of benzene and imidazole fused together.Condensation of o-phenylenediamine with formic acid, or the corresponding trimethylorthoformate, yields benzimidazole.The discovery of 2-(4-chlorobenzyl)-3-methyl-1-oxo-1H,5H-pyrido[1,2-a]benzimidazole-4-carbonitrile as a potent antitubercular drug, as well as structural alterations that have resulted in analogues with improved potency and lower toxicity[17].

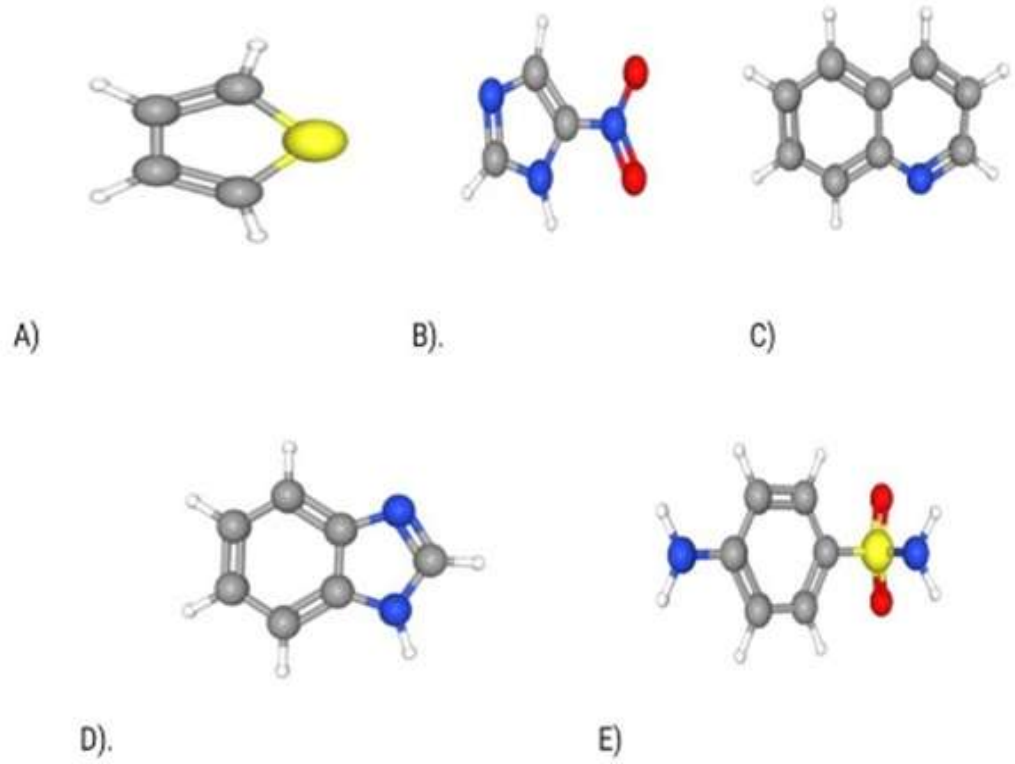

Figure 3: 3D structure ofA) Thiophenes, B) Nitroimidasole, C) Quinolones, D) Benzimidazole and E) Sulfonamides

III.PROTEIN MOLECULES-

1.amyloid A

The acute-phase protein serum amyloid A (SAA) is primarily produced by the liver and is highly conserved.SAA has important immunological properties, such as promoting the production of various cytokines and acting as a chemotactic for neutrophils and mast cells[18].One of tuberculosis's distinguishing features is the formation of granuloma. Furthermore, an increase in the concentration of acute phase response proteins, particularly serum amyloid A, is a marker for tuberculosis-related chronic inflammation[19].

2.Beta lactamase

Pathogenic bacteria use beta lactamase as a primary defensive mechanism against beta-lactam drugs. Antimicrobial action is lost when the beta-lactam ring of this antibiotic class is hydrolyzed. In clinical isolates, enzymes with varying capacities to

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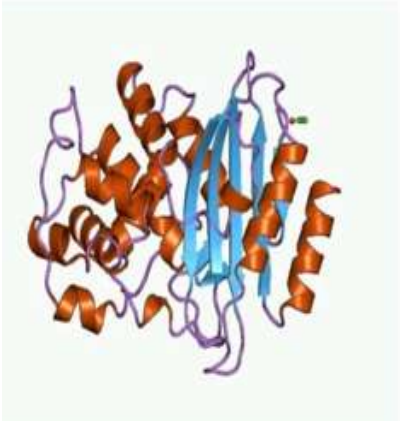
hydrolyze certain penicillins or cephalosporins are becoming more common[20].Beta-lactamase enzymes render beta-lactam antibiotics ineffective by hydrolyzing the peptide bond of the four-membered beta-lactam ring. The bacterium develops resistance to the antibiotic after it is rendered inactive.[21]



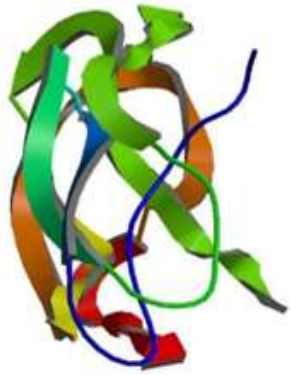


Fig.4 Amyloid beta precursor protein(APP) **Fig.5 Beta lactamase 3 D structure protein**

III. CONCLUSION

Tuberculosis is highly infectious disease which primarily affects human body's lungs, but in other cases it can affect other parts of the body by the same bacteria Mycobacterium Tuberculosis , which is responsible for lungs infection. People usually ignore the early symptoms of TB (latent TB doesn't show any symptoms) and it get diagnosed in its critical stages, which makes it dangerous.Many drugs and medications being used in anti-tuberculosis chemotherapy but still permanent solution is not found.Due to unavailability of the required ANTI-TB drug ,it becomes more important to work on treatment of Tuberculosis with the help of available natural compounds and proteins. Quinolones, Nitroimidasoles , Thiophenes, Sulfonamides , Benzimidazoles are few antibiotic natural compounds that we have studied in our review showing the positive effects against TB. They show antibiotic properties towards TB . Apart from this, there are few proteins like amyloid A , transthyretin and Beta lactamase, which shows connection with TB in their recent studies. Further future research can show the way to cure this highly infectious disease with the help of these very helpful natural compounds more efficiently. Research work can be done to make ANTI- TB drug from these compounds and proteins as the permanent cure of Tuberculosis.

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