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Tuberculosis: History, Pathophsiology, Antituberculosis Drugs and Herbal Approach of The Treatment

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Abstract

Tuberculosis (TB) is a major health issue in underdeveloped nations, with India having the largest TB burden. The disease is caused by the bacteria *Mycobacterium tuberculosis* and has been a leading cause of death in India. The search for anti-TB agents has received extensive study, and the immune mechanisms and hereditary risk factors for TB-related lung injury are being explored. The history of TB treatment has seen remarkable advancements since the invention of streptomycin in 1947. In 2015, the World Health Organization recorded 9.6 million new cases of tuberculosis (TB) and 1.5 million fatalities related to the disease. Amongst these cases, 5% were expected to be multidrug-resistant TB. The disease has a long history, with evidence of spinal caries and TB in ancient times. The document provides information on the diagnosis and treatment of tuberculosis. It discusses various diagnostic methods such as microscopy, antigen detection, and tuberculin skin testing. Additionally, it outlines the treatment intentions for tuberculosis and the WHO's standardized DOTS/cease TB program. The document also details the metabolism, route of elimination, and toxicity of anti-tuberculosis drugs like Ethambutol and Ethionamide. Various methods for the extraction and quantitative analysis of artemisinin, a compound with potential medicinal properties has been discussed. These methods include liquid chromatography-mass spectrometry, ultrasonic-assisted maceration, Soxhlet extraction, microwave-assisted extraction, and supercritical fluid extraction. The challenges of quantifying artemisinin due to its low concentration and thermolability are also highlighted.

Keywords: Tuberculosis; Mycobacterium; WHO; Artemisinin; Taxus; Vetiveria; Propolis

Introduction

In underdeveloped nations, tuberculosis, a chronic granulomatous illness, is a serious health issue. India is the country with the largest TB burden, a dubious distinction. TB has been a daily cause of death for roughly 600 persons in this nation for many years. Therefore, TB is the infectious disease that kills the most adults in India [1]. The highly infectious disease known as tuberculosis (TB) is believed to be caused mostly by Mycobacterium tuberculosis, or Mtb. Due to In silico techniques such as

molecular docking, dynamic simulations, 3-dimensional quantitative structure activity relationships, target-driven anti-tuberculosis drug discovery strategy, pharmacokinetic toxicity and determination by means of in silico and/or in vivo mode as the first indications of tuberculosis (TB), the search for anti-TB agents has recently received extensive study [2]. Evidence found in some Egyptian mummies demonstrates unequivocally that spinal caries existed as early as 2400 BC. Gibbus imagery is a blatant indication of spinal tuberculosis in pre-Columbian and Ancient Egyptian statuettes [3].

The 2015 study by the World Health Organization states that TB, together with HIV, is the top cause of death globally and the primary source of morbidity for millions of people. An estimated 9.6 million new cases of tuberculosis are predicted to occur annually, and 1.5 million people die from the ailments. Nearly 60% and 26.7% of the deaths were reported to be caused by men and HIV-positive individuals, respectively. The report also showed that 3.3% and 20%, respectively, of MDR-TB cases were among newly diagnosed cases of TB and cases of TB that had already been treated. Multidrug-resistant TB (MDR-TB) was projected to account for 5% of TB cases [4]. People did not reside in permanent settlements or villages throughout the Paleolithic era, nor did they gather in sizable numbers. While infectious diseases like tuberculosis and others may have appeared occasionally, they probably did not spread in an epidemic manner. *Mycobacterium bovis* was the most likely infectious organism starting around 8000 B.C., and it's possible that M. Bovis was the source of the first human infections. It is also plausible that *M. tuberculosis* was present in subhuman primates before it spread to humans because it affects all species of apes [5].

Before the invention of chemotherapy, tuberculosis was a leading cause of death in many non- Western as well as Western nations. The prognosis for untreated TB remains critical since many individuals will not receive appropriate therapy because their illness was not correctly recognized as TB. Since the 1950s, there has been an effective chemotherapeutic treatment for tuberculosis (Isoniazid, launched in 1952; less effective treatments, Para-aminosalicylic acid and Streptomycin, were introduced somewhat earlier) [6].

Although the first anti- tuberculosis medications were originated 60 years ago, tuberculosis, which has afflicted humanity for thousands of years, still claims the lives of an approximate 1.3 million people every year. Throughout history, immunological dysfunction has played a major role in the control of tuberculosis. Currently, the most common causes of reduced immunity that favor the development of tuberculosis are HIV/AIDS, aging, malnutrition, and, most recently, diabetes mellitus and smoking [7]. One of the nations with a high prevalence of both diseases is India. According to the 2012 Global TB Report, 3.1 million individuals worldwide have TB and 2.3 million new cases were reported in 2011. Similar to this, the prevalence of diabetes has dramatically increased in India (Anjana, Pradeepa, Deepa, Datta, Sudha, 2011) [8].

History

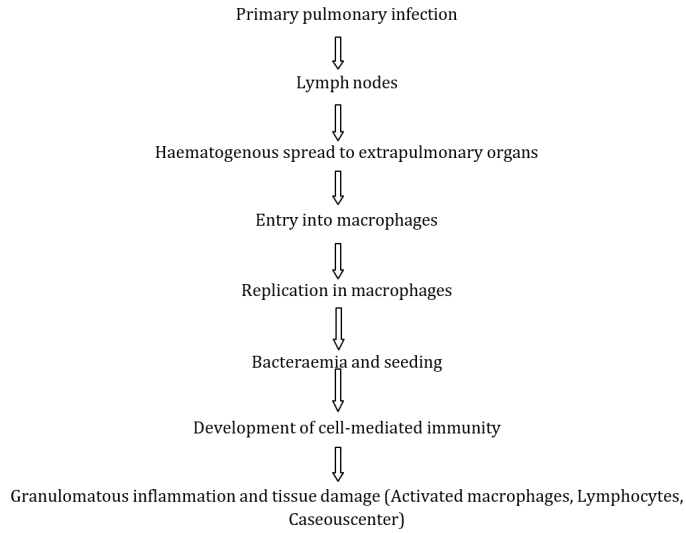
Since the invention of streptomycin in 1947 for the treatment of tuberculosis, remarkable advancements have been made. Only after 1952, when isoniazid was created to accompany it, could its full therapeutic potential be employed. The tactics used in the treatment of tuberculosis have evolved as a result of the discovery of ethambutol in 1961, rifampin in 1962, and a redefining of the function of pyrazinamide. Since 1970, it has been proven that short-term (6-9 month) and home-based regimens are effective, and specific treatment recommendations have been developed [1].

In Gottingen, Jakob Henle (1809-1885) hypothesized that phthisis might be communicable "under certain circumstance, where there is a more Or less marked predisposition" a year later (1844). He reached the core of the issue here. 150 years after Henle, we now know that only 10% of those infected with TB actually develop symptoms. Henle also wrote of a woman who had the illness Consumption, and her cat had succumbed to it. Henle proposed three hypotheses in 1840 to demonstrate the contagiousness of a disease: (1) the disease's causal agent must be identified in each and every instance [3]. In London in 1834, F.H. Ramadge caused the first successful therapeutic pneumothorax, and he stated that his patient had been cured. The artificial pneumothorax process was first employed in 1894 by Carlo Forlanini, who meticulously documented his findings. Pneumoperitoneum was used for the voids in the lower lobes. Because it frequently led to cavity closure and sputum conversion to negative, it is likely that pneumothorax was an effective treatment. It is difficult to know how to conduct such trials, thus there aren't any controlled studies of its efficacy, so one must rely on evaluations

of several treated individuals. The Trudeau Sanatorium at Saranac Lake, New York treated 557 patients with pneumothorax between 1930 and 1939. Roger Mitchell reported the results of their treatment in a series of essays published in 1951. 326 of them were employed. In addition, 119 people died from tuberculosis, 60 were permanently crippled due to the disease [5].

Pathophysiology of Tuberculosis

A coordinated interplay of pathogenic and physiological processes characterizes Mycobacterium tuberculosis infections, commonly referred to as tuberculosis. M. tuberculosis has developed to thrive by entering a host and remaining there for a long time, taking advantage of the immune system of the host. The intracellular pathogenic bacteria Mycobacterium TB is immobile, has a coating of mycolic acid, and divides its cells once every 18 to 24 hours. Because of the lengthy coevolution between the bacteria and humans, the bacterium has acquired special antibacterial defenses that allow it to stay inside the host [9]. Treatment failure is an unfortunate reality due to the slow emergence of resistant Mycobacterium tuberculosis strains, particularly in nations lacking the health care organizations required to give the extensive and expensive treatments tailored to individual patients. This year, at least two million individuals will pass away from tuberculosis as a result of inadequate or inappropriate treatment. This infectious disease attracted new scientific attention starting in the middle of the 1990s. M. tuberculosis, the tuberculosis-causing agent, has been the subject of extensive investigation during the past ten years [10]. Following inhalation, the contagious Droplets disperse throughout the airways. The mucus-secreting Goblet cells found in the upper portions of the Airways are where the majority of the bacilli are trapped. Mucus is produced to trap foreign objects, and the cilia on the cell surface continuously beat the mucus as well as its fragments upward to be eliminated. For the majority of people exposed to tuberculosis, this mechanism offers the body a first line of physical defence that prevents infection [11]. Lymphatic spread from the mediastinal lymph nodes usually results in cervical adenitis after a recurrence of a primary lung infection. However, tuberculous lymphadenitis might be the first sign of a nontuberculous mycobacterial infection. It can be acquired in children by direct spread from bacilli in the oropharyngeal mucosa. The likelihood of tuberculous infection at additional extrapulmonary locations rises when necrotic lymph nodes are present. The bacteria invade the lymph nodes through hematogenous dispersion, settle in the sinuses, and are then phagocytosed by macrophages that are in a latent state. The inhaled bacilli proliferate within the macrophages, whereupon they are released by the macrophages as proteolytic enzymes and cytokines, which cause cell death. To suppress the infection and restrict the bacilli's ability to replicate, monocytes and activated macrophages come together to create a granuloma. This is the stage at which the granuloma turns into a lesion with a necrosis center and peripheral granular tissue [12]. The variance in the genes that code for or regulate host immune responses may also contribute to the heterogeneity in lung injury, according to our other hypothesis. Understanding the immune mechanisms and hereditary risk factors for TB-related lung injury may help to guide the development of medicines that particularly target the immunological causes of lung injury [13].



Causes

The microorganism that causes tuberculosis is called Mycobacterium tuberculosis. Individuals who have active tuberculosis in their lungs can infect others. The bacteria are released in the form of tiny droplets in atmosphere. If you inhale these droplets on a daily basis for a protracted length of time, you could contract TB. This could happen when they laugh, sneeze, cough, or speak. A person could become infected after inhaling the droplets. The disease is more likely to spread when people congregate indoors for extended periods of time. This means that the disease can spread swiftly in places where people live or work nearby regularly. Furthermore, crowded environments facilitate the transmission of this disease. It is impossible for someone with latent tuberculosis to infect others. A person with active TB disease is usually unable to spread the illness after 2 to 3 weeks of treatment [14, 15].

Mycobacterium Tuberculosis

M. tuberculosis is the pathogenic agent of tuberculosis and the primary cause of death through a single infectious pathogen. This member of the phylum Actino bacteria is becoming more and more known for its drug resistance, which is caused by mutations and rearrangements in its single circular chromosome [16].

Symptoms

At the time of the clinical examination, patients self-reported experiencing cough, dyspnoea, night sweats, haemoptysis, and chest discomfort. These symptoms were recorded by a certified trial nurse [17].

Diagnosis

Microscopy and culture

Clinical samples are examined under a microscope meant for acid-fast bacilli by using Ziehl-Neelsen stain in order to facilitate an early and prompt diagnosis of tuberculosis. Microscopy can detect 60% to 70% of culture-positive samples, with a probable lower detection limit of 5x103 organisms/mL. ZN stain should be avoided in favour of more recent fluorochrome stains like rhodamine and auramine. It is inexpensive, quick, and simple to conduct these tests. Sputum production is uncommon in younger children with pulmonary tuberculosis therefore samples of stomach aspirates are frequently collected in the early morning. Sputum or gastric aspirate samples from infants with confirmed tuberculosis rarely test positive for ZN stain, but adult cases do 75% of the time [18].

Antigen detection

The basic concept of the sandwich enzyme-linked immunosorbent test states that circulating Mtb antigens can be found in clinical samples such as sputum, urine, and serum. One unique element of the Mtb cell membrane is lipoarabinomannan (LAM), which may one day be used as a biomarker to diagnose tuberculosis. The urine lateral flow LAM test is called FujiLAM. FujiLAM has an accuracy and specificity of 70% and 93% for adult TB, respectively, compared to 51% and 87% for paediatric TB. In patients with HIV infection, it performs better and has a higher diagnostic sensitivity in both adult and paediatric populations.

Tuberculin skin testing

The PPD called purified protein derivative of tuberculin is used in the traditional TST method to identify type IV hypersensitivity. Patients with MTB infection can develop lymphocytes that are sensitized and capable of identifying MTB antigens [19].

Treatment of Tuberculosis

The intentions of TB Treatments are:

- To prevent a TB relapse.
- To defuse the spread of tuberculosis to other people.
- To avoid death from tuberculosis or it's after effects.

- To prevent the emergence of developed drug resistance.
- To manage the TB patient.

Method of TB management and to improve TB suppression and control, the World Health Organization has designed a uniform DOTS TB (tuberculosis) program [20]. The prior WHO recommendations (2011) categorized medications into five groups according to decreasing order of efficacy and toxicity. First-line medications were included in group 1, while second-line drugs were included in groups 2-5 [21].

First-Line Anti-Tuberculosis Drugs

Isoniazid.
Rifampin.
Pyrazinamide.
Ethambutol.
Streptomycin.

Ethambutol

Tuberculosis has been treated with Ethambutol since 1966; it was first produced in 1961. It works mostly on bacilli that are developing quickly, both extracellular and intracellular. Minimum inhibitory concentration of Ethambutol for Mycobaterium tuberculosis ranges from 1 to 5 μg/mL. Ethambutol has antibacterial properties at standard dosages [22].

Indication

A racemic combination of the L and D types of EMB was the initial formulation. The therapeutic effects of ethambutol were well-established for its D form, whereas its toxicity led to the discontinuation of its L form. In order to cure pulmonary tuberculosis, ethambutol is utilized. In order to effectively treat tuberculosis, it should be administered in conjunction with at least one additional medication, such as isoniazid [23].

Mechanism of action

Ethambutol is regarded as a bacteriostatic medication because it prevents bacilli from proliferating by interfering with the formation of arabinogalactan in the cell wall. The underlying chemical pathways are still unknown, though. Ethambutol prevents arabinogalactan, the main carbohydrate, from being biosynthesised. On the cell wall of mycobacteria Ethambutol inhibits the arabinosyltransferase enzyme, which is responsible for mediating the polymerization of arabinose into arabinogalactan, and is encoded by the embB gene. Ethambutol resistance in vitro develops gradually. It is most likely caused by changes in the embB gene [23, 22].

Administration

Adults often take oral tablets with 100 mg or 400 mg. In youngsters, it varies from 15 to 20 mg/kg of body weight. When starting or continuing treatment, ethambutol should not be used on its own. It must be taken in addition to another anti-TB medication. Isoniazid, pyrazinamide rifampicin, and ethambutol are the four-month regimen of quadruple therapy that is currently used as first-line therapy for tuberculosis. This is followed by a 4-month continuation of isoniazid, rifampicin, and/or ethambutol [23].

Toxicity of ethambutol

Ocular toxicity - The traditional description of optical toxicity is duration- related and dose-related, with significant reversibility upon medication withdrawal; however, this has lately been contested.

Dose related - Ethambutol-induced retrobulbar neuritis has been reported to occur in fewer than 1% to 6% of patients getting 25 mg/kg daily, 18% of patients taking more than 35 mg/kg daily, and 5% to 6% of patients taking 15 mg/kg daily for longer than two months. There is no known "safe dose" of ethambutol because toxicity can occur at as little as 12.3 mg/kg daily.

Duration related - After therapy, ocular toxicity usually takes time to appear, usually taking at least 1.5 months. There is a reported 3 to 5 month mean gap between the start of medication and harmful effects. It has also been documented that poisoning symptoms might appear up to a year after therapy starts [24].

Half-life

The half-life of ethambutol is 3.3 hours in patients with normal renal function. It is possible for the half life to be seven hours or more in individuals with renal failure [25].

Metabolism

Ethambutol is primarily converted to an aldehyde metabolite by aldehyde dehydrogenase, which then transforms it into 2,2'-(ethyline-diimino) di-butyric acid, a dicarboxylic acid [25]. Following oral treatment, 12 to 19% of the EMB dose is eliminated as metabolites and 50 to 70% of the dose is eliminated unaltered in the urine. Although cytochrome P450 enzymes (CYPs) have been demonstrated to be strongly inhibited by EMB in vitro, particularly CYP1A2 and CYP2E1, nothing is known about how CYP polymorphism influences the pharmacokinetics (PK) of EMB in humans [26].

Route of elimination

Half of the ethambutol excreted in urine is its unmetabolized parent molecule, and the remaining 8-15% is its inactive metabolite. The excrement retains 20-22% of a dosage unaltered.

Second-Line Anti-Tuberculosis Drugs

Ethionamide.
Rifabutin.
Capreomycin.
Levofloxacin.
Amikacin.

Ethionamide

As a prodrug, ETH needs to be metabolically activated in order to start acting cytotoxically. Early in the 1950s, ethionamide was introduced as a treatment for tuberculosis. The bioactivation of a hepatotoxic metabolite was shown to be facilitated by S-oxygenation of the thiourea moiety of ethionamide. The therapeutic effectiveness of ETH is also determined by this S-oxygenation [27].

Moa of ethionamide

It is well known that the anti-TB medication ethionamide (ETH), a structural analogue of isoniazid (INH), significantly inhibits the production of mycolic acid in Mycobacterium tuberculosis [28]. Prodrug ethionamide is activated by the Mycobacterium tuberculosis mono-oxygenase enzyme ethA. It subsequently forms an adduct with NAD+ that inhibits InhA in a manner similar to that of isoniazid. It is believed that mycolic acid disruption is the mode of action [29].

Metabolism

When EtaA oxidizes ETH, S-oxide, a metabolite that is known to retain all of ETH's antituberculosis activity, is produced. After more S-oxide oxidation, the unstable sulfonic acid and the non-mycobacterial 2-ethyl-4-carboxamidopyridine metabolite are eventually

produced.PTA, isoxy (4,4-diisoamyloxydiphenyl-thiourea), thiacetazone, and other related chemicals were also found to be activated by M. tuberculosis EtaA. The metabolites ETH nitrile, ETH amide, and ETH alcohol have also been found in the whole cell bacterial systems [27].

Indications

Ethionamide is mainly recommended for the treatment of active tuberculosis in those who are intolerable to other medications or who have M. tuberculosis that is resistant to isoniazid or rifampin. Resistance to it develops quickly when it is used alone to treat tuberculosis.

Administration

Adults typically receive a daily dose of 15-20 mg/kg/day of trecator (ethionamide), or divided doses up to 1 gram if the patient has poor gastrointestinal tolerance [30].

Herbal Approach of The Treatment

The creation of medications that are brought to market and the extraction of lead compounds both heavily rely on natural products. A great database for the possible identification of sources that may provide lead compounds with bioactive qualities is provided by the applications of traditional knowledge and the usage of plant extracts in medical practices. The active inhibition of microbial proliferation is possible with various medicinal herbs found in South Africa [31].

Herbal medicines also show great promise as a source of anti-mycobacterial mixtures, which may be extremely effective in the treatment of tuberculosis and other respiratory illnesses. Parts of the medicinal plants such as leaves, stem bark, root, stem, bloom, and natural objects were utilized for a very long time as traditional TB prescriptions by nearby people far and wide through infusions, macerations, tinctures, and decoctions [32].

Plant extracts have yielded a variety of structurally distinct bioactive chemicals. This has prompted extensive research on plants that have historically been known to be traditionally utilized to treat illnesses in the perspective of medication discovery. The aromatic plant *LippiaJavanica* (Verbenaceae) is used in Mozambique to make infusions of its leaves that are believed to treat a variety of illnesses, including stomach aches, coughs, and flu symptoms. The plant *Knowltonia vesicatoria* (Ranunculaceae), which is widely available in South Africa, has long been used to treat tuberculosis. *Artemisia capillaries* thumb (Asteraceae), a plant that has long been used to cure malaria, was the source of ursolic acid and hydroquinone, which were evaluated for its anti- mycobacterial activity against MDR-TB strains [33].

The Asteraceae plant *Artemisia afra* is commonly found throughout Southern Africa and is used commonly in traditional medicine practices to manage respiratory diseases such as fever, colds, coughs, bronchitis, asthma, and chest complaints. Because of its resemblance to *A. vulgaris*, also known as English wormwood, it is also referred to as Africa wormwood [31].

Artemisia

Within the Astraceae family, the genus Artemisia is one of the largest and most widely distributed genera. The genus is widespread, with approximately 500 species spread primarily across temperate regions in Asia, North America and Europe. These species are tiny shrubs or herbs that grow perennially, biennially, or annually. *A.absinthium*, *A. annua*, *A. afra*, *A. vulgaris*, *A. arborescens*, and *A. capillaris* are among the several species of artemisia [34].

Numerous species in the genus Artemisia have been demonstrated to be effective against COVID- 19 and have various other established medical uses, including the treatment of hepatitis, cancer, and malaria. Various infections, such as mycobacteria, can be neutralized by artemisia species and their extracts both in vitro and in vivo in a tuberculosis mouse model. Worldwide, people use *Artemisia annua* and *Artemisia afra* to cure fever and cough, which are prevalent signs of numerous illnesses, including tuberculosis [35].

Artemisia annua

An annual herb native to China, *Artemisia annua L*. is a member of the Asteraceae family. It grows natively in the steppe vegetation found in the northern regions of Chatar and Suiyan province at 1,000-1,500 meters above sea level. Up to 2.4 meters can be reached by this plant. The stem has branches and is cylinder-shaped. Alternate dark green or brownish green leaves are seen. The taste is harsh, with a distinct and pungent smell [36].

Phytoconstituents of artemisia annua

Artemisinin is the active ingredient in *Artemisia annua*. Artemisinic acid, artemisinnoin B, and artemisitene are sesquiterpenes that are connected through biosynthesis. The essential oils of *Artemisia annua* include linalool, camphor, camphene, 1,8 cineole, sabinene, and germmacrene- D. The primary ingredients in the oil were germacrene-D and camphor [37].

Figure 1: Artemisia annua plant.

Anti M.tuberculosis activity of Artemisinin and Artesunate

The antitubercular medicine artemisinin (ART), which is produced by *A. Annua*, also has antimalarial properties. In vitro as well as in a rat-infected model, ART and its derivative artesunate were both found to be effective against Mtb [35]. Mtb growth and proliferation can lead to serious problems and TB in people with weaker immune systems. Artesunate and artemisinin successfully reduced this growth and proliferation, demonstrating their anti-Mtb action and effects. When compared to artemisinin, artesunate specifically and concentration-dependently significantly reduced the growth of Mtb. Diverse anti-Mtb indication tests, such as the Ogawa slant medium assay, the MGIT 960 system, and the REMA (resazurin microtiter assay), were used to demonstrate the anti-Mycobacterium tuberculosis effects of artemisinin and artesunate [38].

An artemisinin derivative attached to a mycobactin T homologue, a Mtb siderophore essential for growth under iron restriction, may enable the peroxide medication to be effectively absorbed by the pathogen, according to a different study that finds artemisinin has no antituberculosis activity on its own. Reactive oxygen species, which are thought to be the primary mechanism of action or conjugation, are produced when mycobactin-artemisinin conjugate is used to treat tuberculosis caused by Mycobactin [39].

Moreover, investigations that employed *M. tuberculosis* H37Ra and *M. bovis* BCG bacterial strains assessed the synergistic effect of artemisinin and rifampicin. It is possible to effectively repurpose artemisinin as an anti-mycobacterial agent. Artemisinin and rifampicin together have the ability to synergistically inhibit both Mycobacterium TB H37Ra and Mycobacterium bovis BCG.For the H37Ra and BCG straisns, the drug's inhibitory concentration was 100 µg/mL and 200µg/mL, respectively, which was extremely high. The present duration of tuberculosis treatment may be shortened with the combination of artemisinin and rifampicin, which achieves a quicker clearance rate. It's interesting to note that artemisinin also interacts additively and synergistically with other anti-TB medications like

moxifloxacin, ethambutol, amikacin, and isoniazid. In the presence of Fe^{2+} ions, artemisinin produces free radicals with a carbon center. It is demonstrated that the synergistic action of artemisinin and rifampicin against mycobacteria depends on capacity of artemisin into produce hydrophobic free radicals, which encourage membrane breakdown [40].

Taxus Baccata

In the northern hemisphere, yews, or *Taxus L.* (Taxaceae), are extensively dispersed. In the world, there are two hybrids and eight distinct Taxus species. In Turkey, the European yew, Taxus Baccata L. is the only recognizable species. The anti-cancer medication paclitaxel was initially extracted from the *Taxus brevifolia Nutt. Taxus baccata L.*, often known as the European yew, is a native evergreen gymnosperm that is non-resinous and can grow to a height of 20-28 meters. It is found throughout Europe and Asia. The only portion of this plant which is not poisonous is the red, oval- shaped, gelatinous fruits, or arils. These fruits only have one seed and measure about 10 mm in diameter. A microplate technique using Alamar blue was used to test five extracts of *Taxus baccata* in order to determine the minimum inhibitory concentration for Mycobacterium tuberculosis H37Ra strains in an In-Vitro study. The results of this study demonstrate the anti-tuberculosis activity of T. baccata on MTB strain H37Ra. To find the true minimum inhibitory concentrations (MIC values), active extracts that showed variable levels of inhibition in the in vitro initial screen test at 200 mg/ml were retested at a lower concentration. Anti-mycobacterial activity of various extracts was contrasted with that of kanamycin, isoniazid, and rifampin. At 200 g/ml, activity was seen in the CHCl3 fraction of the heartwood and tShe ethanol extract of the leaves. It was discovered that the remaining extracts were ineffective [41, 42].

Figure 2: Taxus Baccata.

Propolis

The word Propolis, which derived from Greek word pro indicates “at the entrance to” and polis indicate “community” is a naturally occurring substance that honeybees primarily produce when they gather plant secretions, such as resins and sticky discharge on leaf buds and plant damage. Propolis is used by bees as an antiseptic covering to generally preserve from external contamination and as a repair and construction material to seal gaps and smooth out internal walls in their hives. Depending on where in the world it is harvested, propolis can have a very different chemical composition. Since bees in tropical countries have access to different plant sources, propolis from temperate areas of the world is rich in phenolic substances derived from poplar tree exudates, while other phytochemicals like benzophenones and prenylated favonoids, terpenoids, lignans, and phenolic lipids are also abundant in these propolis categories [43].

Propolis has long been utilized as a conventional TB cure in addition to being used to treat wounds, sores, HIV infections, and gastrointestinal issues. Experiments conducted in vitro have demonstrated that propolis extracts can both prevent tuberculosis (TB) germs from growing and boost the effectiveness of anti-TB medications such as streptomycin, isoniazid, and rifampicin [44].

Vetiveria Zizanioides L.

It is a member of the Poaceae family and is commonly referred to as Khas or Khus grass. According to the study, hexane, the soluble division of ethanolic concentration, was tested for antimycobacterial activity. The results indicate that *Vetivera zizanioides*, both wasted and impeccable, was effective against virulent and dangerous strains of tuberculosis (M. tuberculosis).

Figure 3: Vetiveria Zizanoids.

It was almost probable that the added component or synergistic effect of several blends, including vetiverin, was the reason why the basic vetiver oil recently appeared to exhibit antimicrobial function [32].

Conclusion

To treat pulmonary tuberculosis, the DOTS (Directly Observed Therapy Short) course approach is employed. Primary and secondary antitubercular medications are included in this category. Artemisinin, a phytoconstituent derived from *Artemisia annua*, is an antimalarial medication that also exhibits anti-tuberculosis properties. Research has shown that the artemisinin and mycobactin conjugates exhibit antituberculosis activity and that they may have synergistic benefits when used in combination with other anti-TB medications. According to an in vitro study, Propolis extract exhibits antituberculosis activity, and another medication, *Vetiveria zizanioides*, has antituberculosis activity with its ethanol extract. Additionally, an in vitro study on H37Ra MTB strains found that *Taxus baccata* is effective against Mycobacterium tuberculosis. Thus, these medications are useful for treating tuberculosis.

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