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REVIEW ON - HERBAL DRUGS FOR TUBERCULOSIS.

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ABSTRACT

Tuberculosis (TB), an old disease caused by the bacteria Mycobacterium tuberculosis is still responsible for more Deaths worldwide each year than any other infectious disease, effectsof TB are Haemoptysis, fatigue, coughing, loss of weight, torment within the chest, blood coloured sputum, perspiring/fever, is some noteworthy signs and symptoms of TB. Treatmentfor diseases like tuberculosis (TB) might become increasingly challenging due to the development of cross- or multidrug resistance, which is linked to allopathic drugs. In this case,Herbal Remedies are the most effective in treating this disease many recent studies have shownthat Ayurveda medicines can reduce mortality dramatically when administered in such circumstances because they engage with the natural environment of the body. Ayurveda medicine is growing in popularity due to its low toxicity study and lack of side effects when compared to allopathic treatments India is one of a Nation offers an amazing variety of healingplants and a wealth of traditional knowledge about using medication for various conditions as a home remedy. As a result, the article will include information on a number of medicinal plantsand the phytochemical components of those plants that aid in the treatment and curing of tuberculosis.

Keyword: Mycobacterium tuberculosis, phytochemicals, anti-tuberculosisactivity medicinal plant.

1. Introduction

With over 2 billion people now infected, 8.6 million new cases reported annually, and more than 1.3 million fatalities from the disease, tuberculosis (TB) is a serious public health hazard [1]. As anendemic ailment of the urban poor in the 19th and early 20th centuries, tuberculosis sparked great public concern[2]. As per the World Health Organization (WHO) [3], tuberculosis (TB) is a bacterial infection produced by Mycobacterium tuberculosis that very usually attacks the lungs. The infection is conveyed through people to people by wet particles from both lungs and throats of persons who have prevalent respiratory diseases [4]Mycobacterium tuberculosis predominantly influences the lungs, which is common reason to cause its of the body may likewise be influenced prompting extra pulmonary tuberculosis [5]The normal side effects of TB are hemoptysis, chest pain, reduction in the weight, fever, fatigue, and coughing [6] Globally, traditional medicines (TM) make a vital contribution to the health care industry. In some countries, TM is the main source of health care or even the sole health care service available, especially in the rural sector [7] In absence of effective therapeutic drug for TB, hope is built on plant based natural products due to their chemical diversity and important role as phyto- drugs [8] Medicinal plants are an immortal gift of nature that have been used since ancient times to treat many human ailments. According to an estimate of WHO, 80% population in developing countries rely on traditional medicines for the primary health care [9]. India is one of the countries with a unique variety of medicinal plants and a wealth of traditional knowledge about using home remedies and medications to treat various illnesses.[10,11] Lastly, we go over the elements that shaped traditional medicine's evolution and its projected trajectory.

The purpose of the article is to stimulate the research and development of potential novel plant-based anti-TB medicines. Since tuberculosis spreads through the air, breathing polluted air is the only way to contract the disease. A person who is actively ill can spread tuberculosis (TB) by talking, coughing, sneezing, or speaking. As the microorganisms are not surface- dwelling, tuberculosis cannot spread. By:

1. Shaking hands
2. Using a toilet Sharing drinking glasses or eating utensils Touching other surfaces. [12]

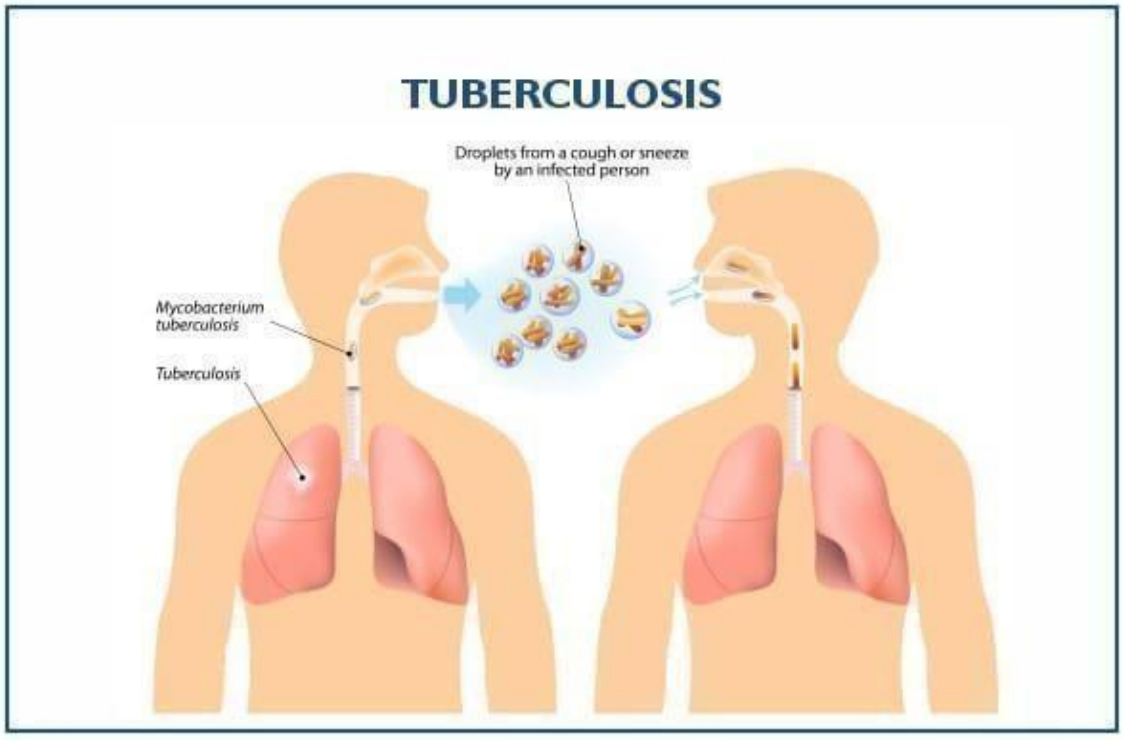


fig no.1: causes and risk factor of tuberculosis

Symptoms of active tuberculosis included.

- A general sense of being unwell
- Coughing
- Coughing up blood or phlegm
- Chest pain
- Trouble breathing
- Loss of weight and appetite
- Night sweats
- Intermittent fever
- Generalized body aches
- Fatigue [12]

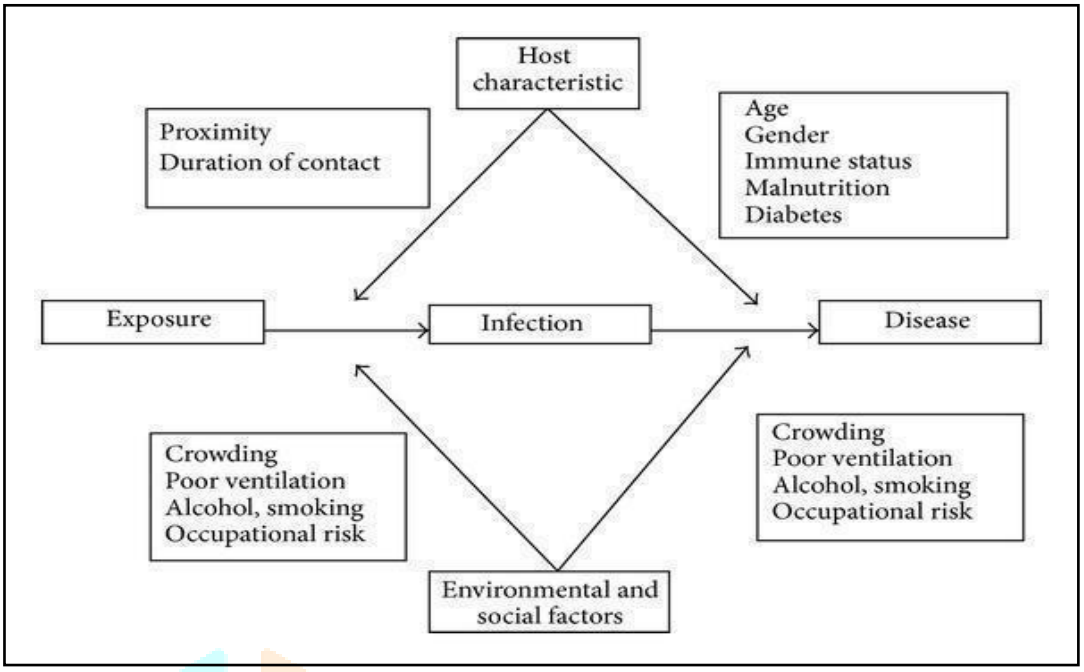


fig no. 2: risk factor of tb

Historical Background

One of the oldest and most contagious diseases affecting people is tuberculosis. According to an old Indian sacred text Vedas, the TB was alluded to as Yakshma (which means the Wasting illness). The revelation of the tubercle bacillus was declared by the Robert Koch during the monthly evening Meeting on 24th of March 1882 which was of the Berlin Physiological the Society. For this reason, March 24 is being recognized as "World TB Day" on that day.[13]

2. Mycobacterium tuberculosis Overview

2.1. Etiology

In 1993, the World Health Organization (WHO) deemed tuberculosis (TB) a worldwide health emergency. Recently, the rate of deaths from tuberculosis (TB) surpassed the total number of deaths from gastrointestinal tract diseases and HIV combined. It is widely believed that over the past two centuries, TB killed one billion people [14] Tuberculosis, the vitally overwhelming cause of death all over the planet, is an infection of the lungs that spreads through talking, sneezing, coughing, or spitting aerosols that contain mycobacteria. The lower airways can be reached by these aerosol particles. Four steps determine how pulmonary tuberculosis (TB) develops and progresses; these are the phagocytosis of the bacilli, their intracellular growth, the latent phase of infection, and finally, the active form of TB. These stages can result in different clinical outcomes: spontaneous cure [15].

2.2. Epidemiology

According to the Global Tuberculosis Report (2022), progress made in the past to eradicate TB has been slowed down due to the emergence of COVID-19 [16] . there are an estimated 38.4 million people living with HIV (PLWH), and 537 million with DM, mostly type 2 DM.[17] In 2022, the global estimate of HIV-coinfected patients with TB was 710,000 (6.7% of all TB cases), and 187,000 death.[18] With a pooled DM prevalence of 15.3% in TB patients, [19] Soon after HIV infection, the risk of TB disease increases 2–5-fold compared to non-HIV-infected individuals. With progression to HIV-induced severe immunodeficiency, the risk of TB is further increased at least 20fold greater than in the general population. Antiretroviral therapy (ART) for HIV-1 does not fully restore the baseline level of risk.[20] India is the second-most populous country in the world. It accounts of more than one quarter of the global incident TB cases and deaths annually[21]Globally, in each year India has the highest number of new TB cases, MDR-TB and deaths related to TB[22]. In 2014, the estimated incidence of TB cases in India was nearly 2.2 million while the estimated TB prevalence figure was 2.5 million. An estimated 5 % of the incident TB cases were HIV-positive. India,2.2 % of new TB cases were estimated to have had MDR-TB [23].

Drug	Adverse effects
Isoniazid	Skin rash, hepatitis
Rifampicin	Abdominal pain, nausea, vomiting, hepatitis, thrombocytopenic purpura
Pyrazinamide	Arthralgia, hepatitis
Streptomycin	Vestibular and auditory nerve damage, renal damage
Ethambutol	Retrobulbar neuritis, ocular side effects
Thioacetazone	Skin rash, Exfoliative dermatitis
Para-aminosalicylic acid	Anorexia, nausea, vomiting, hypersensitivity reactions
Kanamycin	Vertigo, auditory nerve damage, nephrotoxicity
Ethionamide	Diarrhoea, abdominal pain, hepatotoxicity
Cycloserine	Dizziness, headache, depression, psychosis, convulsions

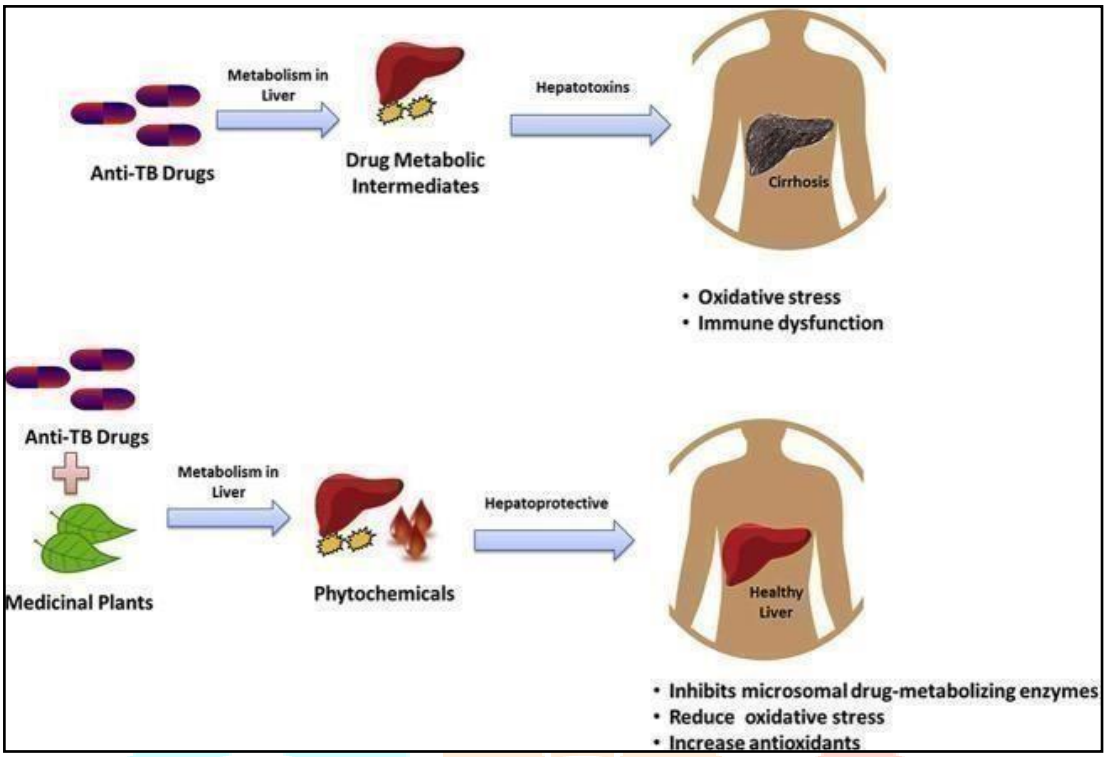
adverse effects associated with anti tb therapy [24,25]

3. How Is Tuberculosis Diagnosed?

Conventional diagnostic techniques, such smear microscopy and culture, are insensitive or slow. Modern, more sensitive methods like Xpert MTB/RIF (Xpert) are expensive, scarce, and dependent on a specific infrastructure. Moreover, TB is harder to diagnose in PLHIV, since manyof the patients have extrapulmonary TB (approximately 25%), produce paucibacillary sputum samples, or cannot reliably produce a sputum specimen [26,27] .TB in PLHIV is often fatal if undiagnosed or left untreated. New, rapid, non-sputum-based point-of-care (POC) diagnostic solutions to detect TB, especially in vulnerable groups, are urgently needed [28] The commerciallyavailable Alere Determine TB LAM lateral flow assay (LF-LAM; Abbott, Chicago, US; in previous studies also called AlereLAM) is a rapid, inexpensive POC TB test [29]. While its use is associated with a mortality benefit in severely ill and immunocompromised PLHIV [30,31], it has only moderate sensitivity in patients with a low CD4 count and has had low programmatic uptake [32]. The innovative Fujifilm SILVAMP TB LAM (SILVAMP-LAM; Fujifilm, Tokyo, Japan;also known as Fuji LAM) test has already been published by us in earlier research. Similar to LF- LAM, SILVAMP-LAM uses a visually read lateral flow test to identify the presence of lipoarabinomannan (LAM) in urine; however, SILVAMP-LAM uses silver amplification instead of LF-LAM. For inpatients with HIV, it offers on average an increase in sensitivity of approximately 25%–30% compared to LF-LAM across CD4 strata, while maintaining a high specificity when a composite reference standard is used [33,34].

4. Antimycobacterial and hepatoprotective activity of plants:

Since ancient time, ethno botanical knowledge subsists in India and people use herbs as a source of medicines, especially for primary healthcare. The country has about 45,000 plant species and many of them have been studied for their medicinal properties [35]. Plants are abundant in biologically active substances that have been shown to be powerful antibacterial agents. Traditionally, infections caused by Mycobacterium are treated with a variety of herbs. Phytochemicals present in plants are reported to inhibit multidrug efflux system of microbes [36]. The traditional plants used to cure tuberculosis are also a rich source of phytochemicals, which are beneficial to the liver among other parts of the body. In contrast to anti-TB medications or chemically caused hepatotoxicity, phytochemicals are well-established hepatoprotective agents that can restore normal function, enzymatic activity, and histology of hepatic cells. The increased levels of blood enzymes, total bilirubin, and protein can be decreased by the herbs. They can help reverse liver damage brought on by anti-TB drugs and the aberrant activity of enzymatic antioxidants drugs [37],[38],[39].



5. Herbal medicine

One of the largest traditions of plant-based medicine in the world is found in India. In India, there are a predictable 25,000 efficient herbal-centre medicines that are utilised in religious remedy and are known to rural populations [40]. Over 1.5 million people practise traditional medicine, which uses medicinal herbs for preventative, promotional, and curative purposes. India is expected to have about 7800 medical medicine production plants, which utilise over 2000 tonnes of herbs each year. The creation of effective therapeutic medicines relies heavily on medicinal plants. Approximately 100 novel herbal-based medications were released into the American drug market between 1950 and 1970, deserpidine, reserpine, vinblastine, vincristine and reseinnamine are only a few examples of compounds originating from higher plants [41] Many natural products are biologically active and have better pharmacokinetic properties (e.g., superior absorption, distribution, and excretion) when compared to synthetic compounds [42]. Although the field of natural product discovery faces certain challenges, such as the distinct cell wall of M. tuberculosis, intricate biosynthetic pathways, and decreased solubility of certain compounds, the domains of biology, pharmacology, and medicinal chemistry hold significant promise for the development of natural product-based therapeutics for the treatment of tuberculosis [43]. Natural compounds form the basis for many commonly used. When Chinese research scientist Ty You was granted the Nobel Prize in Physiology or Medicine in 2015 for her discovery, this gained international recognition of the herbal antimalarial compound artemisinin [44]

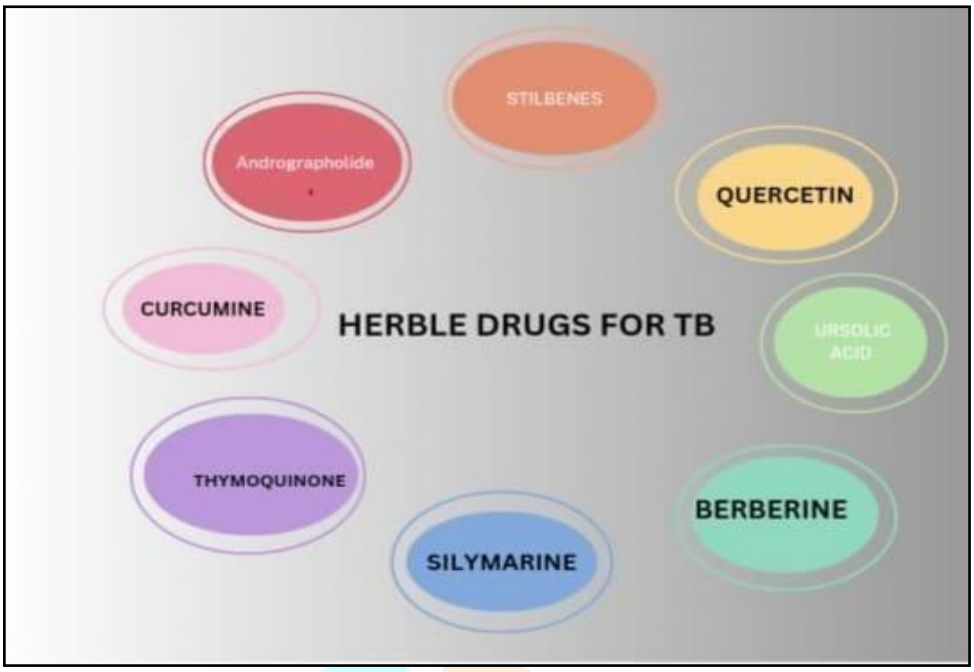


fig no. 3: commonly used herbal drugs for tb

5.1. Quercetin:

a quercetin is ingolyphenolic flavonol occurs in fruits and vegetables. It interact with various interacellar signaling cascades to provide protection from oxidative damages [45]. The substance increases the expression of genes linked to oxidative stress and the Nrf2/HO-1 pathway.. Thus helpful in overcoming oxidative hepatic damage [46,47]

5.2. Ursolic acid:

a triterpenoid that was isolated from plants such as Mirabilis jalapa, Calendula officinalis, Bouvardia ternifolia, Byrsonima crassa, and Hedyotis corymbosa. It is a strong antioxidant that also prevents mice from producing ROS. It suppresses MAPKs, CYP2E1 and NF-kB activation thereby protecting liver from stress [48,49].

5.3. Berberine :

Plants like B. aristata, Hydrastis canadensis, Coptis chinensis, Berberis aquifolium, Berberis vulgaris, and Hydrastis canadensis contain berberine, an alkaloid with antioxidant qualities and a hepatoprotective effect [50].in vitro, berberine exhibits hepatoprotective action in experimental model partly through inhibition of microsomal drugmetabolizing enzymes and inhibitory action K/Ca currents [51], [52]. It also decreases oxidative stress by repressing TNF-α, COX-2 and iNOS expression [53].

5.4. Silymarin:

Silymarin, is a flavonoid-complex containing silybin, silydianin and silychristin [54]. It's one among the several hepatoprotective natural products that have been investigated in depth. Seeds of Silybum marianum are source of Silymarin, which in turn is very effective against anti-TB drug induced toxicity and used as hepatoprotective reference compound in many experimental studies [55], [56]. Because of its antioxidant capacity and interactions with components of the cell membrane, it has qualities that protect cells. This compound exhibits anti-inflammatory activities by downregulating the expression of inflammatory genes; NF-κB, ICAM-1 and IL-6[57].

5.5. Thymoquinone(TQ):

The monoterpenoid thymoquinone (TQ) is present in Nigella sativa seeds. It lowers the level of hepatic antioxidants, protecting the liver from oxidative stress. In an experimental setting, it boosts the production of the chemoprotective enzymes superoxide dismutase and glutathione peroxidase. During drug induced inflammation, TNF-a, iNOS, COX2 and IL-1b gets activated. TQ can stop them from acting, which will lessen the harm to the liver. TQ interact with oxidative stress induced factors (e.g. glutathione S-transferase) and fix oxidative damage [58,59].

5.6. Artemisinin:

Artemisnin of that Artemisia annua (sweet wormwood) is a centuries-old natural medication found by Chinese researchers. The medication got from this spice, artemisinin, is utilized to treat jungle fever brought about by Plasmodium falciparum. Presently, specialists have motivation to accept that we can likewise utilize this natural medication to treat tuberculosis. One investigation discovered that artemisinin prevented Mycobacterium tuberculosis from being torpid. Robert Abramovitch, the lead specialist, made sense when the microorganisms arrive at lethargy, the opportunity that they will become impervious to antitoxins is higher. Obstructing the lethargy, he said, can make TB microscopic organisms more delicate to the medications and could try and abbreviate the treatment time.[60]

5.7. Curcumin:

Curcumin is a polyphenolic compound obtained from rrhizome of Curcuma species. Through Keap1/Nrf2 pathway activation, it demonstrates hepatoprotection. The route controls how well cells defend themselves from oxidative damage. Additionally, curcumin can reduce the liver's production of NADPH oxidase (NOX). This enzyme generates ROS, which in turn cause hepatic damage [61,62]. Enzymes like NAD(P)H quinone dehydrogenase 1 and heme oxygenase- 1 are also induced by curcumin. Both antioxidant enzymes and phase II detoxification play a role in drug metabolism and detoxification. Curcumin also inhibits oxidative stress by downregulating the levels of Prx1 and CYP2E1. In vitro, attenuation of inflammatory responses in liver by curcumin is by down regulating the expression of NF-kB, TLR2 and TLR4 has been reported. Additionally, the AMP-activated protein kinase (AMPK) pathway is activated in liver cells [63,64].

5.8. Andrographolide:

A. paniculata yields andrographolide, a diterpenoid with antioxidant qualities. It up-regulates the expression of hypoxia-inducible factor-1 alpha (HIF-1α), SOD-1, HO-1 and GST under oxidative stress [65,66,67]. Interaction of this diterpenoidd with Glutathione (GSH) significantly induces CYP1A1 expression in experimental models. The expression of CYP1A1is crucial for drug metabolism, while GSH is a vital liver defense against oxidative stress. Andrographolide synergistically induces CYP1A1 expression [68,69].

5.9. Stilbenes:

Stilbenes are well-known phytochemicals that have been the subject of in vitro hepatoprotective mechanism research. They all maintain various defense mechanisms to prevent harm to the liver cells. Plants including Paeonia lactiflora, Vitis vinifera, and Arachis hypogaea contain stilbenes such trans-resveratrol and its glucoside. Resveratrol (trans-3,5,4′trihydroxystilbene,1) is most studied hepatoprotective phytochemical. Mice's liver damage caused by ISH and RIF is prevented by resveratrol. This phytochemical's defensive action results from hepatic cells' modification of SIRT1, PPAR-γ, and PGC-1α mRNA expression. Through its involvement in the pathways of lipid metabolism in the liver, SIRT1 shields the liver from oxidative damage stress [70,71].

6. Need for Future Research -

Although this review presents a plant with effective anti-TB activities from different traditional medicine systems, there is a need of better therapeutic drug monitoring systems and high throughput in vitro assays for the routine screening to identify potentially serious and clinically significant herb-drug interactions [72]. In addition, little in vivo data is available about drug metabolism-related interactions in relation to conventional therapies and tuberculosis treatment. This necessitates that medical professionals make sure that people are informed about the potential drawbacks of using some TMs and prescription medications at the same time [73,74] impact the anti-TB efficacy of the medicinal plant's constituents, such as variance inpotency brought on by species differences and lack of an integrated coding system for each species used commonly in TMs, varying geographical location of growth and incorrect identification of drugs, and nonuniform quality control standards [75]. The crude extracts were not the subject of any documented clinical trials, and even the pure chemicals derived from medicinal plants require further investigation to fully understand their constituents and mode of action. Few substances derived from plants have been modified further for use in clinical settings up to this point. With the help of this review, we intend to identify a potential strategyfor improving anti- TB outcomes by combining plant-derived chemicals based on the different TB-killing mechanisms.

7. Conclusion-

Nature a widespread stock of plants used to cure illness of mankind. Herbs play a significant and fundamental role in traditional medicinal systems and have a wide range of effects on preserving human health. The discovery of chemically unique compounds and plants as viable hepatoprotective and antimycobacterial agents is an example of how the search for the perfect medication is progressing. Thus, combining the various health advantages of medicinal plants with the target-specific qualities of anti-TB medications may be a useful strategy for managing tuberculosis and its side effects. Many people in poor nations take both prescribed medications and herbal supplements at the same time. Consequently, this predominant prevalence needs to be counterbalanced with relevant research. There hasn't been much discussion of the fundamental mechanism underlying the interaction between herbal constituents and anti-TB drugs. There exists huge knowledge gap regarding medical use of herbal adjuvant by the attending physician. Plants that possess inherent antioxidant and anti-tubercular qualities could be investigated for their active biomolecules and utilized to create cutting-edge formulations that are approved by a larger spectrum of medical professionals. Therefore, prior to widespread human use, the herb-drug interaction must be carefully studied in a variety of conventional experimental setups to assure the safety and effectiveness of such combinations.

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