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NEW APPROACHES FOR TARGETING TO TREAT TUBERCULOSIS

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ABSTRACT:-

Tuberculosis(TB), induced by Mycobacterium tuberculosis(M. tuberculosis), is still a global health challenge, especially in the context of emerging multiresistant (MDR) and extensively drug-resistant (XDR) strains. Although traditional anti-TB treatments are effective, they necessitate long periods of administration, which often results in poor patient adherence, treatment failure, and the emergence of further resistance. Recent knowledge advances in molecular biology, immunology, and drug delivery systems have, however, necessitated the establishment of new treatment strategies that seek to improve treatment efficacy, reduce the duration of therapy, and combat resistance.Additionally, host-directed therapies (HDTs) are starting to take center stage. These therapies are designed to modulate the host immune response to enhance bacterial killing with minimal tissue damage. Autophagy, inflammation (e.g., NSAIDs and statins), and immune checkpoint (e.g., PD-1 inhibitors) targeting agents are being investigated for adjunctive use.Nanotechnology-based delivery systems like liposomes, polymeric nanoparticles, and aerosols offered through inhalation deliver improved pharmacokinetics and targeted delivery to infected macrophages. This technology not only improves the bioavailability of drugs but also reduces systemic toxicity. Researchers are also developing CRISPR-Cas-based platforms for gene editing and diagnostics that have the potential to facilitate strain-specific interventions and resistance monitoring.

Keywords:-Tuberculosis,Nanoparticles,rifampicin,DRTB,XDR,MDR,Mtb,HDTs,Co-infection,collaboration,genomic mutation.

1.Introduction:-

Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis (Mtb), continues to be one of the world's major infectious killers with over one million deaths each year. Although TB is often curable with first-line drugs, the advent of multidrug-resistant (MDR) and extremely drug-resistant (XDR) forms threatens the worldwide effort to contain the disease. Existing standard treatment regimens, which are typically long and fraught with horrid side effects, highlight the need for innovative and more efficient therapeutic strategies.Current research has focused on the identification of novel molecular targets in the Mtb bacterium and host-directed therapies (HDTs) to modulate immune response and eradicate bacterial persistence. For instance, small-molecule thymidylate kinase inhibitors—enzymes critical for DNA synthesis—held promise through in silico design and virtual screening approaches, validating candidates with expected nanomolar activity and good pharmacokinetics(1). Similarly, the novel anti-TB candidates targeting DNA gyrase B, a critical enzyme for bacterial replication, have been identified through in silico screens of microbial-derived from natural products and beyond(2). Nanotechnology-based drug-delivery systems are also revolutionizing TB therapeutic models. Nanoparticles crafted for bone and joint tuberculosis have demonstrated enhanced drug retention, targeted delivery, and reduced toxicity, thereby enhancing patient outcomes and facilitating precision approaches(3).

Nanotechnology has proved to be a revolutionary approach in TB treatment by developing new drug delivery systems that can enhance therapeutic effectiveness, reduce dosing frequency, and restrict systemic side effects. Nanocarriers such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles enable first-line TB drugs to be encapsulated and targeted to infected macrophages—the primary reservoir for Mtb infection(4). Nanotechnology has also shown promise in revolutionizing TB diagnostics and immunotherapies. Recent studies highlight the fact that nanomaterial-based platforms—such as gold nanoparticles and carbon nanotubes—can increase the sensitivity and specificity of TB detection and aid in the development of innovative vaccine delivery systems(5). Nanoparticles—man-made carriers ranging from 1 to 1000 nm in size—have unique physicochemical properties that allow drug delivery to be targeted, sustained, and controlled. In TB chemotherapy, particles such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles are shown to efficiently entomb first-line anti-TB drugs such as rifampicin, isoniazid, and pyrazinamide, enhancing their solubility, bioavailability, and cellular delivery to infected macrophages(6). Further, recent advances highlight the potential of nanoparticle-based diagnostics and vaccine platforms in TB control. Nanoparticle formulations are demonstrated to enhance immune activation and antigen presentation, and hence, they are good prospects for components of next-generation TB vaccines and immunotherapies(7). Theranostics, or the union of therapy and diagnostics, offers a holistic approach that holds potential to revolutionize TB treatment by providing simultaneous detection of the disease, monitoring of treatment, and targeted drug delivery. Progress in nanotechnology-based theranostic platforms is of particular interest in TB treatment. The platforms combine diagnostic agents (e.g., imaging probes or biosensors) with therapeutic loads (e.g., anti-TB agents), allowing real-time monitoring of infection sites and personalized drug delivery. For instance, graphene oxide-based optical microfiber

biosensors have achieved quick detection of TB antigens like Mpt64 and Ag85B with high sensitivity, offering near-instant detection of infection in human and bovine samples(8). Drug-resistant tuberculosis (DR-TB) in the forms of multidrug-resistant (MDR) and extensively drug-resistant (XDR) poses a threat to global TB control. Resistance to first-line drugs like isoniazid and rifampicin severely undermines the effectiveness of standard treatment regimens, leading to prolonged disease, increased transmission, and death. Spontaneous genetic mutations in Mycobacterium tuberculosis (Mtb) are driven by emergence of resistance and are sped up by poor treatment adherence, poor dosing, and delayed diagnosis(9). Molecular diagnosis and computational advances now promise precision treatment of DR-TB. For instance, sputum sequencing platforms addressing resistance-conferring mutations like ARapidTb have demonstrated brilliance in the identification of resistance-conferring mutations directly from clinical material within 24 hours, enabling timely initiation of appropriate treatment regimens(10). Moreover, the application of bioactive molecules like silymarin with hepatoprotective and antimicrobial action in combination with conventional drugs has been demonstrated with potential to restore frontline agent efficacy and minimize side effects(11).

Aim:-

Investigate and report on new therapies for host and bacterial targets to improve TB treatment, especially MDR TB and XDR TB. Current anti-TB regimens, although effective, are plagued by long treatment duration, patient compliance, and resistance mutations in Mycobacterium tuberculosis.

Objective:-

Identification and evaluation of new molecular targets of mycobacterium tuberculosis such as DNA gyrase B, thymidylate kinase, and Dap B.To explore host-directed therapeutic strategies (HDTs) that not only enhance the immune response of the host, decrease tissue damage, shorten the duration of treatment, but also fail to induce resistance.To measure how nanotechnology contributes to treating TB, i.e., how drug delivery systems of nanoparticles may enhance the efficacy of drugs, achieve controlled release, and target infected macrophages.To talk about how the diagnostic and treatment functions work together for real-time tracking and personalized TB treatment regimens.To investigate the use of genetic and genomic resources, such as machine learning and whole-genome sequencing, to forecast drug resistance and guide personalized therapy.

2. Novel Drug Targets and Therapies

New treatment strategies for TB have expanded to target both pathogen-directed and host-directed targets in order to combat the rising threat of Mtb strains that are multidrug-resistant (MDR) and extensively drug-resistant (XDR). Among bacterial targets, two enzymes, DprE1 and Ddn, have been promising. DprE1 is essential for biosynthesis of the cell wall of Mtb, while Ddn activates redox-activated nitroaromatic prodrugs such as pretomanid. These targets offer selective toxicity and are being pursued for designing second-generation anti-TB drugs(12).

On the host side, transcription factors such as TP53, KLF5, and GATA2, as well as the AKT1 pathway, have been shown to contribute to modulating immune responses against Mtb, pointing towards host-directed therapies (HDTs) with the possibility to augment antibiotic therapies(13).In addition, adjuvant therapies like the use of silymarin, a flavonoid with hepatoprotective and anti-inflammatory properties, together with isoniazid have also proven useful in augmenting drug efficacy and reducing toxicity, yielding a twofold benefit for TB patients(14).Besides, next-generation vaccine technologies, including mRNA-based platforms and multi-antigen formulations, are being developed to address the limitation of the BCG vaccine, especially in MDR-TB settings(15).

2.1Targeting Persistent TB Bacteria (Latent TB)

Targeting latent tuberculosis (LTBI)—a covert form of Mycobacterium tuberculosis that avoids immune detection and is refractory to conventional treatment—is the focus of worldwide TB eradication initiatives. One such potential pathway is host-directed therapy and diagnostics, in which immune reactions are sensed and manipulated rather than targeting Mtb directly. Further studies have underscored the prognostic significance of interferon-gamma inducible protein 10 (IP-10), a chemokine that is elevated in latent and active TB infection among BCG-vaccinated children and is also a candidate to be used as an alternative or complementary biomarker to interferon-gamma (IFN-γ) in the application to immune-based detection systems(16).

Therapeutically, thymidylate kinase (TMK) inhibition, an enzyme crucial for Mtb life in replicating and non-replicating forms, has been promising. The application of sophisticated computational drug design has led to novel TMK inhibitors with projected nanomolar activity and favorable pharmacokinetics, which are likely to offer effective means for eliminating resting bacterial populations(17).

2.1.1.Drugs active against non-replicating Mycobacterium tuberculosis (e.g., bedaquiline, pretomanid)

Effective treatment of tuberculosis (TB) not only requires killing actively dividing bacteria but also eradicating the non-replicating or latent populations of Mtb, responsible for relapse and persistence. Bedaquiline acts through the mechanism of inhibiting the mycobacterial ATP synthase, thereby disrupting energy metabolism even in non-replicating cells—a feature that renders it sterilizing and beneficial in the treatment regimens of MDR-TB. A recent transcriptomic study proved that bedaquiline induced a "quiescent" bacterial phenotype in vivo with overall suppression of protein synthesis and metabolism, consistent with action against resting organisms(18). Additionally, pretomanid, a nitroimidazole, is activated under anaerobic conditions like latent TB lesions, where it produces reactive nitrogen species that damage Mtb proteins and DNA. It has shown robust efficacy against eliminating hypoxic, non-replicating bacilli and is currently a key part of the BPaL regimen for extensively drug-resistant TB(19).Of particular interest, resistance to bedaquiline is increasing and has been associated with poor clinical outcomes, which underscores the need for monitoring resistance as well as combination regimens(20).

2.1.2.Inhibitors of bacterial energy metabolism (e.g., ATP synthase inhibitors)

Targeting the energy metabolism of bacteria is a new frontier in tuberculosis (TB) drug discovery, and inhibition of ATP synthase as a principal enzyme for ATP production in Mycobacterium tuberculosis is one of them. Bedaquiline is a diarylquinoline and the lead ATP synthase inhibitor with sterilizing activity against replicating and non-replicating Mtb. It acts by binding to the c subunit of the ATP synthase (atpE) and suppressing proton translocation and energy generation. Recent findings have shown that bedaquiline causes a systemic metabolic collapse in Mtb, which creates a dormant phenotype ideally adapted to combat chronic infections(21).Taking this idea a step further, type II NADH-dehydrogenase—a member of the oxidative phosphorylation pathway—is also discovered to be an equally good target for redox-based antimicrobials since it provides vital reducing equivalents for the formation of ATP(22).

2.1.3New Drug Classes and Molecules

New treatments for tuberculosis are advancing both through new drug classes and repurposed agents that target previously unexploited bacterial targets. The Ag85 complex proteins, vital to Mycobacterium tuberculosis (Mtb) cell wall biosynthesis, have been identified as potential targets through recent studies. Computational repurposing identified selamectin, imatinib, and eltrombopag as high-affinity binders of the Ag85 complex with stable binding and good drug-like properties in molecular dynamics simulations(23).

Additionally, new vaccines like mRNA-based TB vaccines and multi-antigen platforms are transforming immunoprophylaxis, and host-directed therapies like combinations of silymarin-isoniazid are promising in the reversal of toxicity and resistance(24).

3.Shorter and More Effective Regimens

Current advances in the management of tuberculosis aim at shorter, highly effective regimens in order to improve the compliance with treatment and avoid resistance. One of the major advances is the BPaL regimen—bedaquiline, pretomanid, and linezolid—which has resulted in the immediate suppression of transmission of drug-resistant TB. In a human-to-guinea pig model of transmission, patients receiving BPaL experienced complete suppression of TB transmission in as little as 72 hours compared with patients receiving traditional regimens(25).In addition, intensified 4-month regimens have been established in non-severe childhood TB to substitute prolonged durations without reducing effectiveness(26).But with these newer regimens come issues of safety, specifically linezolid-associated toxicities, which can influence regimen completion unless countered vigorously(27). The BPaL regimen, consisting of bedaquiline, pretomanid, and linezolid, is a significant breakthrough in treating drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. As a completely oral, 6–9 month regimen, BPaL has replaced old, toxic, and injectable therapies. Patients treated in a 2025 human-to-guinea pig transmission model were treated with BPaL achieved an overall suppression of air-borne TB transmission within 72 hours of initiating treatment—a dramatic contrast with infectivity persistence among the patients receiving standard regimens(28).

This emphasizes the strong early bactericidal and sterilizing effect of BPaL. While the linezolid-related adverse events (mainly peripheral neuropathy and myelosuppression) are a concern, forceful dose reduction and close monitoring can preserve efficacy with decreased toxicity(29).

4.Host-Directed Therapies

Host-directed therapies (HDTs) aim to enhance the host immune response or suppress Mycobacterium tuberculosis (Mtb)-mediated immunopathology, offering adjunctive benefit to conventional antimicrobial treatment. An attractive strategy is the repurposing of existing approved drugs like metformin, vitamin D, imatinib, and VEGF inhibitors, which act on immune processes, reduce inflammation, and allow bacterial clearance(30).In another study, lovastatin-loaded inhalable microspheres effectively suppressed MMP-2 and MMP-9 activity in infected macrophages to prevent lung tissue damage and synergize with anti-TB medications(31).Progress in 3D lung organoid models has also identified HERPUD1 and MFN2 as host determinants of intracellular Mtb survival and pro-inflammatory cytokine response, opening new avenues for HDT research(32).

4.1.Modulating the Immune Response

Statins, traditionally used in hyperlipidemia, possess anti-inflammatory actions by blocking cytokine storms and MMPs implicated in TB-induced lung injury. Inhalation of lovastatin microspheres brought about a dramatic reduction in MMP-2 and MMP-9 activity and inflammatory cytokines in M. tuberculosis-infected macrophages, with synergy with standard TB drugs(33).Metformin is an antidiabetic drug that induces autophagy, regulates mitochondrial reactive oxygen species (ROS), and improves host immunity. It had preclinical and early clinical efficacy in reducing TB severity and outcomes by enhancing macrophage killing of Mtb(34).Vitamin D has a role in macrophage activation, induction of antimicrobial peptides like cathelicidin, and T-helper cell response regulation. Supplementation in TB patients has been useful in accelerating sputum conversion and inhibiting hyperinflammation, particularly in the vitamin D-deficient group.

4.2.Anti-inflammatory and Adjunctive Therapies

Corticosteroids such as dexamethasone and prednisolone are already adjuvantly employed in TB meningitis and pericarditis, where they reduce inflammatory morbidity and mortality. Their role in pulmonary TB is more situation-dependent and predominantly limited by immunosuppression risks. Corticosteroids inhibit pro-inflammatory cytokines (e.g., IL-6, TNF-α), which limit granuloma lysis and fibrosis of tissue(35).Novel anti-inflammatory agents like statins, N-acetylcysteine, and MMP inhibitors are under investigation. For example, inhalable microspheres loaded with lovastatin suppressed MMP-2 and MMP-9—proteases implicated in ECM degradation and fibrosis—secreted by Mtb-infected macrophages, significantly reducing inflammatory cytokines and lung tissue injury in vitro(36).

5. Nanotechnology and Drug Delivery Innovations

One such promising example is the use of inhalable microspheres of lovastatin, which were prepared by spray-drying technology. Gelatin particles had optimal aerodynamic properties (~2.4 μm) for targeted delivery to the deep lung and were actively taken up by macrophages—the primary host cells of Mycobacterium tuberculosis. The particles had strong anti-inflammatory effects by inhibiting inflammatory cytokines and matrix metalloproteinase expression and also synergized with first-line TB drugs, suggesting dual function through drug delivery and host-directed treatment(37).Advanced materials science like bioresponsive polymers, nanocarriers, and hydrogels are enabling site-specific and controlled drug delivery, particularly beneficial in TB where the lesions may be intracellular, fibrotic, or hypoxic. Such systems promise to bypass resistance mechanisms, improve bioavailability, and reduce toxicity(38). Nanotechnology transforms the treatment of tuberculosis (TB) by employing targeted drug delivery systems for enhancing the stability of drugs, bioavailability, and tissue targeting. Nano-formulations such as polymeric nanoparticles, liposomes, and inhalable microspheres enable targeted delivery to alveolar macrophages, the primary reservoir of Mycobacterium tuberculosis. A novelty is the employment of inhalable gelatin microspheres with lovastatin, which possessed ideal particle sizes (~2.4 μm) for deep lung deposition, enabling macrophage uptake and modulation of inflammation by blocking matrix metalloproteinases(39).

6. Vaccine development

Despite global BCG vaccination nearly all along, its comparatively weak performance in adults has spurred much research into new TB vaccines. Among the most promising of these is the M72/AS01E subunit vaccine, which demonstrated 50% efficacy against active TB disease in adults with latent infection in a phase IIb trial. A 2025 systems biology study discovered molecular immune signatures and vaccine-induced protection gene expression profiles, for instance, for Th1/Th2/Th17 response and T-cell signaling(40).At the same time, new platforms such as baculovirus surface-displayed particles displaying antigens MTB39A and MTB32C have shown acceptable immunogenicity in mice and calves, with the indication of potential for multi-antigen vaccine constructs(41).Nevertheless, problems like genomic heterogeneity of Mtb isolates, population stratification, and delivery system limitations have slowed advances in human trials, especially for high-burden facilities(42).The limitations of BCG, particularly its inconsistent protection in adolescents and adults, have motivated the research into next-generation TB vaccines. The furthest along among the contenders is M72/AS01E, a subunit vaccine made up of a fusion protein (Mtb32A and Mtb39A) plus the AS01E adjuvant. It demonstrated 50% efficacy in phase IIb clinical trial among adults with latent TB infection. Systems biology studies that came more recently identified adaptive immune signatures (e.g., Th1/Th17 response) and immune gene networks as markers of disease correlation, which would steer putative biomarkers in future trials(43).

7. Genomic and Precision Medicine Approaches

The convergence of genomics and precision medicine is revolutionizing the diagnosis, treatment, and characterization of host-pathogen in TB. Among the steps taken has been the application of CBNAAT (Cartridge-Based Nucleic Acid Amplification Test) and whole genome sequencing (WGS) for the quick identification of Mycobacterium tuberculosis and its drug resistance profile. In a recent Indian cohort study, CBNAAT was 97% sensitive and 90% specific compared to smear microscopy and culture for drug-resistant TB detection, particularly extrapulmonary and immunocompromised TB(44).

8. Research Investment and Collaboration

Tuberculosis (TB) remains one of the major causes of death from infectious diseases worldwide, and sustained research investment and robust global collaboration are required. Combating TB must be treated at a global level, especially when drug resistance is rising and budgets are strained. Understanding the magnitude of existing research investment and collaboration can support strategic policy, enhance research quality, and accelerate advancement toward the WHO's End TB Strategy targets.

1.Social and Community Investment:

Investment in social capital — networks, participation in communities, and trust — has a significant effect on public engagement in control and prevention of TB. In a Chinese large-scale study, social capital was found to enhance TB control practices by acting through knowledge and attitudes. It recommends multi-sectoral assistance, which involves funding for research, to develop and apply better diagnostics and treatments(45).

2.Research Integrity and Funding Risks:

A survey of retracted TB studies found that nearly half were externally funded, suggesting potential misdirection of funds for research. The most prevalent causes were falsification and plagiarism, which compromise quality assurance for grant-funded TB studies. This calls for more regulation and openness requirements in collaborative grant-based research(46).

3.Transborder Clinical Cooperation:

The initial Ukrainian patient of an Italian-treated individual with pre-XDR TB using the BPaL regimen (bedaquiline, pretomanid, linezolid) demonstrates how political instability elicits international cooperation in the treatment of TB. The study emphasizes that sustaining such treatment lines across borders requires integrated healthcare systems and harmonized research protocols(47).

9.Challenges and Future Directions

Management and control of tuberculosis (TB) are faced with several challenges that are persisting, particularly in developing and launching new therapeutic interventions. The most significant challenge is equipping treatment innovations to be affordable and accessible equitably. Patients are faced with significant barriers such as financial constraints, lack of transport availability, and food insecurity in the majority of high-burden, low-resource settings that undermine adherence and sustained care retention. Despite the availability of newer drugs like bedaquiline and pretomanid, they are often limited in their availability due to high costs and unequal procurement mechanisms, particularly to low-income countries(48).Complementing this worry is the extremely high rise in drug-resistant TB types, including multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), with more complex, expensive, and prolonged regimens. New drugs and immunomodulatory therapy have been promising against resistance but with such interventions being in preliminary stages and requiring to be validated comprehensively(49).

One of the main bottlenecks in the clinical development pipeline is at the stage of vaccine and drug trials, where complexity in regulations, high costs, and logistics stop them. Vaccine development, for instance, is hampered by issues like antigen diversity and variable efficacy across populations. For late-stage drug trials, dropout from participants, long timelines, and poor finance are the hindrances. Future strategies must concentrate on accelerated regulatory pathways, funding for experimental designs, and global collaborations to bring new drugs to the most vulnerable populations(50).

10.RESULT:-

Recent investigations into new strategies for the targeting of Mycobacterium tuberculosis, the causative organism of tuberculosis (TB), have led to several hopeful plans with an emphasis on novel molecular targets and computational drug design. One of the plans involves the development of improved thymidylate kinase (TMK) inhibitors, a vital enzyme in DNA synthesis, using quantitative structure-activity relationship (QSAR) models and pharmacophore-based design. These compounds proved to be efficacious and possessing acceptable pharmacokinetics in blocking in silico .Another study explores microbial-derived natural products as blocking agents of DNA Gyrase B, a required enzyme for bacterial DNA replication. 1-Hydroxy-D-788-7 was one of them that showed good drug-likeness and binding. Similarly, small molecules interacting with 4-hydroxy-tetrahydrodipicolinate reductase (DapB), a bacterial protein which is not present in human beings, have been found to possess high binding affinity and specificity and hence hold a potential and safe drug candidate route .

11.DISCUSSION:-

New strategies for targeting Mycobacterium tuberculosis (M.tb) have emerged with growing drug resistance and failure of conventional treatments. One of the significant advances has been in the discovery of novel molecular targets, one of which is DNA gyrase B, a key enzyme involved in DNA replication. Natural product-derived inhibitors like 1-Hydroxy-D-788-7 have been identified in silico with high binding efficiency and good drug-like properties(51).One such promising target is 4-hydroxy-tetrahydrodipicolinate reductase (DapB), a key enzyme in bacterial cell wall formation but not found in human cells, thus reducing off-target activity. Molecular docking has led to the identification of small molecules like DapB inhibitors with high binding affinity values compared to available candidates(52). At the same time, dual-acting compounds such as calix[4]pyrrole derivatives provide a multi-directed strategy by showing both anti-TB and antioxidant activity. This dual action can potentially counteract TB-associated oxidative stress to enhance host resilience.These strategies are supplemented by precision drug delivery technologies. Nanocarriers can be used to directly target infected macrophages, delivering higher drug concentrations to infection sites with lower systemic toxicity. In addition, host-directed therapies (HDTs) are being explored for their immune-modulating capabilities and improved bacterial clearance, but their clinical translation is still limited(53).

12.CONCLUSION:-

Tuberculosis remains a powerful global health hazard, especially with the increasing hazard of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Mycobacterium tuberculosis strains. Classic antibiotic treatments, though still the norm, are increasingly ineffective against these new enemies because of extended treatment durations, toxicity, and drug resistance. Thus, the treatment landscape for TB is being reshaped by new paradigms for therapy.New target molecules, such as enzymes DNA gyrase B and DapB, are facilitating the identification of next-generation antimicrobials with new modes of action. These efforts are not just to kill the pathogen efficiently but also to inhibit the development of additional resistance. Computational drug discovery and in silico screening are enhancing the discovery of highly potent inhibitors against vast chemical libraries, providing speed and accuracy in early-stage drug discovery.

Concurrently, host-directed therapies (HDTs) are reshaping the therapeutic agenda by targeting the modulation of the host immune system. By activation of innate immunity or blockade of tissue-damaging inflammation, HDTs hold promise to diminish disease severity and reduce treatment duration. In addition, nanotechnology-facilitated drug delivery—e.g., macrophage-targeting nanoparticles and inhaled formulations—is enhancing pharmacokinetics, drug stability, and patient compliance.The employment of dual-action agents, i.e., with antimicrobial and antioxidant action, adds additional therapeutic synergy, particularly against TB-induced oxidative stress. When taken together, these multi-faceted strategies are leading to less, safer, and better therapy.Assuming these encouraging developments, clinical implementation will involve overcoming issues of cost, access, and clinical proof. Future success will hang on continued investment in translational science, international cooperation, and distributive healthcare policy.In total, these new approaches are a step closer to precision, multi-targeted, and host-compatible therapies for TB, a welcome step in the centuries-long fight against tuberculosis.

13.REFERENCES:-

1. Konaté S, N'Guessan K, Allangba PG, Fofana I, Kre N'Guessan R, Megnassan E, et al. Improved Inhibitors Targeting the Thymidylate Kinase of Multidrug-Resistant Mycobacterium tuberculosis with Favorable Pharmacokinetics. Reproductive and Developmental Biology 2025;15:173. https://doi.org/10.3390/life15020173.
2. Elsaman T, Awadalla Mohamed M, Mohamed MS, Eltayib EM, Abdalla AE. Microbial-based natural products as potential inhibitors targeting DNA gyrase B of Mycobacterium tuberculosis: an in silico study. Frontiers in Chemistry 2025;13. https://doi.org/10.3389/fchem.2025.1524607.
3. Ding Y, Li BP, Yi Y, Liu C, Jie W, Jian X, et al. Progress in the role of nanoparticles in the diagnosis and treatment of bone and joint tuberculosis. Frontiers in Medicine 2025;12. https://doi.org/10.3389/fmed.2025.1536547.
4. Shah R, Nadaf S, Bhagwat DA, Gurav S. Trends in Nano Drug Delivery System for Infectious Diseases 2025:181–206. https://doi.org/10.1002/9781394200559.ch8.
5. Nanotechnology-Enabled Biomaterials: Transforming Tuberculosis Management through Advanced Diagnosis, Targeted Drug Delivery, and Immunotherapy. Letters in Applied NanoBioScience 2025;14:15. https://doi.org/10.33263/lianbs141.015.
6. Shah R, Nadaf S, Bhagwat DA, Gurav S. Trends in Nano Drug Delivery System for Infectious Diseases 2025:181–206. https://doi.org/10.1002/9781394200559.ch8.
7. Nanotechnology-Enabled Biomaterials: Transforming Tuberculosis Management through Advanced Diagnosis, Targeted Drug Delivery, and Immunotherapy. Letters in Applied NanoBioScience 2025;14:15. https://doi.org/10.33263/lianbs141.015.
8. Liu R, Song TMK, Chen X, Yu Z, Yang C, Zhang X, et al. Graphene Oxide-Assisted Tapered Microfiber Super-Sensor for Rapid Detection of *Mycobacterium tuberculosis* Antigens. Biotechnology and Bioengineering 2025. https://doi.org/10.1002/bit.28929.
9. An Y, Ni R-X, Li Z, Yang L, Ye Z, Li L, et al. Tuberculosis vaccines and therapeutic drug: challenges and future directions. Molecular Biomedicine 2025;6. https://doi.org/10.1186/s43556-024-00243-6.
10. Dou H-Y, Huang T-S, Wu H, Hsu C-H, Chen F-J, Liao Y-C. Targeted sputum sequencing for rapid and broad drug resistance of Mycobacterium tuberculosis. Infection 2025. https://doi.org/10.1007/s15010-024-02463-y.
11. Jatav PC, Shrivastava R. Silymarin and Isoniazid Combination for the Treatment of Drug-Resistant Tuberculosis: A Mini Review. Anti-Infective Agents 2025;23. https://doi.org/10.2174/0122113525357725250102112741.
12. Paoli-Lombardo R, Primas N, Vanelle P. DprE1 and Ddn as promising therapeutic targets in the development of novel anti-tuberculosis nitroaromatic drugs. European Journal of Medicinal Chemistry 2024;274:116559. https://doi.org/10.1016/j.ejmech.2024.116559.
13. Yan N, Yang Y, Sun L, Huang Y, Zhang J. Screening of drug targets for tuberculosis on the basis of transcription factor regulatory network and mRNA sequencing technology. Frontiers in Molecular Biosciences 2024. https://doi.org/10.3389/fmolb.2024.1410445.
14. Jatav PC, Shrivastava R. Silymarin and Isoniazid Combination for the Treatment of Drug-Resistant Tuberculosis: A Mini Review. Anti-Infective Agents 2025;23. https://doi.org/10.2174/0122113525357725250102112741.
15. An Y, Ni R-X, Li Z, Yang L, Ye Z, Li L, et al. Tuberculosis vaccines and therapeutic drug: challenges and future directions. Molecular Biomedicine 2025;6. https://doi.org/10.1186/s43556-024-00243-6.
16. Druszczyńska, M., Seweryn, M. T., Wawrocki, S., Pankowska, A., Kulbachko, A., Jurczak, M. J., & Kowalewska-Pietrzak, M. (2025). Interferon (IFN)-gamma (γ) inducible protein 10 (IP-10) in the diagnosis of latent and active tuberculosis in Bacille Calmette Guerin (BCG)-vaccinated pediatric population. *PLOS ONE*, *20*(1), e0314400. https://doi.org/10.1371/journal.pone.0314400
17. Konaté S, N'Guessan K, Allangba PG, Fofana I, Kre N'Guessan R, Megnassan E, et al. Improved Inhibitors Targeting the Thymidylate Kinase of Multidrug-Resistant Mycobacterium tuberculosis with Favorable Pharmacokinetics. Reproductive and Developmental Biology 2025;15:173. https://doi.org/10.3390/life15020173.
18. Wynn EA, Dide-Agossou C, Al Mubarak R, Rossmassler K, Ektnitphong V, Bauman A, et al. Emergence of antibiotic-specific *Mycobacterium tuberculosis* phenotypes during prolonged treatment of mice. Antimicrobial Agents and Chemotherapy 2025. https://doi.org/10.1128/aac.01310-24.
19. Saha P, Kumar M, Sharma DK. Potential of *Mycobacterium tuberculosis* Type II NADH-Dehydrogenase in Antitubercular Drug Discovery. ACS Infectious Diseases 2025. https://doi.org/10.1021/acsinfecdis.4c01005.
20. Mdlenyani L, Mohamed Z, Stadler JAM, Mtwa N, Meintjes G, Warren RM, et al. Treatment outcomes of bedaquiline-resistant tuberculosis: a retrospective and matched cohort study 2025. https://doi.org/10.1101/2025.01.21.25320876.
21. Wynn, E. A., Dide-Agossou, C., Al Mubarak, R., Rossmassler, K., Ektnitphong, V., Bauman, A., Massoudi, L. M., Voskuil, M. I., Robertson, G. T., Moore, C. M., & Walter, N. D. (2025). Emergence of antibiotic-specific *Mycobacterium tuberculosis* phenotypes during prolonged treatment of mice. *Antimicrobial Agents and Chemotherapy*. https://doi.org/10.1128/aac.01310-24
22. Saha P, Kumar M, Sharma DK. Potential of *Mycobacterium tuberculosis* Type II NADH-Dehydrogenase in Antitubercular Drug Discovery. ACS Infectious Diseases 2025. https://doi.org/10.1021/acsinfecdis.4c01005.
23. Iskandar IW, Nurhasanah A, Hatta M, Hamid F, Handayani I, Chaera U, et al. Computational drug repurposing for tuberculosis by inhibiting Ag85 complex proteins. Narra J 2025;5:e1130. https://doi.org/10.52225/narra.v5i1.1130.
24. An, Y., Ni, R.-X., Li, Z., Yang, L., Ye, Z., Li, L., Parkkila, S., Aspatwar, A., & Gong, W. (2025). Tuberculosis vaccines and therapeutic drug: challenges and future directions. *Molecular Biomedicine*, *6*(1). https://doi.org/10.1186/s43556-024-00243-6
25. Stoltz A, Nathavitharana RR, Kock E, Ueckermann V, Jensen P, Mendel CM, et al. Estimating the Early Transmission Inhibition of new treatment regimens for drug-resistant tuberculosis. The Journal of Infectious Diseases 2025. https://doi.org/10.1093/infdis/jiaf005.
26. Owusu SK. Childhood Tuberculosis—Advances in Treatment and Prevention. Pediatric Pulmonology 2025. https://doi.org/10.1002/ppul.27375.

27. Atshemyan H, Khachatryan N, Khachatryan A, Mirzoyan NR. The Management of Linezolid-Induced Adverse Events in Shorter and Longer Treatment of Rifampicin-Resistant Tuberculosis. Annals of Pharmacotherapy 2025. https://doi.org/10.1177/10600280241296841.

28. Stoltz, A., Nathavitharana, R. R., Kock, E., Ueckermann, V., Jensen, P., Mendel, C. M., Spigelman, M., & Nardell, E. A. (2025). Estimating the Early Transmission Inhibition of new treatment regimens for drug-resistant tuberculosis. *The Journal of Infectious Diseases*. https://doi.org/10.1093/infdis/jiaf005

29. Atshemyan H, Khachatryan N, Khachatryan A, Mirzoyan NR. The Management of Linezolid-Induced Adverse Events in Shorter and Longer Treatment of Rifampicin-Resistant Tuberculosis. Annals of Pharmacotherapy 2025. https://doi.org/10.1177/10600280241296841.

30. Xavier AM, Ravichandran M. Repurposing Drugs as Host-Directed Therapy in Tuberculosis. Current Respiratory Medicine Reviews 2024;21. https://doi.org/10.2174/011573398x310509240816053650.

31. Jhilta, A., Jadhav, K., Sharma, R., Singh, R., Negi, S., Sharma, N., Singh, A. K., & Verma, R. K. (2025). Host-Directed Therapy with Inhalable Lovastatin Microspheres for Matrix Metalloproteinase Inhibition in Tuberculosis. *ACS Applied Bio Materials*. https://doi.org/10.1021/acsabm.4c01723

32. Kim S-Y, Choi J, Choi S, Kim KK, Song C, Kim E-M. Advances in an In Vitro Tuberculosis Infection Model Using Human Lung Organoids for Host-Directed Therapies. PLOS Pathogens 2024;20:e1012295. https://doi.org/10.1371/journal.ppat.1012295.

33. Jhilta A, Jadhav K, Sharma R, Singh R, Negi S, Sharma N, et al. Host-Directed Therapy with Inhalable Lovastatin Microspheres for Matrix Metalloproteinase Inhibition in Tuberculosis. ACS Applied Bio Materials 2025. https://doi.org/10.1021/acsabm.4c01723.

34. Xavier, A. M., & Ravichandran, M. (2024). Repurposing Drugs as Host-Directed Therapy in Tuberculosis. *Current Respiratory Medicine Reviews*, *21*. https://doi.org/10.2174/011573398x310509240816053650

35. Xavier AM, Ravichandran M. Repurposing Drugs as Host-Directed Therapy in Tuberculosis. Current Respiratory Medicine Reviews 2024;21. https://doi.org/10.2174/011573398x310509240816053650.

36. Jhilta, A., Jadhav, K., Sharma, R., Singh, R., Negi, S., Sharma, N., Singh, A. K., & Verma, R. K. (2025). Host-Directed Therapy with Inhalable Lovastatin Microspheres for Matrix Metalloproteinase Inhibition in Tuberculosis. *ACS Applied Bio Materials*. https://doi.org/10.1021/acsabm.4c01723

37. Jhilta A, Jadhav K, Sharma R, Singh R, Negi S, Sharma N, et al. Host-Directed Therapy with Inhalable Lovastatin Microspheres for Matrix Metalloproteinase Inhibition in Tuberculosis. ACS Applied Bio Materials 2025. https://doi.org/10.1021/acsabm.4c01723.

38. Rabbani SA. Revolutionizing Drug Delivery: The Impact of Advanced Materials Science and Technology on Precision Medicine 2025. https://doi.org/10.3390/pharmaceutics17030375.

39. Jhilta A, Jadhav K, Sharma R, Singh R, Negi S, Sharma N, et al. Host-Directed Therapy with Inhalable Lovastatin Microspheres for Matrix Metalloproteinase Inhibition in Tuberculosis. ACS Applied Bio Materials 2025. https://doi.org/10.1021/acsabm.4c01723.

40. Taofeek, O. O., Alile, S. O., Elcanah, E. M., Ezediuno, L. O., George, I. A., Oyewole, O. M., Owiti, P., & Sulaimon, L. A. (2025). *Systems and network biology analysis combined with machine learning identifies key immune response profiles and potential correlates of protection for the m72/as01e tuberculosis vaccine.* https://doi.org/10.1101/2025.01.13.25320455

41. Wang P, Zhang G, Jiang L, Zhang S, Gao W, Wu Z, et al. Development of a Vaccine Candidate Based on Surface-Displayed Particles of Mycobacterium tuberculosis from the MTB39A Protein. International Journal of Molecular Sciences 2025;26:797. https://doi.org/10.3390/ijms26020797.

42. Hamisi M, Asri NAM, Yassim ASM, Suppıan R. A systematic review on malaria and Tuberculosis (TB) vaccine challenges in sub-Saharan African clinical trials. PLOS ONE 2025;20:e0317233. https://doi.org/10.1371/journal.pone.0317233.

43. Taofeek, O. O., Alile, S. O., Elcanah, E. M., Ezediuno, L. O., George, I. A., Oyewole, O. M., Owiti, P., & Sulaimon, L. A. (2025). *Systems and network biology analysis combined with machine learning identifies key immune response profiles and potential correlates of protection for the m72/as01e tuberculosis vaccine.* https://doi.org/10.1101/2025.01.13.25320455

44. Mansuri MZ, Jain S, Singapurwala MS, Jain S, Julka A, A C. A study of impact of cbnaat in the diagnosis of tuberculosis at a rural based tertiary care teaching centre in india. International Journal of Advanced Research 2025;13:90–6. https://doi.org/10.21474/ijar01/20167.

45. Gu, Z., Zhu, L., Ren, F., Qi, W., Cao, R., Zhang, Y., Dong, J., & Chen, A. M. (2025). *Research on the effect of social capital on public tuberculosis prevention and control practices based on stimulus–organism–response theory*. https://doi.org/10.21203/rs.3.rs-5807604/v1

46. García-Solórzano FO, De la Cruz Anticona SM, Pezua-Espinoza M, Chuquispuma Jesus FA, Sanabria-Pinilla KD, Véliz C, et al. Analyzing the Drivers Behind Retractions in Tuberculosis Research. Publications 2025;13:4. https://doi.org/10.3390/publications13010004.

47. Fumagalli G, Riccardi N, Catalano G, Ferrarese M, Repossi AC, Codecasa LR. TB Anywhere, TB Everywhere. The First Case of pre-Extensively Drug Resistant Tuberculosis Treated with BPaL in Italy: Challenges and Opportunities for Transborder Collaboration. Microbial Drug Resistance 2024. https://doi.org/10.1089/mdr.2024.0045

48. Mphothulo N, Hlangu S, Furin J, Moshabela M, Loveday M. Navigating DR-TB Treatment care: a qualitative exploration of barriers and facilitators to retention in care among people with history of early disengagement from drug-resistant tuberculosis treatment in Johannesburg, South Africa. BMC Health Services Research 2025;25. https://doi.org/10.1186/s12913-025-12265-z.

49. Sun, Q., Li, S., Gao, M., & Pang, Y. (2024). *Therapeutic Strategies for Tuberculosis: Progress and Lessons Learned*. *37*(11), 1310–1323. https://doi.org/10.3967/bes2024.168

50. An, Y., Ni, R.-X., Li, Z., Yang, L., Ye, Z., Li, L., Parkkila, S., Aspatwar, A., & Gong, W. (2025). Tuberculosis vaccines and therapeutic drug: challenges and future directions. *Molecular Biomedicine*, *6*(1). https://doi.org/10.1186/s43556-024-00243-6

51. Elsaman T, Awadalla Mohamed M, Mohamed MS, Eltayib EM, Abdalla AE. Microbial-based natural products as potential inhibitors targeting DNA gyrase B of Mycobacterium tuberculosis: an in silico study. Frontiers in Chemistry 2025;13. https://doi.org/10.3389/fchem.2025.1524607.

52. Exploring Small Molecules as Novel Drug Candidates Targeting 4-Hydroxy-Tetrahydrodipicolinate Reductase in Mycobacterium tuberculosis: Insights from Molecular Dynamics Simulation and Principal Component Analysis. Letters in Applied NanoBioScience 2025;14:2. https://doi.org/10.33263/lianbs141.002

53. Parmar N, Bhatt K, Parikh J, Patel N. Multifunctional Calix[4]Pyrrole Derivatives: Optimized Synthesis and a Dual-Action Study Targeting Tuberculosis and Oxidative Stress. Polycyclic Aromatic Compounds 2024:1–11. https://doi.org/10.1080/10406638.2024.2444338.