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Does the Aura Around Allopathic Modern Medicines Eclipse Over Medical Potentials of Traditional Medicines Against *Mycobacterium Tuberculosis* (MTB) and TB?

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Abstract: One third of the humans are exposed to *Mycobacterium tuberculosis (*MTB) of which 5-10% becomes latently infected without symptoms and this predominantly occurs in the early in the life. Of this population about 10% population lead to much aggravated active TB which is the cause for the morbidity and mortality associated with TB. TB is curable upon proper treatment but there is a growing concern over the emergence of MDR and XDR drug resistant MTB. This high degree of resistance and adverse side-effects warrants alternative method of treatment such as traditional medicine systems of Indian subcontinent. Unfortunately such anti TB drugs is not available in the pipeline of alternative medicine systems. In spite of various obstacles that anti MTB allopathic medicines face it stays as main stream because these drugs undergo rigorous scientific testing and evidence based selection. In contrast drugs from traditional medicine system are not backed by such evidence-based scientific testing. It is perhaps the major setback for traditional medicines rather than the perception of aura of modern medicine eclipsing over traditional system of medicines. Unless there is a revolution occurs in the discussed biomedical issues in this review the chances of using traditional medicines as sole treatment method may remain on the horizon.

Keywords: *Mycobacterium tuberculosis*, Medicinal Plants, Drug Resistant, MDR and XDR-TB, Anti-tubercular, Natural, Ayurveda. , Unani, Surrogate, GeneXpert, BSL-3.

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Introduction

In 2014, a study conducted on the reconstruction of DNA genome from remains in southern Peru suggested that human tuberculosis is less than 6,000 years old[1]. In 400 BC, Hippocrates described the clinical symptoms of tuberculosis and Galan described the treatment for TB using tranquilizers and pain killers [2]. While Galan believed that TB is hereditary others like Aristotle convinced it is contagious [3]. At different era TB had been described as romantic disease, consumption, phthisis, scrofula, Pott's disease, and the White Plague. 1n 16th century a royal touch from Christian monarchs of British and French was believed to be the cure for TB illness. The field mycobacterioses gradually developed in eighteenth and nineteenth century. One of the significant milestones in Mycobacteriology was that on 24th March 1882 Robert Koch revealed that TB was caused by an infectious agent [4]. This was followed by Wilhelm Roentgen (1895) discovering the X-ray, which allowed physicians to diagnose and track the progression of the disease [5] . In spite of these advancements the proportion of the disease and mortality was on a growing trend until the discovery of antibiotics. In 1944 Albert Schatz, Elizabeth Bugie and Selman Waksman isolated streptomycin produced by a bacterial strain *Streptomyces griseus*[6]. Streptomycin was the first effective antibiotic against *Mycobacterium tuberculosis* and this discovery was generally considered the beginning of the modern era of tuberculosis. But a significant breakthrough occurred with the discovery of isoniazid in1952. This was the first oral mycobactericidal drug [7]. With the advent of rifampicin in 1980s TB cases declined significantly until 1980s. Hopes that the disease could be completely eliminated were dashed in the 1980s with the rise of drug-resistant strains [8]. Emergence of multi drug resistant (MDR) and extensive drug resistant (XDR) MTB was stumbling block in TB therapy and the complete scenario was sabotaged by the emergence of HIV from 1981. All these developments forced WHO to declare TB as global health emergency in 1993. Every year, nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) are estimated to occur world wide[9].

The first TB vaccine dates back to Robert Koch (1890) using bovine tuberculosis bacteria after seeing monumental success against small pox using cowpox organism. But first genuine success in immunizing against tuberculosis was developed from attenuated bovine-strain of mycobacterium by Albert Calmette and Camille Guérin in 1906. It was called "BCG" (Bacille Calmette-Guérin)[10]. The BCG vaccine was first used on humans from 1921 in France, United States, Great Britain, and Germany. The current belief is that BCG immunization is fairly effective for infants and children TB meningitis and military TB. However its adult efficacy ranges from 0% to 80% depending upon their race and ethnicity[11].The other MTB vaccines are MVA85A, rBCG30, 72F fusion protein and ESAT6-Ag85b fusion protein[12].The problems associated with BCG are widely variable protective efficacy and development of side-effects. Since complete protection against TB is equivocal by BCG we rely primarily on drugs to manage the disease. Proper administration of anti TB drugs can cure TB however the required time ranges depending upon the severity and at times more than 6 months [13].

Because of this tuberculosis is still considered to be a highly infectious and contagious disease and BSL-3 containment pathogen. It accounted for about one third (2.5 billion) of the world's population (7.4 billion) including 40 per cent from India estimated to be infected by tuberculosis [14]. However not all the infected individuals lead to primary infection and majority of the primary infection occurs in children. Of the tuberculosis exposed individuals roughly 10% of them retain the bacteria (primary complex) and this population may develop symptom-less latent tuberculosis. These patients may be positive to tuberculin test but no abnormal lung X-ray. Later due to weakened immunity active or reactive tuberculosis develops which requires medical attention. If untreated the patient may even die. The incident rate of tuberculosis is almost one case per second worldwide. According to WHO's 2016 report[15], in 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new tuberculosis cases. There were 1.4 million deaths globally in 2015 alone. In the same year, there were an estimated 480,000 new cases of Multidrug-Resistant tuberculosis (MDR-TB) and an additional 100,000 people with Rifampicin-resistant tuberculosis (RR-TB) who were also newly eligible for MDR-TB treatment. India, China and the Russian Federation accounted for 45% of the combined total of 580 000 cases.

Conventional anti MTB drugs:

Drugs such as isoniazid (INH or H), rifampicin (RMP or R), streptomycin (STM or S), Ethambutol (EMB or E) and pyrazinamide (PZA or Z), are all considered first line of drugs to control MTB. Besides that second line and third line of drugs are being administered when drug resistance surfaced [16]. Multi drug resistant tuberculosis (MDR-TB) or Vank's disease show resistance to isoniazid and rifampicin and Extensively drug-resistant tuberculosis (XDR-TB) is a rare type of multidrug-resistant tuberculosis (MDR-TB) that is resistant to isoniazid and rifampin, plus any fluoroquinolones and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) [17]. Though these drugs are in clinical practice they are known for their adverse side-effects. First line of drugs though effective in killing MTB they are known to show side-effects. Second-line drugs have many more adverse effects than the first-line anti-TB drugs[18].

Side-effects caused by conventional anti MTB drugs:

Besides developing drug resistance long term administration of isoniazid can cause side effects such as nausea, vomiting, epi-gastric pain and in some cases of cutaneous pruritus or itching [19]. Similarly administration of rifampicin can cause fatigue, dizziness, headache, dyspnea, and ataxia can also occur in patients treated with rifampicin [20]. Pyrazinamide administration for longer period can develop dermatitis. Another effective anti MTB drugs is Ethambutol and chronic administration can lead to Retrobulbar neuritis, nausea, vomiting, abdominal pain, and hepatotoxicity, hematological symptoms (eosinophilia, neutropenia, and thrombocytopenia), cardiovascular symptoms (myocarditis and pericarditis), neurological symptoms (headache,

dizziness, and mental confusion), hyperuricemia/ gout (due to a reduction in the excretion of uric acid by the kidney), hypersensitivity (skin rash, arthralgia, and fever), and (occasionally) pulmonary infiltrates[21].Treatment with streptomycin reported to cause vestibular and auditory nerve damage and occasionally renal damage[22].

Anti MTB drugs derived from Indian Medicinal Plants:

Increased drug resistance and development of side-effects warrant novel anti tuberculosis drugs to effectively control tuberculosis. One of the oldest medicine systems is naturopathy in which humans derive medicines from natural sources and use pseudoscientific and non-invasive protocols to promote spontaneous self-healing of diseases. A little refined system of medicine was proposed by Samuel Hahnemann (1810) and he coined the term "homeopathy' meaning *like cures like* and he also coined term allopathy for non-homeopathic form of medicine practice [23]. According to homeopathy, there are substances present in the healthy individual's body which lacked among sick patients. During the same period homeopathy practitioners used to refer non-homeopathy practitioners as allopathic practitioners (allos-others, pathos-suffering) on a snarling and ridiculing way. Later on allopathic medicine gained momentum since it was believed to be evidence based medicine. Though it developed into an alternative medicine initially it became the main or core system of medicine and now popularly known as modern medicine. In allopathic practice, symptoms are not treated rather the cause for the symptoms.

While different ethnic medical systems practiced in different parts of the world, three predominant types of medicine practices were followed in Indian subcontinent. They are Ayurveda, Siddha and Unani. Ayurveda means *life-knowledge*. It is believed that Hindu God of Medicines, Dhanvandri taught the art of ayurvedic medical practice in Varanasi to various sages including Sushrutha who eventually wrote the ayurvedic medicine literature [24] and Ayurveda describes TB as Rajayakshma. Ancient Ayurveda texts also taught surgical techniques, including rhinoplasty, kidney stone extractions, sutures, and the extraction of foreign objects [25]. While allopathic medicine relies on evidence based medicines, Ayurveda relies mostly non-evidence based and it is called pseudoscience or protoscience or transscience. In Ayurveda single or compendium of plant materials is incorporated in the advocated medicines. Almost parallelly another ancient medical system Siddha was generated from Tamil culture. The doctrines of Siddha medicine were originally written in palm leaf manuscripts (hence was called chittai-medicine which eventually became Siddha medicine) was first described by Lord Shiva to his wife goddess Parvathi. Goddess Parvathi explained all this knowledge to her son Lord Subramanya. He taught all these knowledge to his disciple sage Agasthya. Agasthya taught 18 Siddhars and they spread this knowledge to human beings. Hence it was originally practiced by 18 siddhars it was subsequently called as Siddha medicine. Like Ayurvedha, Siddha also advocates single or amalgamation of several plants for each disease and there appears many over-lapping of many medicinal plants in their ingredients. After understanding the benefits Siddha medicine it is being used as supportive therapy against HIV/AIDS. In contrary, Unani has a perso-arabic origin spread by moguls and Delhi sulthanates in India in 13th century. In all these medicine systems the plants overlap and successfully used to control several human ailments. All these

medicine systems are practiced now in India and national funding agencies such as AYUSH promote such activities [26].

One of the complications with traditional system of medicines is the success seen with medicine compendium or mixture rather a single plant derivative. In addition the recovery process is extremely time consuming. Some of the effective ayurvedic mixture with anti TB property are *Aswagandha, Shilajeet*, *Vasantamalati, Kanchanabhra rasa, Rajamriganka rasa*, *Bhallataka (Semicarpus anacardium) rasayan, Mallasindura, Vasa (Adatoda vasica) etc[27]*. However it took more than a decade to see the beneficial effects. Several studies evaluated individual plant derivatives and found remarkable anti TB activities. We and others had shown the anti MTB efficacy of leaves of *Acalypha indica, Andrographis paniculata* and *Aloe ver*[28,29] Leaves of *Adhatoda vasica* and gloves of *Allium sativum* were reported to be possessing Anti MDR-TB activities[30] .Studies on *Urtica dioica*[31], *Plumeria bicolor*[32], *Punica granatum*[33] showed better anti MDR and XDR-TB activities. An over view of the literature indicated that about 27 medicinal plants from all over the globe found to be possessing anti TB activity[34].

Tumbling blocks for the herbal medicines for the wide spread usage in the pharmacies:

The rapid development of new herbal anti-TB drugs has been hampered by several obstacles. First of all, the TB drug market is associated with insufficient profit opportunity or investment return to instigate pharmaceutical industries to develop new. Even if there are anti MTB drugs development initiatives they predominantly on synthetic drugs and development of herbal medicines are the last choice [35]. One of the obstacles with MTB is that it is an extremely slow growing bacteria [36] and long term administration of allopathic medicines in the susceptible individuals. Indian traditional medicines by virtue are slow acting medicines and hence fail to attract pharmacies or biotech industries. Besides that emergence of HIV among TB patients lead to HIV overshadowing TB. Unless there is some break-through in rapid cultivation methods and quicker treatment regimens herbal medicine may take a back seat at the moment.

A second challenge in TB drug development is the difficulty to identify new compounds with activity against MTB. Regimens against TB should kill both the rapidly growing mycobacteria (bactericidal activity) and the persisting mycobacteria in lesions (sterilizing activity) [37]. Even though MTB is one of the long known bacteria we don't have good lab animal models which simulate human infections. Because of this pathogenesis of MTB is not fully understood. Other riddles associated with MTB are the molecular mechanisms of development of latent infection and factors associated with reactivation of the bacteria from dormancy[38]. Among the lab animals mice and rabbit are resistant to MTB infection. Guinea-pigs and non-human primates could be used but using these animals is extremely expensive and hence developing a good animal model for MTB is still on the horizon [39]. Lack of such animal models hampers herbal anti MTB drugs research.

Lack of animal model could be overcome with in vitro molecular tools using direct or surrogate marker identification. MTB produces several secretary proteins and some are virulent and can

serve as surrogate marker. 88 kDa secretory proteins have been documented as marker for active clinical tuberculosis [40]. Ze-Jia Cui, *et al*. 2016 used bioinformatics programs and found that using single nucleotide polymorphism (SNP) predicted that Pro-Pro-Glu (PPE) family proteins play important role in drug resistance [41]. K.S Jayaraman, 2016 described that using bioinformatics tools CCMB scientists identified 140 major proteins of which 46 has been already known. The remaining 94 proteins could serve as an eye opener in MTB diagnosis, vaccine development and drug development [42]. However we have to admit that these studies are at early stages and we have to wait and watch for a successful bioinformatics based TB intervention with traditional medicines.

Another nagging problem is improper and less reliable TB diagnostic and prognostic tools. It is extremely challenging if it is pediatric TB. When a drug target or vaccine candidate is tested for its efficacy there are no simple and reliable methods available. False positive and false negative reports leading to inappropriate treatment are disturbing. We and others have shown the reliable serological test to depend on the diagnosis [43]. However we have to admit that our samples were clinically and by other means confirmed cases. But its reliability in real time situations must be confirmed by others. Several molecular tools such as GeneXpert-Rif[44], TB microarray[45], multiplex real time PCRs[46]while available they are known for their prohibitive cost and bringing such set-up to rural areas impractical[47]. In addition generation time and non-availability of vegetative form of MTB in the sputum and other samples takes these procedures again to back seat [48].

Another set-back to MTB research is emergence of overly prohibitive biased human and animal institutional ethical committees. MTB is classified under BSL level-3 category pathogen and to do either animal or human research the departments must be equipped with BSL-3 labs and these labs are extremely expensive to construct. Many times building infrastructures relied on the host institution and not by the research funding agencies. ICMR and Government of India have setup a few ultra-high-tech facilities to handle high burden TB cases but considering the proportion of TB cases more and more such facilities needs to be developed especially when private research on TB research is withering-off. Unfortunately government has to shell out lot of its financial resources towards management of prevailing TB rather than building newer infra-structure. Thus, future development of effective anti TB drug including the one from traditional medicine systems relies on improvement of infrastructure, better design algorithm and adequate money flow in to drug research. Hence it may be wrong to have a notion that the allopathic medicine against MTB really eclipsing over traditional medicines it is rather the intrinsic problems associated with these medicines for sealed to the misconception.

Conclusion:

TB related death is the second largest next to HIV/AIDS. MTB are highly immune evasive and once it causes full blown pulmonary or extra pulmonary infections fate of the victim become bleak unless appropriate treatment with allopathic medicines. Though there is no gold standard SOPs to treat TB with modern medicine it is a delusion that modern medicine overshadows

traditional medicine system. Traditional medicine has its own problems that needs to be rectified and that is the reality. This is partly because MTB generation time, time consuming recovery process, lack of proper animal model and in vitro surrogate markers for the early diagnosis, lack of adequate state-of-the-art facilities and over-powered institutional regulatory forums. Once such obstacles are revamped traditional medicine system will reserve its own space and create a strong base in treating human diseases including TB in the future.

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