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TREATMENT OF TUBERCULOSIS BY NATURAL DRUGS : A REVIEW

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Abstract

Tuberculosis is a serious infectious bacterial disease. The disease is highly contagious and mostly transmitted from person to person, usually by bacteria and it is mostly transmitted by inhaling bacteria-carrying air droplets. Tuberculosis most generally attacks the lungs, but it can also infect other organs. It has resulted in progressive increase in number of orphans due to parental deaths which is estimated to be 10 million out of which 6%-15% is maternal mortality, which counts up to 15%-34% if only indirect causes are taken into account. Tuberculosis screening is done using an intelligible clinical technique that checks for the absence of current cough, sputum production, fever, weight loss, and night sweats. The concern of discovering new, imperatively needed anti-TB drugs from natural sources necessitates a multidisciplinary research. The use of allopathic drugs in such a convoluted disease gives rise to more dangerous complexities like cross resistance whereas natural drugs have proven to be better in this scenario. The investigation of new remedies for the successful weakening of the unhealthy condition associated with tuberculosis is the crucial requirement. Anti-tuberculosis agents: *Actinobacteria, Artemisia annua, Camellia sinesis.*

Keywords: Tuberculosis, MDR-TB, XDR-TB, Natural drugs.

Introduction

Tuberculosis is a deadly contagious bacterial disease that is the second biggest killer in the world. Robert Koch; A German microbiologist discovered the causes of tuberculosis in 1882 which is a bacteria of a Mycobacterium genus named as *Mycobacterium tuberculosis*. Following his discovery, Development of efficacious drug treatment along with vaccines promised the ultimate cure of the disease (Gracia *et al*., 2012). Indeed, at one point, Predictions were made by the United Nations regarding the elimination of tuberculosis worldwide by 2025 (Gengenbacher *et al*., 2012).

TB at first was thought to be a mild disease that could be managed with antibiotics. The first antibiotic was introduced in 1944 and it worked wonders but soon the monotherapy of streptomycin stopped showing results due to its drug resistance and gave a lesson of defining a new therapy with multiple drug system to prevent the further resistance of the bacteria.

Soon the multi drug regimen initiated, accompanied by assorted drugs with anti- tuberculosis activity but then, new type of antibiotic resistance emerged which is Multidrug-resistant TB (MDR-TB), caused by the bacteria resistant to at least rifampicin and isoniazid; the first line drug for the treatment of the TB. Extensively drug-resistant (XDR) TB strains are resistant to front-line and second-line drugs for TB (Gilpin *et al*., 2018). This antibiotic-resistance catastrophe has become the serious issue of discussion amongst the physicians, researchers, governments and the public. Knowledge from the history of antibiotic discovery and the new understanding of cell's biology and antibiotic mechanism have the potential to compose medicines that would be able to control the infection (WHO, 2015).

Current Drug Therapy

Current Drug therapy uses a combination of drugs that boost the ability of the body to respond better to the treatment and helps in reducing the length of treatment. Rifampicin and isoniazid are amongst the first line drugs used today, Rifampicin is of utmost importance in the regimen as it compresses the duration of treatment and assures desired results. Nine months regimen is undertaken by using rifampicin and isoniazid, along with streptomycin and ethambutol. According to one of the studies done by UK's Medical Research Council, inclusion of pyrazinamide for the first two months of regimen can reduce the treatment length to six months and still be able to maintain cure rate of 95% or even higher (Chan and Iseman, 2002).

In order to eliminate TB, the outstanding strategy is to first prevent the infection from spreading which can be done by prioritizing the treatment of those patients who are sputum smear positive that is those individuals which can spread the disease. These individuals can be tested and treated through DOTS which stands for Directly Observed Treatment Short course which is highly effective and economical strategy for TB control recommended worldwide. DOTS constitute of five elements that include continuous political and financial obligation, quality ensured diagnostic procedures, consistent supply of superior quality anti-TB drugs, regulated recording and reporting, standardized short-course (SCC) anti-TB treatment given under direct and supportive observation (DOT) (Davis, 2003).

Problems with the current drug therapy:

Due to the extensive length of the treatment of the tuberculosis there is low patient compliance and due to large amount of medicines sometimes it becomes inconvenient for the patients to administer their daily doses. Current treatment is also very susceptible to the side effects and has shown antagonism by interacting with other drugs. Moreover the lengthy treatment brings large cost amount needed for the medicines for the treatment. The current Multi-Drug regimen has less to no effect against latent TB (Quan *et al*., 2017).

It has also caused Multi-drug-resistant TB. Drug resistance occurs if incorrect or inadequate treatments are used, Which can be due to inconsistency in administration of drugs, leaving the treatment in-between or by leaving any one of the drug (standard treatment is at least two drugs) prescribed in the regimen (Zang and Yew, 2009).

Multidrug-resistant TB (MDR-TB) can be treated with second line drugs which include fluoroquinolones, amino glycosides, and others which are less efficient, comparatively more toxic and are uneconomical Gandhi *et al*., 2018). Second line drugs are expensive than the first line drugs but the ultimate problem is with their length of the treatment which is almost double the length of standard TB treatment which makes it even more harder for some patients to afford the treatment, continue the treatment for the full period and increase the chance of spreading of the disease due to which further resistance can develop leading to XDR-TB, ultimately increase the number of mortality (Udwadia, 2012).

Natural drugs as a Ray of hope

As the cases of XDR-TB and MDR-TB are spiraling more and more it's demanding for the need of new drug to combat the resistant bacteria and help prevent and eliminate TB from all around the world. Natural sources are appealing starting points in the exploration for new and better anti-tubercular drugs because they are remarkably prosperous in chemical diversity and bear prodigious antimicrobial activity. Herbal products are not utilized up-to their full potential due to lack of knowledge and research regarding their chemical compositions. This industry can be expanded by composing appropriate standardization methods to ensure quality and accountability of the products. Allopathic medicines are evidence based which provides ultimate care to a sick person, but treatment is often symptomatic, costly and treatment of chronic disorders often leads to adverse effects (Sukuru *et al*., 2009).

The natural drugs have chemical diversity with higher hit rates in High throughput screening and high capability to approach their site of action within target cells (Kumar *et al*., 2017 and Kumar *et al*., 2016). Traditionally, natural products were the pedigree of diverse medicinal agents from which the potential leads of heterocycles like pyrans, flavones, chalcones, coumarins, pyrimidones and oxzolidines were architectured to grant the origin of potential candidates for the mitigation of diverse ailments as anticancer, anti-inflammatory, antimicrobials, antiviral and anti-TB (Nepali *et al*., 2014; Kumar *et al*. 2009; Sharma *et al*., 2015; Kumar *et al*., 2016; Kumar *et al*., 2018).

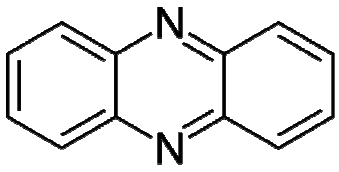
This has revived the interest in the exploration of natural resources for the establishment of new anti-tubercular agents. Several studies have stated the potential of natural resources to obtain new templates for drug design (Kumar *et al*., 2016, Kumar *et al*., 2018, Guzman *et al*., 2012, Dashti *et al*., 2014, Santosh, *et al*., 2016, Chinesembu, 2016). However, they have yet to be earnestly investigated in every realm (Sieniawska, 2015 and Veronique, 2015).

Propolis

Propolis is a complex resinous substance which is commonly known as bee glue is the natural product made by honeybees to build beehives (Velikova *et al*., 2000; Cuesta *et al*., 2002; Raghu *et al*., 2010). Bees make this glue by collecting plant's secretion or from the sticky exudates on buds of cone bearing trees. The chemical composition of Propolis can vary with the geographical areas (Kardar *et al*., 2014).

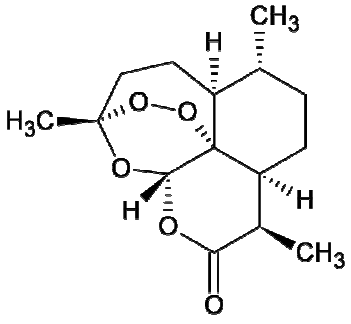
Propolis is used in the treatment of sores, wounds, viral infections including HIV, gastro-intestinal problems and it has already been used as a traditional method for curing TB (Zhang, 2006, Buraev, 2011, Silva, 2011, Wagh, 2013). *In vitro* studies have proved that Propolis extracts can inhibit the growth of TB bacteria while increasing the efficacy of the already established anti-TB drugs like rifampicin, isoniazid and streptomycin (Valcic *et al*., 1999, Scheller *et al*., 1999). Propolis has shown to work by lowering the formation of granulomas in infected individuals thereby inhibiting TB development (Yildirim *et al*., 2004, Lou *et al*., 2010, Jackson *et al*., 2013). Enzymes involved in vital physiological functioning o the bacteria can be the appealing targets for the development of new anti-TB drugs (Mdluli *et al*., 2014, Baugh, 2015, Ali *et al*., 2018).

Phenazines



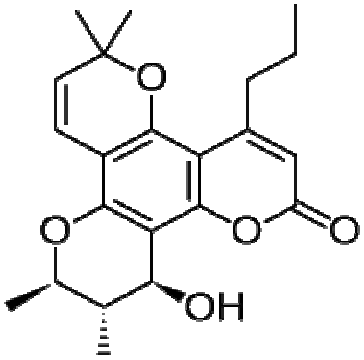
Phenazines are the aromatic compounds obtained from many species of actinobacteria phylum (Laursen and Nielsen, 2014; Jonge *et al*., 2004). Riminophenazines, which are derived from lichens, were developed several years ago as potential anti-TB agent. These compunds are again under investigation as lead compounds for TB treatment due to the antitubercular activity of clofazimine. Clofazimine is used for the treatment of leprosy and it has been successfully able to control that disease, it has shown clinical efficacy in tuberculosis, in particularly towards MDR. Clofazimine does not induce resistance and also prevents its emergence to isoniazid in TB treatment. Several novel riminophenazine derivatives like B746 and B4157 have been synthesized and evaluated, aiming to reduce lipophilicity and improve activity (Quan *et al*., 2017; Borrero *et al*., 2014; Reddy *et al*., 1999).

Artemisinin



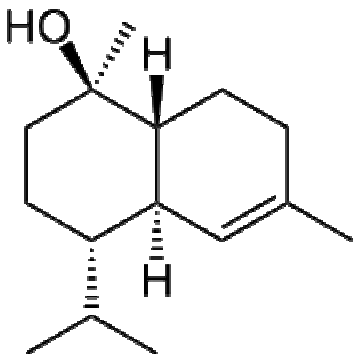
Artemisinin can be obtained from the plant *Artemisia annua*. It is a herb employed in Chinese traditional medicine. According to a study, artemisinin has the ability to treat and increase the efficacy of the standard drugs in treatment of TB. It acts as an anti-TB agent by preventing the TB bacteria to become dormant. Dormancy is the state of bacteria in which it is hard to kill as it protect it-self from low-oxygen environments, which is usually produced by the immune system to control the growth of bacteria and prevent the infection. The dormant bacteria on the other hand become highly tolerant to drugs. Artemisinin target the heme molecule of bacteria in order to prevent bacteria from sensing oxygen level and therefore preventing it to attain dormancy and hence die. This could help to shorten the course of treatment and slow the evolution of drug resistance (Zhang *et al*., 2012).

(+)-Calanolide A



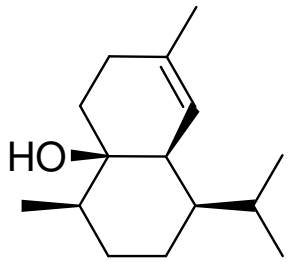
(+)-Calanolide A is a naturally occurring compound which can be extracted from the plant *Calophyllum lanigerum,* which is found in Malaysia. It is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which is claimed to be an anti-HIV-1 agent. According to a study it was tested that the compound is active against every strain of *Mycobacterium tuberculosis* including resistant type. (+)-calanolide A works by rapidly inhibiting DNA, RNA and also protein synthesis. This compound shows similar effects as observed with standard TB drug; Rifampicin which also inhibits RNA synthesis (Bueno *et al*., 2011, Edward, 2002, Flavin *et al*., 1996).

Epi-alpha-cadinol



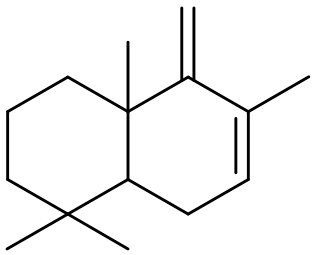
Epi-α-cadinol is a naturally occurring sesquiterpenoid alcohol which can be obtained from the plant *Salvia aratocensis* belonging to family lamiaceae found in Columbia. According to a study, the essential oil isolated from this plant by hydrodistillation proved to exhibit anti-mycobacterial properties and was found to be active against MDR-TB also. Further investigation and research is required to make this a constituent a remedy (Borg, 1981; Boligon *et al*., 2013; Ho *et al*., 2011; Herout and Sykora, 1958).

1,10-di-epi-cubenol



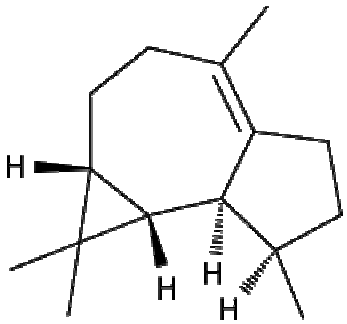
1,10-di-epi-cubenol, a naturally occurring compound belonging to the family of Sesquiterpenes is one of the another active component of the essential oil obtained from the plant *Salvia aratocensis* and constitutes for about 14.2%. It is proved to be active against *Mycobacterium tuberculosis* strains along with the bacteria resistant to standard TB drugs. Further investigation and research is required (Bueno *et al*., 2011).

Drima-7,9(11)-diene



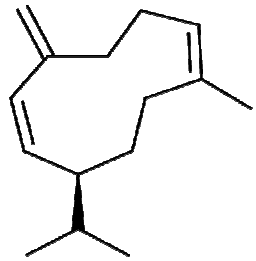
Drima-7,9(11)-diene can be obtained from the essential oil of *Turnera diffusa* commonly known as damiana belonging to the family passifloraceae of southern Texas. According to a study the essential oil of turnera diffusa contains some compounds; possibly drima-7,9(11)-diene is capable of treating tuberculosis and Multi-drug-resistant tuberculosis. The essential oil of this plant can be obtained by the process of hydrodistillation (Bueno *et al*., 2011).

Viridiflorene



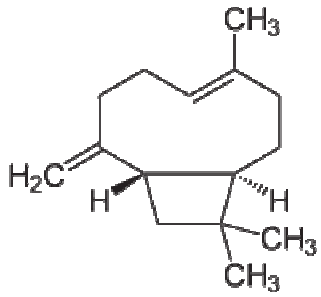
Virdiflorene is a naturally occurring 5, 10-cycloaromadendrane sesquiterpenoid compound. It can be obtained from profuse amount of plant species like damiana shrub which can be found in many parts of USA and Mexico. In a study, virdiflorene was claimed to have the ability to fight against tuberculosis as well as multi-drug-resistant tuberculosis (Bueno *et al*., 2011). In this study, essential oil obtained via hydrodistillation was tested against the different strains of *Mycobacterium tuberculosis*.

Germacrene D



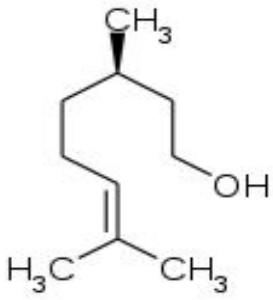
Germacrenes are the naturally occurring volatile compounds belonging to sesquiterpene class. Germacrene D can be obtained from the plant *Lippia Americana* found in Columbia. This compound is well known for its insecticidal and antimicrobial properties. According to a study conducted on effects of essential oil obtained from Lippia Americana on the variant strains of M.tuberculosis showed that germacrene D has the ability to kill tuberculosis causing bacteria along with multi-drug-resistant tuberculosis causing bacteria (Rivero *et al*., 2006; Yang *et al*., 2005; Umlauf *et al*., 2004; Bueno *et al*., 2011; Agnihotri *et al*., 2004; Raal *et al*., 2004; He and Cane, 2004; Arimura *et al*., 2004).

Trans-beta- caryophyllene



Trans-beta-Caryophyllene is a naturally occurring bicyclic sesquiterpene with a cyclobutane and 9-membered ring in its structure (Zheljakov *et al*., 2008; Silva *et al*., 2004; Harvala *et al*., 1987; Calvo *et al*., 2009; Mockute *et al*., 2001; Prashar *et al*., 2004). It can be extracted from the plant *Lippia Americana* belonging to the family verbenaceae. Trans-beta-Caryophyllene constitutes for about 11.3% in the extract obtained through hydrodistillation, has proven to be active against *Mycobacterium tuberculosis* strains as well as multi-drug-resistant tuberculosis strains (Umezu *et al*., 2006; jamshidi *et al*., 2009; Kaul *et al*., 2003; Ahmed *et al*., 2000; Leadro *et al*., 2012; Sausa *et al*., 2011; Boligon *et al*., 2013).

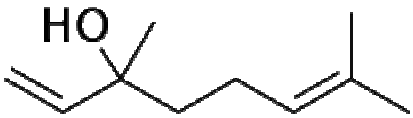
Citronellol



Citronellol, or dihydrogeraniol, is a naturally occurring acyclic monoterpenoid which can be extracted from the plant *Eucalyptus citriodora* commonly known as lemon eucalyptus belonging to the family myrtaceae. Citronellol have proven to exhibit airborne anti-tubercular activity both neat and in various artificial mixtures and it is beneficial as an inhalation therapy for reduction in number of contagious individuals and inhibition of spreading of tuberculosis (Bueno *et al*., 2009; Alvarenga *et al*., 2014; WHO, 2012; Kaul *et al*., 2011; Georgiev, 1994; Petrini and Hoffner 1999; Gao *et al*., 2010).

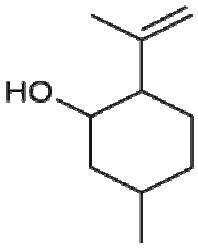
Jassal, 2009; Ma *et al*., 2010; Gandhi *et al*., 2010; Murrel, 1899; Shkurupiy *et al*., 2002; Shkurupiy *et al*., 2006; Sherry and Warnke, 2004; Inui *et al*., 2012; Alvarez *et. al*., 2013; Gao *et al*., 2010; Case *et al*., 2006; Trombetta *et al*., 2005; Cristani *et al*., 2007; Devi *et al*., 2010; Silva *et al*., 2011; Xu, *et al*., 2008; Sharma *et al*., 2013).

Linalool



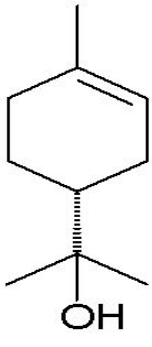
Linalool is an organic compound of terpene alcohol class found in assorted plants like *Eucalyptus citriodora*. Linalool has amazing diversified commercial applications out of which one is profoundly known that is of its amusing scent. According to a study, linalool has the ability to fight against *Mycobacterium tuberculosis* through inhalation therapy and plays a major role in prevention of tuberculosis and various other airborne and bacterial, fungal and viral diseases (Bueno *et al*., 2009; Jassal, 2009; Ma *et al*., 2010; Gandhi *et al*., 2010; Murrel, 1899; Shkurupiy *et al*., 2002; Shkurupiy *et al*., 2006; Sherry and Warnke, 2004; Inui *et al*., 2012; Alvarez *et. al*., 2013; Gao *et al*., 2010).

Isopulegol



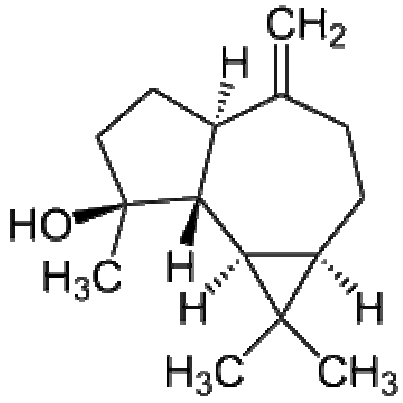
Isopulegol is a naturally occurring organic compound of monoterpene alcohol class, which can be extracted from various plants including *Eucalyptus citriodora* belonging to family myrtaceae. It is used as a fragrance as well as a flavouring agent but a study claimed it to have more valuable abilities like anti-mycobacterial activity (Alvarenga *et al*., 2014; Jassal, 2009; Xu, *et al*., 2008; Ma *et al*., 2010; Gandhi *et al*., 2010; Murrel, 1899; Shkurupiy *et al*., 2006). It can be used as an inhalation therapy for the treatment and prevention of the tuberculosis along with many other airborne diseases. Case *et al*., 2006; Trombetta *et al*., 2005; Cristani *et al*., 2007; Devi *et al*., 2010; Silva *et al*., 2011; Xu, *et al*., 2008; Sharma *et al*., 2013).

α-terpineol



α-terpineol is a monoterpene alcohol and is commonly manufactured from the more readily available alpha-pinene. It can be obtained from *Eucalyptus citriodora* (Inui *et al*., 2012, Alvarez *et al*., 2013, Gao *et al*., 2010; Trombetta *et al*., 2005' WHO, 2012; Sherry and Warnke, 2004). It is frequently used in cosmetics, perfumes and as a flavouring agent. It has proven to show anti-tubercular activities and is active against multi-drug-resistant tuberculosis and extensively drug-resistant tuberculosis (Shkurupiy *et al*., 2002; Cristani *et al*., 2007; Devi *et al*., 2010; Silva *et al*., 2011; Sharma *et al*., 2013; Case *et al*., 2006; Alvarenga *et al*., 2014.)

Spathulenol



Spathulenol is an aromatic organic tricyclic sesquiterpene alcohol compound with viscous consistency and slight bitter and spicy taste. It can be extracted from the plant *Eucalyptus citriodora* commonly known as Lemon eucalyptus belonging to the family myrtaceae (Bueno *et al*., 2009; Sharma *et al*., 2013; Case *et al*., 2006; Alvarenga *et al*., 2014; Jassal, 2009; Xu, *et al*., 2008; Ma *et al*., 2010) Inspite of acting as a flavouring agent and fragrances, it is able to treat and prevent airborne bacterial diseases like tuberculosis and multi-drug-resistant tuberculosis (Gandhi *et al*., 2010; Murrel, 1899; Shkurupiy *et al*., 2006; Gao *et al*., 2010).

Prevention of drug resistance

In order to eliminate the deadly disease from the world, its further resistance needs to be stopped. There are many ways that drug resistance can be prevented (Lobue, 2009; Roland *et al*., 2013).

1. Early diagnosis and treatment: If Tb is diagnosed in early stage and treated as soon as possible, it can prevent the resistance of the bacteria.
2. Patient adherence to full treatment: A patient must coordinate with the required therapy to eradicate the disease and never miss a dose as this can help prevent the resistance and will show positive result fast.
3. Diagnosis of HIV/AIDS patients: The HIV/AIDS patients must also be always diagnosed for the TB as they are highly susceptible to the tuberculosis disease.

How to eliminate Tuberculosis from the world

Prevention is better than cure. Negligence is not an option especially in case of a deadly disease with no turning point after a particular time. TB needs to be prevented by taking appropriate vaccines and preventing TB from further transmission to healthy people. Government of a nation need finance management over treatment for multi-drug-resistant tuberculosis and extensively drug-resistant tuberculosis to provide adequate therapy to the patients especially who are financially weak. All the policy makers must engage all service providers in convenient MDR-TB control and prevention. The DOTS and other organizations and hospitals which provide TB treatment must improve XDR-TB and MDR-TB control and must assure the availability of quality anti-tubercular drugs (Falzon *et al*., 2016, Raviglione *et al*., 1995).

In order to eliminate this deadly disease from the world, everyone should come together and work as a team where all barriers must be overlooked. The government must overcome the hurdle of restricted availability of anti-TB drugs and must Prioritize TB infection control as it will prevent the transmission of the disease and ultimately prevent any further resistance. Surveillance systems must be refined and more investment must be made in research, manufacturing and advancement of new diagnostic mechanisms, medicines, and vaccines (Burwen *et al*., 1995; Cantwell *et al*., 1992; David, 1970).

Conclusion

The burgeoning strain of tuberculosis resistance along with poor development of competent drug is causing catastrophe among the population with no hope visible any where soon to eliminate this fatal disease, there is an urgent need to control this annihilation. Natural sources seem to be the best possible way out with high level of anti-microbial activity against vast range of microbes and are provided with plentiful chemical assortment. Abounding number of naturally occurring candidates have enrolled late-stage development. New drugs with advanced mechanism of action are needed to encounter the expanding drug-resistant tuberculosis cases.

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