



REVIEW ON HERBAL PLANTS USEFUL IN TUBERCULOSIS

Gautam A.H*, Sharma Ramica, Rana A C.

Rayat institute of pharmacy, Railmajra, Distt Nawanshahar, Punjab, India

Article Received on: 17/04/12 Revised on: 28/05/12 Approved for publication: 10/06/12

*Email: abhishekgaugam261017@gmail.com

ABSTRACT

The Anti-Tuberculosis (Anti- TB) drugs are less effective because of emergence of Multi-Drug Resistance (MDR) and extensively Drug Resistant (XDR) strains of M. Tuberculosis. Anti-TB allopathic drugs also results into side effects like Hepatitis, Hypersensitivity reaction, nausea, Vomiting etc. Medicinal plants from Ayurveda (Indian traditional Medicine system) and from foreign origin have been successfully employed to treat TB because of less toxicity and side effects than allopathic medicines. The aim of this review is to highlight some newly studied plants for anti-tubercular activity.

KEYWORDS: Multi Drug Resistance (MDR), Extensively Drug Resistance (XDR), Mycobacterium Tuberculosis, Hepatitis, Nausea.

INTRODUCTION

Tuberculosis (TB) is an infectious disease of worldwide occurrence.¹ Each year approximately 2 million persons world-wide die of tuberculosis and 9 million become infected.² In the United states, approximately 14,000 cases of tuberculosis were reported in 2006, a 3.2% decline from the previous year; however 20 states and the district of Columbia had higher rates.³ India is the highest TB burden country in the world. In 2008 , nearly 2 million cases were reported in India, and 276,000 persons die of this disease.⁴ The prevalence of tuberculosis is countnuing to increase because of patients infected with human immunodeficiency virus (HIV) , bacterial resistance to medications.⁵ Manifestation of TB often includes progressive fatigue, malaise, weight loss, and a low grade fever accompanied by chills and night sweats.⁶ Although the pulmonary system is most common location for TB, extrapulmonary disease occurs in more than 20% of immune-competent patients, and risk for extrapulmonary disease increases with immunosuppression.⁷ Lymphatic TB is the most common extrapulmonary tuberculosis , and cervical adenopathy occurs most often occurs most often and other possible location includes bones, joints, pleura, and genitourinary system.⁸ Another fatal form of extrapulmonary tuberculosis is infection of blood-stream by mycobacteria; this form of disease is called disseminated or miliary tuberculosis, progresses rapidly and can be difficult to diagnose because of its systemic and non-specific sign and symptoms.⁹ Also patient with latent tuberculosis have no sign and symptoms of the disease, do not feel sick and are not infectious.¹⁰ Although co-infection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as uncontrolled diabetes mellitus, sepsis, renal failure, malnutrition, smoking, chemotherapy, organ transplantation, and long-term corticosteroids usage, that can trigger reactivation of remote infection are more common in critical care setting.¹¹

The drugs currently used to treat the TB infections are mainly rifampicin, ethambutol, isoniazid and pyrazinamide but the emergence of multiple drug resistant (MDR) strains of M. tuberculosis (defined resistance against isoniazid and rifampin) is now common in number of patients because of uncontrolled application of these anti-tuberculosis drugs (Gupta et al 2010).¹² At present, the more drug resistant form of tuberculosis XDR-TB (extensively drug resistant

tuberculosis) has been reported such as current front-line drugs (isoniazid and rifampin) in addition to any fluoroquinolone and at least one of the three injectable second-line drugs (capreomycin, kanamycin, and amikacin).¹³ The medicinal properties of plants have been well known from ancient times and plants offer a new source of potent anti-microbial agents in the form of secondary metabolites.¹⁴ Anti-tuberculosis activity has been reported in number of higher plants.¹⁵ In Ayurveda tuberculosis is known as Rajayakshma, Yakshma, Shoosha, Kshaya.¹⁶

Tuberculosis is an infection caused by the rod-shaped non-spore-forming, aerobic bacterium Mycobacterium tuberculosis and is 0.5 μm to 3 μm long, are classified as acid-fast bacilli and have a unique cell wall structure crucial to their survival.¹⁷ The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate.¹⁸ The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria.¹⁹ Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophages.²⁰

TRANSMISSION

Mycobacterium tuberculosis is spread by small airborne droplets called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis ie. Transmission mode can be Inhalation, Ingestion, Inoculation, and Transplacental route .These minuscule droplets can remain air-borne for minutes to hours after expectoration.²¹ Introduction of M tuberculosis into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis.²²

PATHOPHYSIOLOGY (figure 1)

After transmission into immune system, mycobacteria interfere with different immunological mediators. The interaction of T cells with infected macrophages is central to protective immunity against M tuberculosis and depends on the interplay of cytokines produced by each cell .²⁴ TNF- α , IL-12, and IFN- γ are central cytokines in the regulatory and effector phases of the immune response to M tuberculosis. TH1 cells and natural killer (NK) cells secrete IFN- γ , which activates alveolar macrophages to produce a variety of

substances involved in growth inhibition and killing of mycobacteria. Macrophages also secrete IL-12, amplifying this pathway in a positive feedback loop. IL-12 has been implicated in the pathogenesis of T-cell-mediated pathology because it drives antigen-naïve TH cells towards development into TH1 cells.²⁵ TNF- α is believed to play multiple roles in the immune and pathological responses in tuberculosis. M tuberculosis induces TNF- α secretion by macrophages, dendritic cells, and T cells. The production of anti-inflammatory cytokines such as IL-4, IL-10 and TGF- β in response to M tuberculosis may down-regulate the immune response and limit tissue injury, but excessive production of these cytokines may result in failure to control the infection.²⁶ Macrophages are the part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection. The complement system also plays a role in the phagocytosis of the bacteria. The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease called primary progressive tuberculosis.²⁷ After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours. Initial development of TB involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria. Released cytokines attract T lymphocytes to the site, the cells that constitute cell-mediated immunity. In fact, M tuberculosis organisms can change their phenotypic expression, such as protein regulation, to enhance survival. Lesions in persons with less effective immune systems progress to primary progressive tuberculosis.²⁸ In patients infected with M tuberculosis, droplets can be coughed up from the bronchus and infect other persons. Bacilli can also drain into the lymphatic system and collect in the trachea-bronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas.²⁹

TREATMENT

Anti-Tubercular Drugs

Anti-TB allopathic drugs have been prescribed to control symptoms of this disease but they result into side effects like hepatitis, hypersensitivity reactions, nausea, vomiting etc. This problem has become more serious as Mycobacterium tuberculosis developed resistance against both the first line (Essential) and second line (Reserve) anti-TB drugs.³⁰ Essential anti-TB drugs are usually used for the treatment of TB patients with susceptible Mycobacterium Tuberculosis and Reserve anti-TB drugs used for the treatment of multidrug-resistant TB (MDR). Various anti-TB drugs with their side effects and resistance are given below in the table 1.

HERBAL PLANTS USEFUL IN TUBERCULOSIS TREATMENT

Brief Description Of Plants Having Anti-Tubercular Activity

Lantana camara L

Botanical name: *Lantana camara* L

Synonyms: *Camara vulgaris*, *Lantana scabrida*

Family: Verbenaceae.

Lantana camara is a low, subscandent, vigorous shrub which can grow to 2 - 4 meters in height. Leaves are bright green, rough, finely hairy and emits a pungent odour when crushed.³⁸ Reports indicate that Leaf extracts of *Lantana* exhibit anti-microbial, fungicidal, insecticidal and nematocidal properties. *Lantana* oil is sometimes used for the

treatment of skin itches, as an antiseptic for wounds and externally for leprosy and scabies. The leaves are used in the treatment of tumors, tetanus, rheumatism, and reported to possess diaphoretic, carminative, antiseptic properties, and are main source of phosphorous and potassium.³⁹ Chloroform and methanol extracts of *lantana camara*. This plant is claimed for antimicrobial activity. The leaf extract of *lantana camara* L was screened against three strains of mycobacterium tuberculosis using agar-well diffusion method. Methanolic extract of *lantana camara* showed highest antimicrobial activity but it was much less activity than Rifampicin whereas chloroform extract of *lantana camara* L showed activity against all three strains of mycobacterium tuberculosis but it was less active than Methanolic extract.⁴⁰

Morinda citrifolia L

Botanical name: *Morinda citrifolia*

Family: Rubiaceae (coffee family), rubioideae (subfamily).

Common name: Canary wood (Australia), Fromager, Murier indien (French).

Noni is the common name for *Morinda citrifolia* L. It has been reported to have a broad range of health benefits for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain. A number of major components have been identified in the Noni plant such as scopoletin, octoanoic acid, potassium, vitamin C, terpenoids, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin-1-methyl ether, anthraquinone glycoside), β -sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid.⁴¹ A concentration of extracts from Noni leaves killed 89 percent of the bacteria in a test tube, almost as effective as a leading anti-TB drug, Rifampicin, which has an inhibition rate of 97 percent at the same concentration. Although there had been anecdotal reports of the native use of Noni in Polynesia as a medicine against tuberculosis, this is the first report demonstrating the antimycobacterial potential of compounds obtained from the Noni leaf.⁴² Recently, Duncan demonstrated that scopoletin, a health promoter in Noni, inhibits the activity of *E. coli*, commonly associated with recent outbreaks resulting in hundreds of serious infections and even death. Noni also helps stomach ulcer through inhibition of the bacteria *H. pylori*.⁴³

Acacia senegal L

Synonyms - *A. verec* Guillem

Family- Mimosaceae.

Ayurvedic - Shveta Babbuul

Acacia Senegal belongs to the family Fabaceae (mimosaceae). The leaves of the plant is used in traditional medicine to treat illness such as Dysentery, diarrhea, gonorrhoea, cough, gastric disorder and Nodular leprosy. The stem bark extract is commonly used as remedy for respiratory tract infections.⁴⁴ It is reportedly used as for its astringent properties, to treat bleeding, bronchitis, diarrhea, gonorrhoea, leprosy, typhoid fever and upper respiratory tract infections.⁴⁵ *Acacia senegal* produces the only acacia gum evaluated toxicologically as a safe food additive. Nowadays the gum is present in a wide range of everyday products. 60-75% of the world production of gum arabic is used in the food industry and in human and animal medicine. *Acacia Senegal* have been reported various activities like anti-bacterial, anti-microbial, spasmogenic, immunomodulator and anti-oxidant.⁴⁶

Adhatoda vasica* L*Botanical Name:** *Adhatoda vasica* Linn.**Synonym:** *Justicia adhatoda* Linn.**Family:** Acanthaceae.

It is bronchodilatory, expectorant (Indian Herbal Pharmacopoeia.) The Ayurvedic Pharmacopoeia of India indicates its use in dyspnoea. *Adhatoda vasica* (Acanthaceae) commonly known as *vasaka* distributed throughout India up to an altitude of 1300m.⁴⁷ The leaves, flowers, fruit, and roots are extensively used for treating cold cough, whooping cough, chronic bronchitis and asthma as sedative, expectorant and antispasmodic.⁴⁸ Leaves are anti-inflammatory, analgesic effective in skin disorders, cardiotoxic. Leaves are anti-inflammatory, analgesic effective in skin disorders, cardiotoxic. The *Adhatoda vasica* was considered so useful in tuberculosis that it was said that no man suffering from this disease need despair as long as a *vasica* plant exists in this world. The juice of the leaves is used in diarrhoea and dysentery and powdered leaves in malaria in southern India.⁴⁹ The oil obtained from leaves flowers and roots of *vasica* plant possesses significantly high activity against tubercle bacilli. The growth of *M.tuberculosis* B 19-4 (human) is inhibited in a concentration of 2 µg. An important chemical constituent of leaf includes pyrroloquinazoline alkaloids, vasicine, vasicol, adhatonine, vasicinone, vasicinol and vasicinolone. Vasicine has been considered as active principle of *A. vasica* which shows numerous pharmacological activities such as anti-malarial, anti-inflammatory, antioxidant, antidiabetic, Anti-bacterial etc.⁵⁰

CONCLUSION

The above review has been concluded for natural herbal remedies that have been updated with its pharmacological and therapeutic role in treatment of tuberculosis as the synthetic drugs commonly used has many side effects and also causes resistance.

ACKNOWLEDGEMENT

I am very thankful to our director A.C RANA for providing us a scientific environment during my research work and also thanks to rayat institute of pharmacy for the support.

REFERENCES

1. Grange, J.M and Zumla. The global emergency of Tuberculosis. *J R Soc Promot Health* 2002; 122: 78-81.
2. Centers for Disease control and prevention 2007; 56(11): 245.
3. Centers for Disease control and prevention. Trends in Tuberculosis incidence MMWR Morb Mortal wkly Rep 2007; 56(11): 245-250.
4. World Health Organization. Global Tuberculosis Control: a short update to the 2009 report 2009. Doi: WHO/HTM/TB/2009.426.
5. Goldrick BA. Once Dismissed, Still Rampant: Tuberculosis, The Second Deadliest Infectious Disease Worldwide. *Am J Nurs* 2004; 104(9): 68-70.
6. TB elimination: The difference between latent TB infection and active TB disease. Centers for Disease Control and Prevention. Web site. <http://cdc.gov/tb/pubs/tbfactsheets/LTBiandActiveTB.pdf>. Updated October 7, 2008. Accessed January 28, 2009.
7. Surveillance reports: reported tuberculosis in the United States. Centers for Disease Control and Prevention. 2005.
8. Thrupp L, Bradley S, Smith P, Simor A, Gantz N, et al. Tuberculosis prevention and control in long-term-care facilities for older adults. *Infect Control Hosp Epidemiol* 2004; 25:1097-1108.
9. Wang JY, Hsueh PR, Wang SK, et al. Disseminated tuberculosis: a 10-year experience in a medical center. *Medicine (Baltimore)* 2007; 86(1):39-46.
10. Interactive core curriculum on tuberculosis. Centers for Disease Control and Prevention Website. http://www.cdc.gov/tb/webcourses/CoreCurr/TB_Course/Menu/frameset_internet.htm. Accessed January 28, 2009.
11. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet* 2003; 362: 887-899.
12. Leonard MK, Osterholt D, Kourbatova EV, et al. How many sputum specimens are necessary to diagnose pulmonary tuberculosis? *Am J Infect Control* 2005; 33(1): 58-61.
13. Raviglione, M.C. (2006) XDR-TB: entering the post-antibiotic era? *Int J Tuberc Lung* 2006; 10: 1185-1187
14. Cowan, M.M. Plant products as antimicrobial agents. *Clin Microbiol Rev* 1999; 12: 564-582.
15. Jimenez-Arellanes, A., Meckes, M., Ramirez, R., Torres, J. and Luna-Herrera, J. (2003) Activity against multidrug-resistant *Mycobacterium tuberculosis* in Mexican plants used to treat respiratory diseases. *Phytother Res* 2003; 17: 903-908.
16. Vasanthakumari R. "Text book of microbiology". BI Publications 2007; 20.
17. Porth CM. Alterations in respiratory function: respiratory tract infections, neoplasms, and childhood disorders. In: Porth CM, Kunert MP. *Pathophysiology: Concepts of Altered Health States*. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: 615-619.
18. Lee RB, Li W, Chatterjee D, Lee RE. Rapid structural characterization of the arabinogalactan and lipoarabinomannan in live mycobacterial cells using 2D and 3D HR-MAS NMR: structural changes in the arabinan due to ethambutol treatment and gene mutation are observed. *Glycobiology*. 2005;15(2):139-151.
19. Khare CP, "Indian Medicinal Plants" 1st Edn., Berlin/Heidelberg, Springer verlag 2007.
20. Joe M, Bai Y, Nacario RC, Lowary TL. Synthesis of the docosanasaccharide arabinan domain of mycobacterial arabinogalactan and a proposed octadecasaccharide biosynthetic precursor. *J Am Chem Soc* 2007;129 (32):9885-9901.
21. Toth A, Fackelmann J, Pigott W, Tolomeo O. Tuberculosis prevention and treatment. *Can Nurse*. 2004; 100(9): 27-30.
22. American Thoracic Society and Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000; 161(4 pt 1):1376-1395.
23. Kiritkar KR, Basu BD. "Indian Medicinal Plants". International Book Distributors, 1999; 8.
24. Munk ME, Emoto M. Functions of T-cell subsets and cytokines in mycobacterial infections. *Eur Respir J Suppl* 1995; 20: 668-675.
25. Raja A. Immunology of tuberculosis. *Indian J Med Res*. 2004; 120(4): 213-232.
26. Zhang M, Lin Y, Iyer DV, Gong J, Abrams JS, Barnes PF. T-cell cytokine responses in human infection with mycobacterium tuberculosis. *Infect Immune* 1995; 63(8):3231-3234.
27. Li Y, Petrofsky M, Bermudez LE. Mycobacterium tuberculosis uptake by recipient host macrophages is influenced by environmental conditions in the granuloma of the infectious individual and is associated with impaired production of interleukin-12 and tumor necrosis factor alpha. *Infect Immun*. 2002; 70: 6223-6230.
28. Boom WH, Canaday DH, Fulton SA, Gehring AJ, Rojas RE, Torres M. Human immunity to *M. tuberculosis*: T cell subsets and antigen processing. *Tuberculosis (Edinb)*. 2003; 83(1-3): 98-106.
29. Trinchieri G. Interleukin-12: a cytokine produced by antigen-presenting cells with immunoregulatory functions in the generation of T-helper cells type-1 and cytotoxic lymphocytes. *Blood*. 1994; 84(12): 4008-4027.
30. Sharma S, Bose M. Role of cytokines in immune response to pulmonary tuberculosis. *Asian Pac J Allergy Immunol*. 2001; 19(3): 213-219.
31. Portales-Perez DP, Baranda L, Layseca E, et al. Comparative and prospective study of different immune parameters in healthy subjects at risk for tuberculosis and in tuberculosis patients. *Clin Diagn Lab Immunol*. 2002; 9(2): 299-307.
32. Schwenk A, Hodgson L, Wright A, et al. Nutritional partitioning during treatment of tuberculosis: gain in body fat but not in protein mass. *Am J Clin Nutr*. 2004; 79: 1006-1012.
33. Ghosal S, Biswas K, Chaudhuri RK. "Chemical constituents of gentianaceae XXIV: Anti-Mycobacterium tuberculosis activity of naturally occurring xanthenes and synthetic analogs". *Journal of Pharmaceutical Sciences* 1978; 67(5): 721-722.
34. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I and Menzies D. "Incidence of Serious Side Effects from First-Line Anti-tuberculosis Drugs among Patients Treated for Active Tuberculosis". *Am J Respir Crit Care Med*. 2003; 167: 1472-1477.
35. Zaleskis R. "Adverse Effects of Anti-tuberculosis Chemotherapy". *European respiratory disease* 2006; 47-49.
36. Nahar BL, Mosharraf Hossain AKM, Islam MM and Saha DR. "A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period". *Bangladesh J Pharmacol* 2006; 1: 51-57.
37. Howard, R. A. Flora of the lesser antilles, Arnold Arboretum, Howard University, Jamaica Plan, MA. 1989; 6: 658.

38. Liogier, H.A. Descriptive flora of Puerto Rico and adjacent islands. Editorial de la Universidad de Puerto Rico, San Juan, PR. 1990; 4: 617.

39. Oyedapo, O.O, F.C. Sab, and J.A Olagunju. Bioactivity of fresh leaves of Lantana Camara Biomedical Letters 1999, 59: 179-183.

40. Lavand o, Larson HO. Some constituents of Morinda citrifolia plant med, 1979; 36: 186-7.

41. Peerzada N, Renaud .S, Ryan P. Vitamin c and elemental composition of some bush fruits. J plant nutrition 1990; 13: 787-93.

42. Whistler W. Tongan. Herbal medicine isle botanica, 1992; 89-90.

43. Maydell H, tree and shrubs of the sahel, their characteristic and uses Vergal josef Scientific books weikershoin 1990.

44. James A. Duke. Hand book of energy Crops 1983.

45. Cheema ,MSZA and Quadir ,S.A. Autecology of A.S.(L) wild .Vegetia 1983; 27(1-3): 131-162.

46. Adil Ballal, Diwakar B. Arnal Saeed. Anti-malarial effect of Acacia senegal, malaria journal 201; 139.

47. Panthi M.P. and Chaudhary R.P. Scientific world 2006; 117-123.

48. Ilangok, Chitra V., Kanomozhi K., & Balaji R. Journal of Pharmaceutical science & Research 2009; 1(2): 67-73.

49. Atal C.K. Chemistry and Pharmacology of Vascine-A new Oxytocic and Abortifacient 1980; 58.

50. Iwo M. Hand book of African Ethanomedical plant london CRC Press 1993.

DRUGS	ADR's	RESISTANCE
Isoniazid (INH)	Hepatotoxicity, Skin rashes.	Mutation in KatG & inhA gene.
Rifampicin (RMP)	Hepatitis & Flu like Syndrome	Point mutation in rpoB gene.
Ethambutol (EMB)	Gouty Arthritis & Colour Blindness	Point mutation in embB gene.
Pyrazinamide (PZA)	Hepatotoxicity & Hyperuricaemia	Mutation in pcnA gene.
Ethionamide	Gastric irritation, Neurological toxicity, hepatotoxicity	Mutation in inhA gene.
Strptomycin	Nephrotoxicity & Ototoxicity	Point mutation in rpsL and rrS genes.
Capreomycin	Nephrotoxicity & Ototoxicity	Mutation in tlyA gene.
Para-Aminosalicylic Acid (PAS)	Git tolerance, hypersensitivity, Lupus like reaction	ThyA & dfrA gene.

Table 1: Drugs used in treatment of Tuberculosis with their adverse effects and gene responsible for mutation in mycobacterium tuberculosis to specific drugs.³¹⁻³⁷

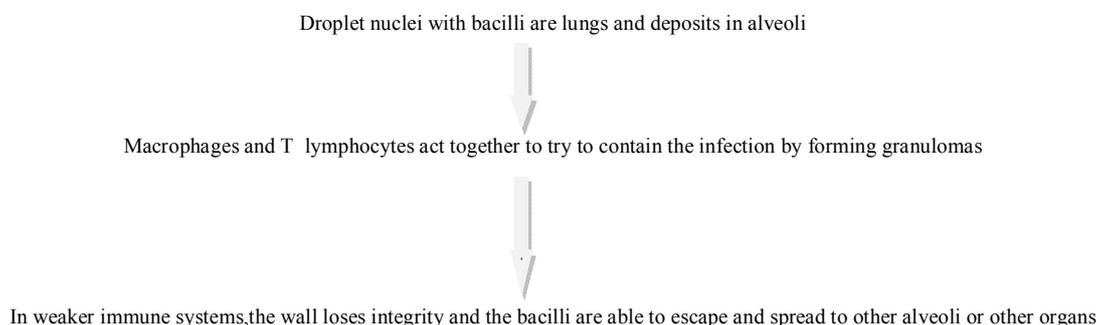


Figure 1 Pathophysiology of tuberculosis: Inhalation of bacilli, containment in a granuloma, and breakdown of the granuloma in less immunocompetent individuals.²³