

A Review on Developing New Anti- Leprotic Drug Againsts Drug Resistant Leprosy

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Abstract

Mycobacterium leprae and *M. lepromatosis* are two extremely slow-growing, uncultivated mycobacterial pathogens that cause leprosy. India, Brazil, and 20 other priority nations account for over 95% of newly reported cases of leprosy worldwide (WHO, 2019), with India accounting for nearly two-thirds of these instances. As recommended by the WHO since 1981, leprosy is being treated using dapsone, rifampicin, and clofazimine, also referred to as multi-drug therapy (MDT). Even though relapses are uncommon in patients receiving MDT, the number of new leprosy cases reported worldwide has remained steady over the past ten years, and resistance to several medications has been reported in various regions of the world. Since leprosy bacilli cannot develop in vitro, testing for antimicrobial resistance against *M. leprae* or assessing the anti-leprosy effectiveness of novel medications continue to be difficult. Furthermore, it is neither financially appealing or feasible for pharmaceutical companies to produce a new leprosy medication via the traditional drug development procedure. Repurposing current pharmaceuticals, licensed therapies, or their derivatives to evaluate their anti-leprosy potential is therefore a promising alternative. It is an effective way to find new therapeutic and medical qualities in licensed medication molecules. Any combinatorial chemotherapy that combines these repurposed medications with the current first-line (MDT) and second-line medications could enhance the bactericidal and synergistic effects against these infamous bacteria and contribute to the much-loved objective of “leprosy-free” world. In order to address resistance to conventional therapeutic techniques, this review identifies new potential for drug repurposing.

Keywords

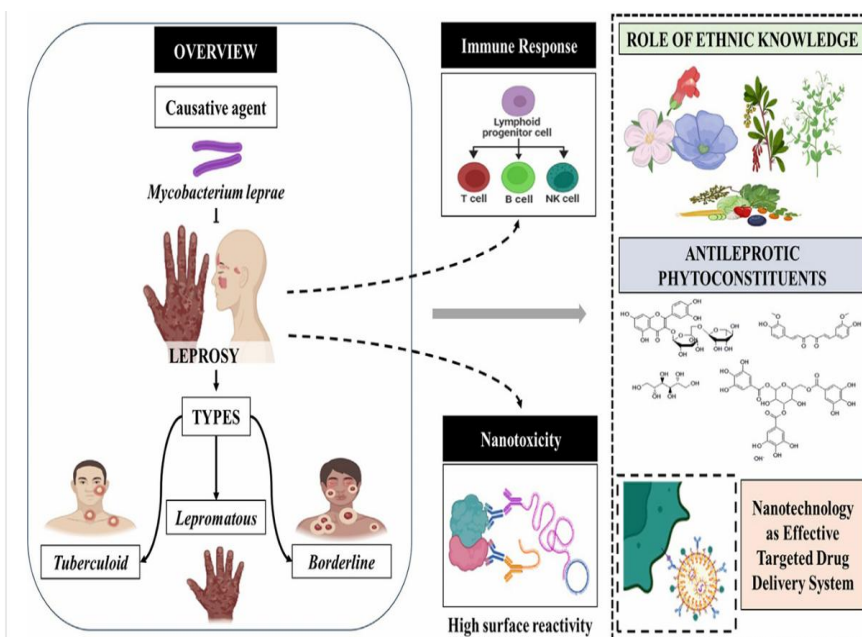
Leprosy, Pathology, Immunology, Ethnomedicinal plants, Secondary metabolites, Nanotechnology.

I. Introduction

Despite being treatable, leprosy is nevertheless a major worldwide health concern since it cannot be avoided. This complicated illness is characterized by two interrelated features. First, people who have a persistent mycobacterial infection experience a variety of cellular immune responses. Second, the infection and the ensuing immune responses cause peripheral neuropathy. *M. leprae*, an obligatory intracellular bacterium that mostly affects mucous membranes, nerves, and the skin, is the cause of leprosy (Talhari S. et al., 2015). It can also affect other body parts in multibacillary individuals (MB), such as the bone marrow, eyes, internal organs, joints, lymph nodes, and the nose (Talhari C. et al., 2015). This illness, sometimes referred to as Hansen's illness, was called for the doctor Gerhard Armauer Hansen. Hansen (1875) and Barbosa-Filho et al. (2007). According to Talhari S. et al. (2015), contact with untreated people who have a high bacillary index is the main way that leprosy transmits from person to person. On the other hand, people who are unable to generate an effective cellular-mediated defense against *M. leprae* may have a variety of symmetrically distributed hypochromic lesions, termed called Multibacillary people (MB), as a result of the bacilli's hematogenous dissemination. During the transmission cycle, patients with MB are thought to be the main source of infection. Although *M. leprae* has been detected in breast milk, cutaneous lesions and respiratory secretions are the primary means of transmission (Kerr-Pontes et al., 2006; Talhari C. et al., 2015; World Health Organization, 2012). If left untreated, the illness may worsen and cause reactions that could seriously harm peripheral nerve trunks. This leads to physical limitations as a result, which further adds to the stigma attached to leprosy. Nerve damage, deforming skin blisters, and progressive weakening are the hallmarks of leprosy. Over 5 million people worldwide were infected with *M. leprae* in the 1980s, with most instances occurring in Latin America, Asia, the Pacific Islands, and

Africa (Barbosa) (Filho and others, 2007). But by 2020, there were less than 129,192 cases of leprosy (Mushtaq, 2019). Leprosy has affected people for about 4,000 years, leaving two to three million permanently incapacitated (Ma et al., 2020). Brazil is

among the nations with the second-highest number of leprosy cases globally due to its high prevalence. It is now treated, despite the fact that it was once thought to be incurable.



A useful human model for studying host reactions to intracellular diseases, especially those affecting peripheral nerves, is leprosy. Thanks to advancements in medical research, leprosy patients can now be analyzed and diagnosed using known pathogen antigens. This comprises antigens that can be found in T-cell and antibody tests, such as glycolipids, proteins, peptides, and phenolics. Leprosy can be effectively treated with a therapeutic approach known as multidrug therapy (MDT) (McDougall, 1984; Manca et al., 2012). This course of treatment not only helps the patient heal, but it also gets rid of the virus that caused the illness. The inability of *M. leprae* to grow in artificial media is a major obstacle in leprosy research (Sharma et al., 2014). A good animal model that can recreate the whole range of leprosy is also limited. An ideal animal model would be one that develops the illness without immunosuppression and shows human-like bacteriological and histological traits, and the disease progresses. There are fewer susceptible animal hosts since animals with body temperatures below 37°C seem to be more vulnerable to *M. leprae* infection (Truman et al., 2014). Nine banded armadillos (*Dasypus novemcinctus*) are the best way to get around the issue that *M. leprae* cannot be grown in vitro. Leprosy research using armadillo species

(Balamayooran et al., 2015). Recently, lepromatous leprosy was discovered in wild chimpanzees in two distinct forest preserves in the West African nations of Guinea Bissau and Ivory Coast. This finding emphasizes how crucial it is to use a variety of animal models in studies in order to fully comprehend illnesses and their possible remedies (Hockings et al., 2021). The development of conservation and healthcare programs has benefited from ethnobotanical studies carried out in different parts of the world (Barbosa-Filho et al., 2007). Medicinal plants have been the source of many natural treatments throughout history. Quinine bark (*Cinchona officinalis*), willow bark (*Salix* spp.), foxglove (*Digitalis purpurea*), and Madagascar periwinkle are common plants that have been used as the foundation for several. Aspirin, digitalis, paracetamol, quinine, and vinblastine are examples of contemporary drugs. Flavonoids, glycosides, tannins, alkaloids, coumarins, and vitamins are among the active ingredients found in these plants. As a result, these metabolites have a wide range of medicinal uses and can safeguard the human body by preventing the growth of pathogens at different phases of growth (Mittal et al., 2014). Ayurvedic herbal therapies have enormous potential for creating

new medications and having a significant worldwide influence (Gupta) (2014) et al.

With an emphasis on nanoscale materials, nanotechnology is a multidisciplinary field that spans science, technology, and engineering (Lu et al., 2022). A key component of nanotechnology, nanoparticles are usually between 1 and 100 nm in size. These tiny particles have outstanding adsorption, increased stability, and reactivity capabilities, mainly because of their high surface area-to-volume ratio and compact size (Hoshyar et al., 2016). The scientific community is very interested in nanoparticles in biomedicine, mainly because of these remarkable physicochemical characteristics (Chakraborty et al., 2022). The medical field uses both organic and inorganic nanoparticles for a variety of purposes, including gene therapy and early medical imaging diagnostic. Nanoparticles are a viable option because of their capacity to cross the blood-brain barrier and show some selectivity for amyloid plaques.

in the field of medicine (Joshi et al., 2021). Nanotechnology has been used to address a number of important healthcare issues, including as preventing drug resistance, reducing side effects from traditional medications, and tackling the complexities of targeted medication delivery in the management of leprosy. Consequently, nanotechnology is becoming a crucial therapeutic area (Mitchell et al., 2021).

The search term "leprosy" was used to gather data from the Web of Science (WOS) between 2003 and 2023. A total of 5668 peer-reviewed publications about leprosy were found using this search. To perform a thorough examination, all of the records and the mentioned references that went with them were exported in plain text format. A keyword co-occurrence analysis was then carried out, and VOS viewer version 1.6.19 was used to illustrate the findings. Figure 1 illustrates how the keyword "co-occurrence analysis" revealed strong associations between leprosy and a number of terms, such as disease, elimination, *M. leprae*, epidemiology, tuberculosis, and lepromatous leprosum.

This review article's main goal is to demonstrate a groundbreaking effort by covering a wide range of data, including pathology, immunology, therapeutic options, pharmacological data, ethnopharmacological ideas, and methods based on nanotechnology. Leprosy still carries a societal stigma despite the advancements of the twenty-first century, highlighting the critical need for

greater education, awareness, and studies in this area. We thoroughly examined the scientific literature using the keyword "leprosy" across multiple databases in order to create this thorough review. Google Scholar, Pub Med, Scopus, Plants for Future Database, Medicinal Herbs Database, Science Direct, Taylor, and others are some of these databases. Wiley, Elsevier, Springer, and Francis Online Library. The study includes research from 1968 to 2023 in a variety of fields, including pharmacology, ethnomedicine, and nanotechnology.

Pathophysiology of Leprotic

Leprosy's immunopathology has been better understood because to research on the skin lesions it causes (Fabel et al., 2019; Ma et al., 2020). TT granulomas show dispersed CD8⁺ T lymphocytes surrounding the periphery and CD4⁺ T cells within the epithelioid cells. B lymphocytes are noticeably lacking in LL. $\gamma\delta$ T cells have been found to be abundant in leprosy granulomas (Ma et al., 2020). Higher amounts of CD1 molecules have been demonstrated in TT and IL response skin lesions (Lewinsohn and Lewinsohn, 2019). While Langerhans cells are reduced in LL, they appear to move into the dermis in T-lep granulomas (Fabel et al., 2019). Antigens from the skin may be more easily transferred to the right T cells for presentation as a result of this migration. Increased dermal lesions cells that produce IL-17 and CD4⁺ during reactional phases. CD4⁺ T cells were also found in earlier lymphopenia LL lesions during erythema nodosum leprosum (ENL) (Fabel et al., 2019). It has also been shown that IgG and IgM are released locally (Qiong-Hua et al., 2013). T-lep and L-lep granulomas express Th1 and Th2 cytokines, respectively. There is a polarization toward the Th1 type in both reversal and ENL reactions (Moraes et al., 2001; Pandhi and Chhabra, 2013). Further evidence for the involvement of IFN γ in eradicating leprosy bacilli comes from studies that injected recombinant IFN γ into cutaneous lesions and found that bacilli were cleared more quickly than in a control group that got only MDT Nathan (2020). Elevated quantities of NO radicals were seen at the injection sites of the lesional cells, which may be the cause of tissue injury and bacterial mortality (Schmitz et al., 2019). These improvements were seen as early as three weeks after IFN γ injection, demonstrating the efficacy of cytokines in comparison to a combination of several anti-leprotic medications. TNF α , iNOS, and TGF β were found in the skin of patients with type 1 diabetes in multicentre research with long-term follow-up 1 response (Lockwood et al., 2011).

Reaction of Leprosy

10% of people have leprosy reactions, which are marked by acute inflammation and vary in frequency and severity by nation. 40%–50% of patients from Latin America and 20% of patients from India Mexico and America, with the latter reporting more severe reactions. These reactions frequently impact adjacent peripheral nerves, necessitating immediate medical care to reduce agonizing pain and avoid nerve damage abnormalities. Two main clinical categories exist: Type 1 or reversal responses (RR), which are limited to the dermal layer, are mainly observed in people with borderline leprosy (e.g., BT, BB, and BL). patch and surrounding nerves, as well as Type 2, also known as erythema nodosum leprosum (ENL), which is primarily associated with lepromatous leprosy (L-lep). In Type 1 reactions, *M. leprae* triggers T cell-mediated responses that cause an inflammatory reaction in the disease-affected skin and nerves (Figure 3). In reaction to *M.*, there is a greater release of proinflammatory cytokines and an increase in lymphoproliferation. *leprae* antigens (Pandhi and Chhabra, 2013; Moraes et al., 2001). According to recent research, reversal reactions may also result in increased blood levels of IP-10, a chemokine that is triggered by IFN- γ (Stefani et al., 2009; Scollard et al., 2011). Type 1 leprosy reactions have been associated with a TLR2 mutation/ (Bochud et al., 2008). Type 2 or ENL reactions were formerly thought to be caused by immune complex deposition in arteries, akin to the Arthus reaction (Garbino et al., 2022). Nevertheless, this deposition is not always noticeable, and ENL is not usually associated with traditional immune complex illness. It has been discovered that ENL lesions include CD3+ CD4+ T cells, temporary antigen-specific T cell activation, and the generation and release of IFN- γ and IL-12. Corticosteroids are used to treat leprosy reactions, especially reversal type 1 reactions (RR) and type 2 erythema nodosum leprosum (ENL). In fact, thalidomide is frequently used to reduce symptoms and stop inflammation from causing more nerve damage. They aid in reducing tissue damage and inflammation brought on by these reactions (Lockwood, 1996). Notably, LL patients' skin tests continue to come back negative, suggesting that delayed-type hypersensitivity (DTH) has not developed in their skin. Increases in IL-4, IL-6, and IL-8 (chemotactic for neutrophils) have been observed in some investigations, which is compatible with histological evidence of neutrophil infiltration in lesions of ENL (Moraes et al., 2001). Studies on the recombinant protein LSR250 and its peptides in ENL

showed that buried bacillus sites could become visible and acknowledged by L-lep. Prior to and throughout ENL, patients were able to identify particular sequences (Tahari C. et al., 2015). ENL was also generated by injecting IFN- γ intra-lesionally or using pure protein derivative (PPD) to induce a delayed-type response (Nathan, 2020). In steroid-resistant ENL patients, thalidomide has been demonstrated to inhibit pro-inflammatory TNF α and neutrophil apoptosis. Additionally, by blocking IL-2 and other cytokines, cyclosporine has therapeutic advantages in ENL. In conclusion, T-cell responses appear suddenly in L-lep patients who are having reactions, and these responses continue long after clinical the symptoms start to go away (Saini et al., 2013).

Nerve damage

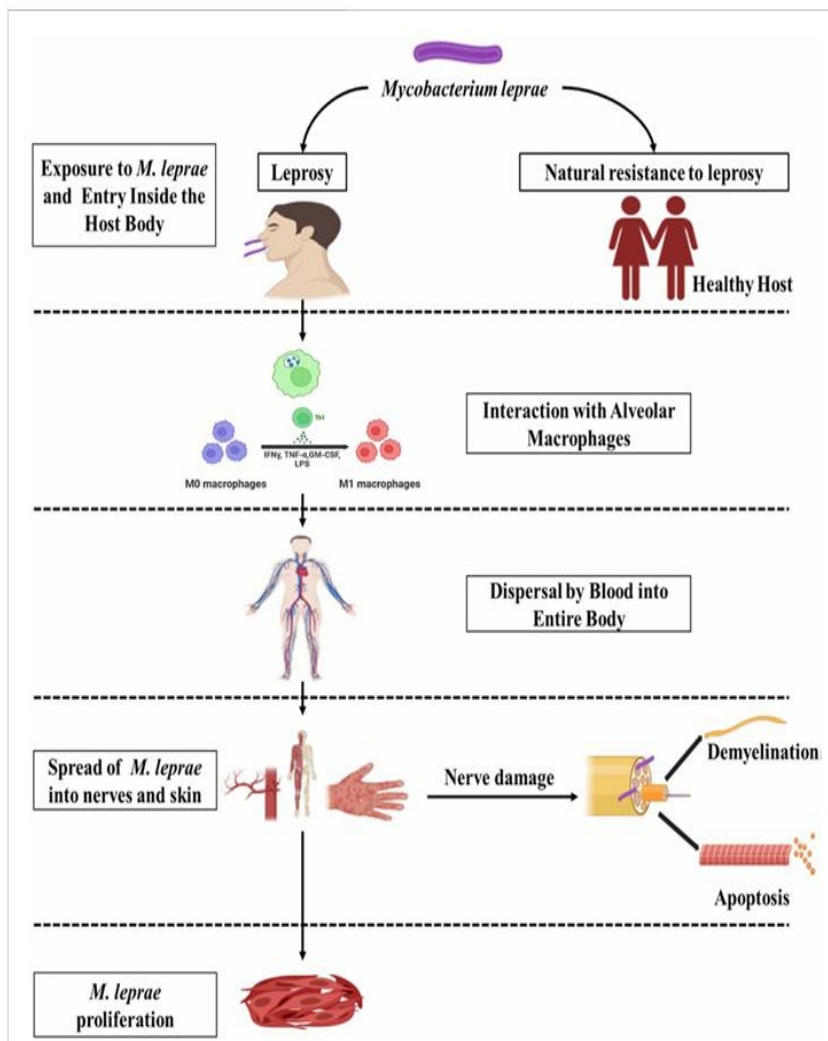
Leprosy appears to involve both immunological and non-immunological processes, and it is characterized by peripheral nerve involvement that causes sensory loss. The Schwann cell (SC) serves as both *M. leprae*'s host and primary target. Phenolic glycolipid 1 (PGL-I) has been shown to be essential for the internalization of Schwannomas in laboratory culture systems of the microorganism and the demyelination that follows (Rambukkana, 2004). Schwann cells protect the bacilli from being destroyed and prolong their survival. Immunological responses to *M. leprae*-infected Schwann cells are the main source of nerve damage in leprosy. Long-term cultures of human Schwann cells have been demonstrated to display CD80 surface, ICAM-1, and MHC class I and II. molecules, all of which are involved in the presentation of antigens. Recent studies have demonstrated that human T cells digest and present both natural and recombinant *M. leprae* proteins and peptides. Schwann cells (Spierings and colleagues, 2000). The infected Schwann cells are then eliminated by activated T lymphocytes. Demyelination may be aided by the stable and reactional forms of TNF α and TNF α mRNA found in leprosy nerve lesions. Additionally, TLR2 on Schwann cells may be responsible for nerve damage in leprosy (Oliveira et al., 2003). Leprosy-related nerve damage is caused by DTH reactions seen in type 1 reactions, local immune complex deposition, and activation of complement in long-term ENL. Contact-dependent demyelination has been seen in culture systems lacking immune cells, indicating that non-immune mechanisms might be involved during the initial phases of nerve infection (Rambukkana, 2004). *M. leprae* heavily colonizes non-myelinating

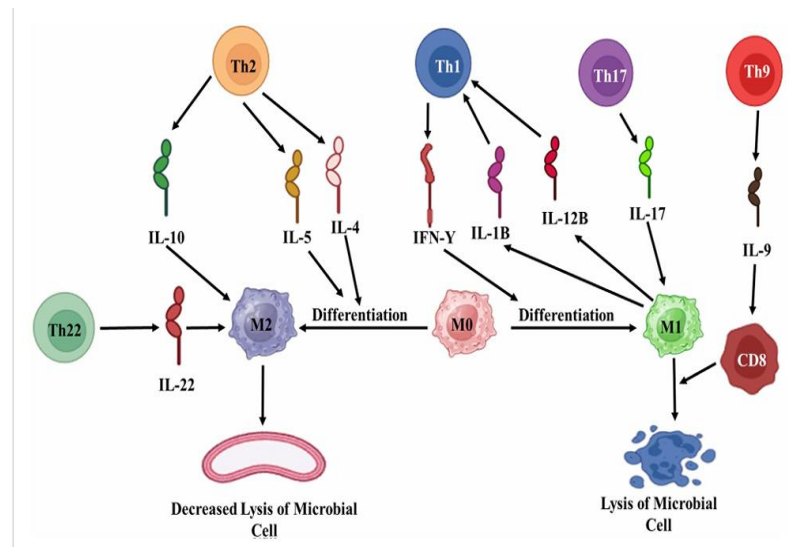
Schwann cells, although myelin-associated Schwann cells are relatively devoid of infection. Previous ultrastructure research on leprosy patients' nerves revealed the presence of bacilli within the Schwann cells of myelinated axons (Cabral et al., 2022).

Immunology of leprosy

Mitsuda carried out a ground-breaking experiment in 1954 that showed that intradermal injection of dead *M. leprae* bacteria caused a skin reaction three to four weeks later, which was characterized by edema and erythema where the injection was made. Crucially, those with LL did not exhibit these symptoms; only those with TT did. This discovery showed that an individual's immunological response to the bacterium was necessary to generate an inflammatory reaction.

Dharmendra then carried out studies demonstrating that a lipid-free soluble component generated from leprosy bacilli could similarly induce such an activity, although in a shorter timescale, usually taking place between 48 and 72 hours. The Dharmendra test's temporal dynamics match those of a delayed-type hypersensitivity reaction, whereas the Mitsuda test evaluates the granulomatous reaction. Even though neither test is specific to leprosy, it is nevertheless used today to evaluate immunological health. As opposed to people with L-lep, who may have antibodies but restricted T-cell function, histological characteristics, skin testing, and according to immunological research, T-lep patients have T-cell immunity and show DTH reactions to the infection (Nathan, 2020).





Innate Immunity

Body's protection against pathogens and foreign chemicals depends on the innate immune response. Dendritic cells, Schwann cells, and macrophages serve as entry points and host cells where *M. lepra* penetrates and resides in the context of leprosy. The entry process is the initial stage of the pathogen's intracellular lifestyle, and *M. leprae* uses a variety of techniques to enter host cells. Receptors like CR1, CR3, and CR4 that identify complement fragments aid in phagocytosis in leprosy. PGL-I, a Complement 3.6 identifies cell wall lipids unique to *M. leprae*. Toll-like receptors (TLRs) and complement are essential for identifying microbial pathogens present in dendritic cells and macrophages. These cells use generic molecular pattern recognition to identify a variety of diseases (Figure 4). The leprosy bacillus is recognized by TLR2 and TLR4, members of the family of TLRs that bind to lipoproteins. Monocytes release IL-12, a cytokine that encourages the death of the Bacillus by proinflammatory cytokines, when these receptors are active. Cytokines such as IFN γ and GM-CSF can raise TLR1 expression, which releases TNF α and causes inflammation. Notably, PGL-I, a glycolipid specific to *M. leprae*, causes the synthesis of negative regulatory molecules such MCP-1 and IL-1Ra (Teles), as well as low levels of TNF α , IL-1, and IL-10. (2010) and Manca et al. (2012). Acquired immune response

The highly specialized interaction known as the acquired immune response involves lymphocytes, dendritic cells, macrophages, and soluble elements such antibodies made by cells that produce plasma. These antibodies are in charge of ensnaring free microbes. On the other hand, T cell-released cytokines can target intracellular

pathogens by penetrating cell membranes (Figure 5). It's interesting to note that some cytokines, such IL-4 (a Th2 cytokine) and IL-10, have been shown to have a negative regulatory function by suppressing TLR2 expression and cytokine production, which arises from the interaction of between acquired and innate immune responses. TLR1 and TLR2 are more highly expressed in tuberculoid leprosy skin lesions, suggesting their significance in the immune system reaction (Gaut metal., 2021).

T Cell- Mediated immune response

Early diagnosis of delayed type responses caused by divergent T cells in the leprosy's spectrum was made achievable by skin tests. T cell numbers, PBMC non-proliferation in mitogen response, and unresponsiveness to *M. leprae* antigens in L-lep were early warning indicators patients. This particular unresponsiveness remained for a long time, even though treatment could alleviate the decreased responses to cell mitogens (Silva et al., 2022). Interestingly, L-lep patients' T cell responses to other antigens, like *M. tuberculosis*, remained unchanged. This implies that different antigen-specific unresponsiveness is present in L-lep patients. The underlying etiology of this immunologic unresponsiveness in L-lep is still up for debate despite a great deal of research. However, it is thought that this lack of reaction is related to peripheral tolerance rather than central tolerance or the loss of *M. leprae*-specific T cells. Over time, the idea that antibiotic-mediated suppression might be a contributing element has lost credibility.

Types of leprosy

In 1953, a classification system was proposed at the Madrid Congress, categorizing leprosy into four

primary disease categories: Indeterminate leprosy, lepromatous leprosy, tuberculoid leprosy, and borderline or dimorphous leprosy (Lockwood et al., 2007). This classification system, which is currently less common, was initially developed at the 1953 International Leprosy Congress in Madrid, hence the name. But in 1962 and 1966, Ridley and Jopling presented a new classification that included both clinical features and histology. Mitsuda's intradermal test results indicate the bacterial burden and the degree of cell-mediated immune (CMI) response against *M. leprae* (Ridley and Jopling, 1966; Singh et al., 2013a; Antunes et al., 2016). Patients are categorized into five groups using this revised system: Elevated CMI, which represents the hyperergic pole, is a characteristic of tuberculoid leprosy (TT), borderline-tuberculoid (BT), borderline-borderline (BB), borderline-lepromatous (BL), and lepromatous leprosy (LL), which has elevated humoral immunity and is weakly resistive (anergic) (Figure 2). Although the Ridley and Jopling system did not include I indeterminate leprosy (IL), this clinical manifestation does not fit into the spectrum since there is no obvious connection between clinical and histological features. According to Britton and Lockwood (2004), the degree of CMI in this stage is still unclear, suggesting an early stage of the illness.

1. Indeterminate leprosy.
2. Tuberculoid leprosy.
3. Borderline leprosy.
4. Borderline- tuberculoid leprosy.
5. Mid-borderline leprosy.
6. Borderline lepromatous leprosy.
7. Lepromatous leprosy.
8. Pure neural leprosy.

1-Indeterminate Leprosy

In the early stages of leprosy, the majority of individuals acquire macular and hypopigmented lesions. People who have not yet established CMI against *M. leprae* exhibit this early clinical manifestation (Britton and Lockwood, 2004). These lesions don't show scaling or stitching and are usually macules with flat surfaces. Depending on the patient's skin tone, they can range in hue from red to coppery and are rather small, typically up to 4 cm in size. Patients continue to experience normal perspiration and body hair despite these changes (Walker and Lockwood, 2007). Sensory impairment, also referred to as anaesthesia, is a critical feature of leprosy lesions. It is sometimes difficult for patients with leprosy lesions to discern between hot and cold stimuli due to a lack of temperature awareness. It's interesting to note that skin lesions are frequently

found after hyperalgesia begins, suggesting that sensory abnormalities are a part of the illness progression (Walker and Lockwood (2007). It is important to note that a patient's genetic predisposition and CMI responses to *M. leprae* can affect the number and severity of skin lesions. Skin lesions are generally less common in those with a high CMI response, but the humoral immune response has a weaker role.

2-Tuberculoid Leprosy

A few tiny lesions with prominent, elevated borders that look as papules and plaques are the hallmark of tuberculoid leprosy (TT) (Nunzi & Noto, 2008). These elevated borders may be a sign of central healing or peripheral lesion expansion (Gaschignard et al., 2016). Anesthesia, scant body hair, and decreased sweating are common signs of normal TT lesions. Patients first experience heat anesthesia, which is followed by loss of touch and pain perception. Patients may experience peripheral trunk nerve expansion or areas of anesthesia in certain TT cases, either with or without skin lesions (Gaschignard et al., 2016). Interestingly, lesions on the face may maintain normal sensitivity because of the weak sensory innervation in this region, making up for the destroyed nerves (Britton and Lockwood, 2004). Patients may see macules in the early stages of TT. These macules may seem uniformly hypopigmented, erythematous, or coppery in people with light skin. These macules have a rough texture and a dry surface due to anhidrosis, or the absence of sweating. Papules may eventually form at the borders of the macules as a result of the strong CMI response linked to TT (Pfaltzgraff and Bryceson, 1985).

3-Borderline Leprosy

The majority of leprosy patients fall into the borderline category according to the Ridley and Jopling categorization (Singhet al., 2013a; Antunes et al., 2016). Patients in this category have different degrees of disability, frequently as a result of substantial peripheral nerve involvement, which can affect many nerves (Britton and Lockwood (2004). Instability is one trait that sets the borderline group apart. If left untreated, borderline patients may develop lepromatous leprosy and eventually exhibit the disease's distinctive clinical symptoms. Additionally, during or after therapy, patients may see improvements or decreases in their classification. Reversal reactions are common in borderline people and may or may not be connected to treatment. If treatment is not received, these reactions might result in paralysis and are usually characterized by

increasing skin lesions and nerve involvement. (Ramos-e-Silva and Rebello, 2001).

4-Borderline- Tuberculoid Leprosy

The skin lesions in borderline-tuberculoid leprosy (BT) are similar to those seen in tuberculoid leprosy, however they are typically more numerous, ranging from 10 to 20. Usually, these lesions are bigger than those found in TT leprosy. The presence of satellite lesions, which can range in color from hypochromic to bright, is a noticeable characteristic of BT le. These smaller lesions extend like finger-like extensions into the normal skin from the edges of plaques or appear next to larger ones the macules. Lesions from leprosy can vary in size, shape, and color within the same patient. In BT leprosy, skin lesions can expand or become ulcerated, especially due to type 1 reactions, which are typical in this form of the illness (Pfaltzgraff and Bryceson, 1985; Lockwood and Britton, 2004). Because nerves play a major role in BT leprosy reactions, prompt treatment is essential to preventing permanent deformity and impairment. Only anaesthetic macules and nerve expansion may be seen in certain situations.

5-Mid- borderline Leprosy

Infiltrating plaques that appear in different sizes are a characteristic of BB leprosy. These plaques are characterized by a center region of spared skin that is typically hypochromic, with a well-defined inner edge and a less distinct outside edge that invades sections of normal skin (Lockwood & Britton, 2004). This combination of lesions results in a type of cheese that is sometimes referred to as Swiss cheese. Usually, these distinctive lesions coexist with other skin abnormalities such macules, plaques, papules, and nodules. Additionally, symmetrically distributed reddish-coppery lesions on the body are linked to BB leprosy (Pfaltzgraff and Bryceson (1985). The rarest and most unstable form of leprosy is represented by BB leprosy. Patients with BB may have a variety of nerve involvement, and it tends to advance quickly toward either the TT or LL polar forms.

6-Borderline Lepromatous Leprosy Hypopigmented macular lesions are the first signs of BL leprosy. In the afflicted patients, these lesions first appear symmetrically dispersed. These macules get larger, becoming erythematous (red), and penetrate deeper into the skin's tissue over time. According to Ramos-e-Silva and Rebello (2001), their borders grow uneven and invade the surrounding healthy skin. These lesions progressively spread to larger parts of the skin as the illness worsens. Lesions that resemble

plaques, papules, and nodules may appear in some BL leprosy patients, mimicking the clinical manifestation of lepromatous leprosy (Gaschignard et al., 2016). Although nerve sensitivity is less common than in BT leprosy, peripheral nerve involvement is evident in the majority of BL patients. But it's crucial to remember that BL leprosy-related reactions might cause serious nerve injury (Gaschignard et al., 2016).

7-Lepromatous Leprosy

Patients may exhibit several, symmetrically distributed hypochromic lesions if they are unable to establish an effective CMI response to *M. leprae*, which causes the germs to spread hematogenous. These people develop polar lepromatous leprosy (LL), a non-resistant form of leprosy, if therapy is not received. Notably, neglecting to treat BB and BL can also lead to LL (Britton and Lockwood, 2004). There are two clinical subtypes of lepromatous leprosy: polar (LLp) and subpolar (LLs). Compared to individuals with LLp, patients with LLs show less anergy and typically reach bacteriological negativity faster after treatment. Type 1 reactions may occur in some patients who first exhibit clinical manifestations of LL (Kumar et al., 2014). The edges of In LLs, the macules, nodules, and plaques are clearly delineated. On the other hand, LLp, which is characterized by scattered skin infiltration with fuzzy, indistinct boundaries, is more common in patients who are very anergic (Gaschignard). (2016) et al.

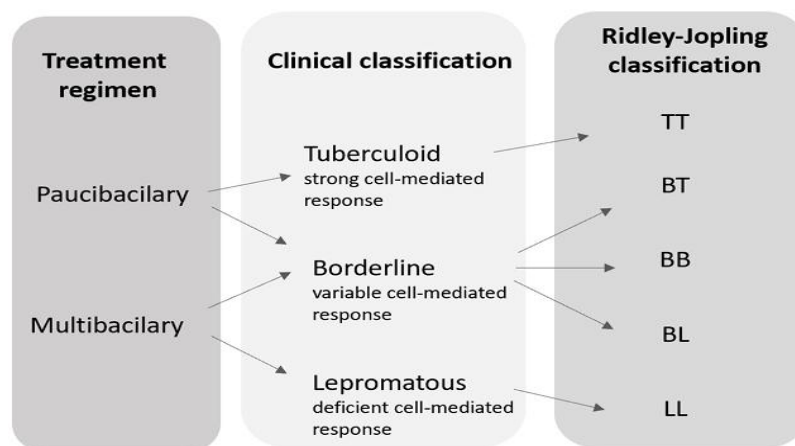
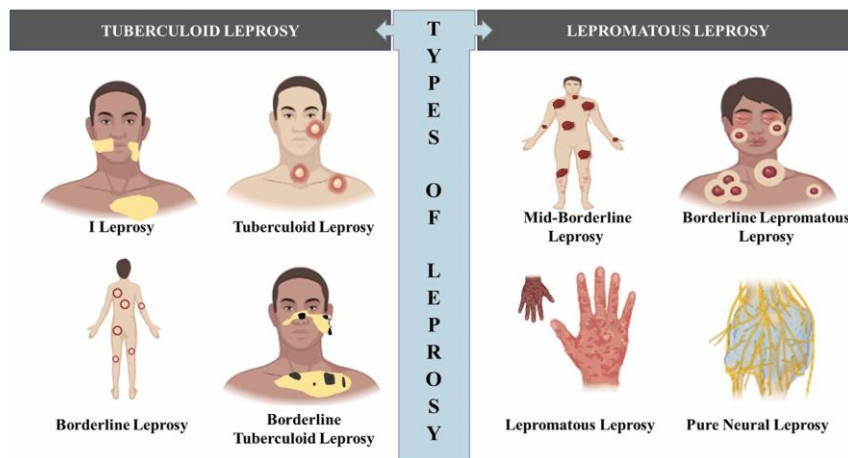
In some instances, the hypochromic lesions start out on the skin and then spread to other parts of the body. If treatment is not received, the afflicted areas may develop worsening wrinkles, greater skin penetration, and spreading erythema (Córsico et al., 1994). One of the most frequent effects in the infiltrated areas is hair loss. Madarosis is a unique disorder caused by the loss of eyebrows, which usually starts at the outer ends. Additionally, certain patients might suffer from eyelash loss (Pfaltzgraff and Bryceson, 1985). Skin folds become more noticeable as skin infiltration deepens, giving facies leonina its distinctive clinical aspect. Infiltration may also be visible on the hands and feet, making the skin appear glossy and sensitive. Papules and nodules may progressively form on the infiltrated skin, either singly or in clusters. It is important to note that some body parts are less impacted than the others, including the head, axillae, midline of the back, perineum, groin, and other warmer skin locations body (Córsico and others, 1994). Peripheral nerves may enlarge as the illness progresses, causing the hands, feet, and other afflicted areas to lose feeling.

Disabilities may arise from these processes (Córscico et al., 1994; Garbino et al., 2022).

8-Pure Neural Leprosy

A very uncommon form of leprosy, pure neural leprosy (PNL), also known as neural leprosy, mainly affects one or more peripheral nerves (Garbino et al., 2022). People who exhibit one or two swollen nerves are generally considered to have paucibacillary (PBL) leprosy. On the other hand, people who have more than two damaged nerves are classified as having MB leprosy. Sensory loss, muscle weakness, decreased sweating capacity, and bloated or uncomfortable anxiety. Additional signs of PNL include weakness, atrophy, and paralysis in the afflicted limbs as a result of motor nerve injury. Additionally, a sign of PNL is peripheral nerve expansion, also referred to as nerve hypertrophy or neuritis. Inflammation and immune cell infiltration of

the nerves in reaction to the illness are the causes of this growth (Khadilkar). et al. (2021). It's not always easy to determine if a nerve is enlarged. Procedures like biopsy, which involves fine needle aspiration and PCR or electroneuromyography, can be very helpful for patients with difficult-to-diagnose PNL instances wherever possible (Flageul, 2012). According to recent research, cases of asymptomatic leprosy with nerve swelling, whether or not there is pain, can be detected and treated early by using high ultrasonography with high resolution. In particular, early diagnosis and treatment are possible for those whose nerve thickness falls outside the normal range in the main leprosy-affected nerves. Even in the absence of symptoms, medical professionals can diagnose silent peripheral neuropathy in these patients by detecting aberrant nerve thickness. cure leprosy-related neuropathy as soon as possible (Volt an et al., 2023).



II. Conclusion and Future Perspective

In many poor nations, leprosy is still a major public health concern, highlighting the significance of early detection for efficient control. The use of synthetic medications, medicinal plants, and new developments in nano-pharmaceutics for the treatment of leprosy are all discussed in this article. Globally, traditional medicine is becoming more and more popular, and its combination with pharmaceutical methods has advanced the development of pharmaceuticals worldwide. Numerous areas of medical study have seen significant advances as a result of nanotechnology and the application of nanomaterials. A prospective paradigm for developing antileprotic research and treatment approaches is provided by the convergence of ethnopharmacology and nanotechnology. By utilizing the Voltan, G., Marques-Júnior, W., Santana, J. M., Lincoln peripheral neuropathy determined by high-resolution ultrasound among contacts of patients with Hansen's disease. *Front. Med.* 9, 1059448. doi:10.3389/fmed.2022.1059448 Voltan, G., Marques-Júnior, W., Santana, J. M., Lincoln Silva, C. M., Leite, M. N., De Paula, N. A., et al. (2023). Silent peripheral neuropathy determined by high-resolution ultrasound among contacts of patients with Hansen's disease between conventional wisdom and contemporary science, we can hasten the process of reaching the ultimate objective of eradicating Leprosy as a public health issue. According to the review, nanoparticles may be useful for targeted medication delivery in the treatment of leprosy since they can improve the mycolic acid cell wall permeability. However, much research is required to create biodegradable nanoparticles that can effectively transport a variety of disease-modifying medications, ultimately resulting in the successful leprosy therapy. It is noteworthy that, in comparison to plant extracts, nanoparticles show greater antibacterial ability. Thus, investigating the production of anti-leprotic nanoparticles from plant extracts may be a potential approach. Because of their potentially detrimental consequences, evaluating the biodegradability and cytotoxicity of nanoparticles is also essential. These innovative methods concentrate on creating safe, biocompatible, efficient, target-specific, and trustworthy nanoparticles with enhanced pharmacokinetic behavior for leprosy treatment. Future studies should concentrate on investigating nanotechnological advancements to improve the stability, effectiveness, and administration of antileprotic medications. Drug pharmacokinetics and tissue distribution can be optimized by customizing

nanoparticle properties including size, surface charge, and targeting ligands. Additionally, the possible benefits of combining conventional treatments with standard antileprotic medications or nanotechnology-based formulations. Combination medicines could lead to more individualized treatment plans by increasing efficacy, lowering medication resistance, and minimizing side effects.

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