CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.23769381

Available online at: http://www.iajps.com Review Article

PHARMACOLOGICAL EVALUATION OF "ANTI-ATHEROSLEROTIC ACTIVITY OF TINOSPORA CORDIFOLIA IN ANIMAL MODEL"

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Abstract:
Neurotuberculosis is one of the most devastating forms of extrapulmonary tuberculosis, often resulting in severe neurological complications because of persistent neuroinflammation, oxidative stress, and poor drug penetration into the central nervous system. Although conventional anti-tubercular therapy has improved patient survival, its effectiveness is frequently compromised by therestrictive nature of the blood–brain barrier, prolonged treatment duration, systemic toxicity, and the increasing prevalence of drug resistant Mycobacterium tuberculosis. In recent years, cerebrospinal fluid has emerged as a promising therapeutic target owing to its central role in Central nervous system homeostasis and its ability to facilitate widespread drug distribution within the brain and spinal cord. Green-synthesized silver nanoparticles represent an innovative nanotherapeutic platform that combines environmentally sustainable synthesis with intrinsic antimicrobial, anti-inflammatory, antioxidant, and neuroprotective properties. This review provides a comprehensive overview of the molecular mechanisms underlying neuroinflammation and neurotuberculosis, highlights the therapeutic significance of Cerebrospinal fluid targeted drug delivery, and discusses the unique advantages of green-synthesized silver nanoparticles in overcoming Central nervous system delivery barriers. Furthermore, it examines their potential to suppress inflammatory signaling, preserve Blood Brain Barrier integrity, enhance anti-mycobacterial activity, and improve therapeutic outcomes. Finally, current translational challenges, safety considerations, and future clinical prospects are discussed, emphasizing the potential of Cerebrospinal fluid targeted green-synthesized silver nanoparticles as a promising next generation strategy for the treatment of neurotuberculosis and other neuroinflammatory disorders.

Keywords: *Green-synthesized silver nanoparticles, Cerebrospinal fluid, Neurotuberculosis, Neuroinflammation, Central nervous system drug delivery.*

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Please cite this article in press ***D Paul Amaranath*** *et al.,* ***Pharmacological Evaluation Of "Anti-Atherosclerotic Activity Of Tinospora Cordifolia In Animal Model.,****. Indo Am. J. P. Sci, 2026; 13(10).*

1. INTRODUCTION

Tuberculosis (TB) infection, caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) bacteria, still ranks amongst the leading infectious illnesses worldwide despite the advancements made in diagnostics, prevention, and anti-tuberculosis therapy. Though the vast majority of cases of tuberculosis affect lungs, hematogenous spread of *Mycobacterium tuberculosis* can result in development of extrapulmonary TB infections[1]. In particular, neurotuberculosis (NTB) is one of the most dangerous complications of TB infection. Neurotuberculosis includes various central nervous system (CNS) disorders such as tuberculous meningitis, intracranial tuberculomas, spinal arachnoiditis, and cerebral abscesses. The above disorders are often associated with significant mortality, neurological disability, and poor prognosis in children, immunosuppressive patients, and patients with the delayed diagnosis[2]. Neurotuberculosis poses a serious therapeutic problem even in spite of the existence of anti-tubercular therapy since effective therapy presupposes not only successful eradication of the pathogen but also the suppression of neuronal injury mediated by inflammation process[3,4]. An increasing number of studies have established that neuroinflammation is a key mediator for the development, progression, and pathogenesis of neurotuberculosis. In the case of central nervous system infection, the causative *Mycobacterium tuberculosis* bacteria elicit an inflammatory response in resident microglia, astrocytes, and immune cells by inducing the production of an excess of pro-inflammatory cytokines, chemokines, ROS, and other inflammatory molecules[5]. Even though initially, this reaction serves to aid the host defenses against the pathogen, prolonged inflammation through NF-κB, MAPK, JAK/STAT, and NLRP3 inflammasome pathways leads to oxidative stress, impaired mitochondrial function, BBB breakdown, neuronal cell death, and neurodegeneration. Therefore, neuroinflammation is not just a response, but a cause of neurotuberculosis pathologies[6,7]. One of the major hurdles faced in the management of neurotuberculosis is the highly selective nature of the BBB and BCSFB that offer an effective protection to the CNS but greatly limit the administration of therapeutics. Though first line anti-TB drugs like isoniazid, rifampicin, pyrazinamide, and ethambutol continue to be used as the primary drugs in the therapy, most of these drugs do not have sufficient access to brain tissues and CSF and hence fail to achieve adequate drug levels at the site of infection[8,9]. Moreover, long duration of therapy, systemic toxicity, non-compliance of patients, MDR and XDR *Mycobacterium tuberculosis* strains, and the persistence of intracellular bacterial niches further impair the therapeutic efficacy[10].

The latest developments in the area of neuropharmacology indicate that cerebrospinal fluid (CSF) can be considered a valuable target for the treatment of various brain and spinal cord diseases. In addition to the traditionally known protective and homeostatic roles, CSF acts as a functional neuroimmune compartment responsible for molecule transportation, immune monitoring, clearance, and intercellular communications[11,12]. While drug administration via the BBB bypasses the potential for drug distribution in all regions of the CNS, the targeted CSF delivery allows the delivery of therapeutic compounds not only to ventricles, but also to meninges and the subarachnoid space of the spine[13]. The latter technique is especially beneficial in the treatment of neurotuberculosis, since pathology mostly affects meninges, CSF pathways, and perivascular spaces. Amidst the nanotechnology platforms developed recently, AgNPs synthesized via the green route are gaining immense popularity since they provide an eco-friendly synthesis method coupled with therapeutic activity[14]. Plant based synthesis methods make use of the phytochemicals present naturally as reducing and stabilizing agents to synthesize nanoparticles that are biocompatible and have lesser toxic effects compared to those synthesized chemically[15]. Besides being efficient nanocarriers used in CNS delivery of drugs, green AgNPs are themselves equipped with antimicrobial, anti-inflammatory, antioxidant, neuroprotective, and BBB protective activities. Their small size, high surface to volume ratio, surface chemistry that can be modified and functionalization property make their delivery through CNS barriers more efficient[16,17]. Even though many separate reviews have been done on tuberculosis, neuroinflammation, nanomedicine or silver nanoparticles, there have not been any thorough reviews that consider all these four factors together while considering CSF delivery, green-synthesis of silver nanoparticles, neuroinflammation suppression, and neurotuberculosis treatment[18]. It is a major deficiency in terms of the knowledge available today, especially because of the need to find out how multifunctional green nanoparticles could help in overcoming drug delivery barriers in the CNS, suppressing neuroinflammation, maintaining the BBB function, and improving antimicrobial action on *Mycobacterium*

tuberculosis[19]. Thus, this review gives a detailed and mechanistic understanding of the pathophysiology of neuroinflammation and neurotuberculosis, stressing the significance of cerebrospinal fluid as an evolving target for delivery of CNS therapeutics[20]. This review discusses the aspects of green-synthesis of nanoparticles, their physicochemical properties, mechanisms of targeting CSF, therapeutic potentials, and preclinical studies on green-synthesized silver nanoparticles, as well as issues related to the safety, translation, regulation, and future directions of these nanoparticles[21,22]. With the help of integration of recent research advancements in the field of nanotechnology, neuroimmunology, and CNS drug delivery, this review stresses the potentials of green-synthesized silver nanoparticles as next generation nanotherapeutics platforms[23].

2. NEUROINFLAMMATION AND NEUROTUBERCULOSIS: PATHO PHYSIOLOGICAL BASIS

2.1 Central Nervous System Immune Homeostasis and Molecular Mechanisms of Neuroinflammation

The central nervous system (CNS) is the site of immune privilegi, which includes neuroprotection while ensuring immune surveillance of the environment. These processes that mediate immune homeostasis are carried out by glial resident cells, such as microglia and astrocytes[24]. These also collaborate with other brain cells like neurons, oligodendrocytes. Besides their role in neural cell maintenance and BBB formation/maintenance and CSF function, both cells are responsible for surveillance of micro environment, cellular/bacterial waste, cytokine communication and innate immunity against pathogens[25]. Neuroinflammation begins when infections, injuries, autoimmune disease, or oxidative damage disrupt this homeostatic equilibrium. Binding of pamp associated molecule recognition patterns (pampss) and the damage associated molecular patterns by toll like receptor (TLR) and NOD like receptor, lead to activate intramolecular signalings through NF-B, MAPK, JAK/STAT and NLRP3 inflmasome, which stimulate and induce producing pro inflammatory mediators, TNF, IL-1, IL-6, IFN, NO, ROS[26,27]. These mediators were beneficial during clearance of infections and to remove pathogen but due to the prolonged stimulation oxidative stress and mitochondrial damage occurs which consequently leads to neurons apoptosis and damage.In chronic neuroinflammatory environment loss of barrier becomes more apparent by damage to endothelial tight junction protein that provides barrier which can also enable peripheral imflammatory cell migration to CNS and potentiates neuroinflation[28,29]. Therefore, neuroinflammation played an important role in nervous damage which provides susceptibility towards infectious disease such as neurotubercolosis[30].

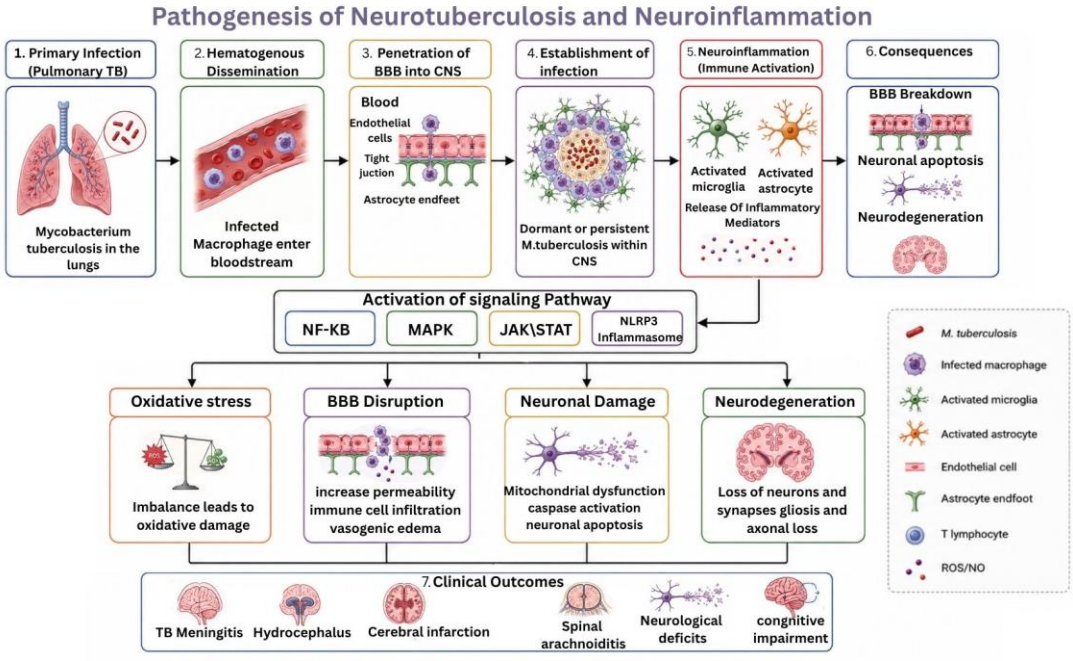


Figure 1. Pathogenesis of neurotuberculosis and neuroinflammation showing pulmonary infection, hematogenous dissemination, blood–brain barrier penetration, granuloma formation, neuroinflammation, and clinical consequences. Created by the authors using BioRender.com [5,6,33].

2.2 Pathogenesis of Neurotuberculosis and Its Crosstalk with Neuroinflammation

Neurotuberculosis (NTB), is one of the common extrapulmonary disease associated with CNS involvement due to infection of primary infected host with widespread mycobacterium infections by *M.tuberculosis*. Therefore the transmission to the brain may occur through multiple mechanisms, one example of which is 'Trojan Horse' where *M. tuberculosis* may enter the host cells as a component of Tuberculosis invades the CNS as a intracellular contents in infected monocyte, penetration of endothelium, or via Trans cellular pathway, thus crossing the blood-brain barrier[31,32]. The invading bacillus once has entered into the CNS forms a granulomatous Focus of *M.Tuberculosis* which is a Rich-foci located either at the basal meninges or brain parenchyma. The rupture of the lesions into subarahnoid space produces a severe inflammation which may lead to Tuberculous meningitis, Tuberculomas, Vasculitis, Hydrocephalas, and Cereberal infarcts[33]. Neurotuberculosis occurs not only through a persistent infection but also due to dysregulated neuroinflammation[34]. Recognition of mycobacterial antigens via microglia, astrocytes, and infiltrating macrophages triggers exaggerated secretion of inflammatory mediators including TNF- , IL-1, IL-6, IFN-, etc[35]. Chronic activation of NF-B and NLRP3 inflammasome upregulates oxidative stress, destabilizes the integrity of BBB, and induces neurotoxicity. In summary, neurotuberculosis with neuroinflammation involves a self-reinforcing vicious loop.The infection enhances chronic neuroinflammation, which in turn aids the bacterial persistence in CNS, leading to inflammation driven tissue injury[36,37]. Restricted BBB integrity and inefficient delivery into CNS render conventional antitubercular therapy incapable of fully curbing infectious diseases. Conclusively, treatment that can overcome both these limitations by suppressing neuroinflammation and simultaneously boosting BBB transport of drugs seems to be of benefit in neurotuberculosis[38].

Table1. Pathophysiological mechanisms underlying neurotuberculosis and neuroinflammation.

Pathological event	Mechanism	Clinical consequence	References
Hematogenous dissemination	*M. tuberculosis* spreads from the lungs to the CNS via the bloodstream	CNS infection initiation	[31-34]
BBB penetration	Trojan horse mechanism, transcellular migration, endothelial invasion	Entry of bacilli into the brain	[31-33]
Rich focus formation	Granuloma formation within meninges or brain parenchyma	Latent CNS infection	[33]
Rich focus rupture	Release of bacilli into the subarachnoid space	Tuberculous meningitis	[33,38]
Microglial activation	Recognition of mycobacterial antigens through TLRs	Cytokine release	[24-27,35]
Astrocyte activation	Amplification of inflammatory signaling	Chronic neuroinflammation	[24,25,35,36]
Cytokine production	TNF-α, IL-1β, IL-6, IFN-γ	Neuronal injury	[26,27,35,36]

Oxidative stress	Excess ROS and RNS generation	Mitochondrial dysfunction	[27,30]
BBB disruption	Loss of tight junction proteins	Increased CNS permeability	[28,29]
Neuronal damage	Persistent inflammation and oxidative injury	Neurodegeneration and neurological deficits	[30,36-38]

3. CEREBROSPINAL FLUID AS A THERAPEUTIC TARGET

3.1 Physiological Role of Cerebrospinal Fluid and Its Relationship with CNS Barriers

Cerebrospinal fluid (CSF) is a clear, cell free, nutritious biological fluid found surrounding the brain and the spinal cord, and it plays multiple and critical functions in the homeostasis of the central nervous system (CNS)[39]. Mainly produced from choroid plexus in the ventricles of the brain, CSF exerts several main actions including act as a physical barrier protecting the CNS, controlling intracranial pressure, transporting nutrient molecules and signaling agents and removing waste[40,41]. The CSF contributes significantly to the intercellular communication in the CNS by enabling and directing circulation of cytokines, growth factors, extracellular vesicles etc between various parts of the CNS, contributing to the functioning of neuronal cells in Physiological and pathophysiological conditions[42]. Movement and composition of the cerebrospinal fluid (CSF) are highly guarded by two distinct diffusion barrier structures within the CNS, the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB). BBB is a single layer endothelium associated by tight cell connections forming selective cell membranes that are permissive for entry of a restricted number of substances into the brain[43,44]. BCSFB is characterized by highly selective cells mainly present on the choroid plexus epithelium and regulates influx and effluence of different substances between BBB and CSF[45]. Both structures play a critical role in establishing CNS immunity with mechanisms including controlling ingress of pathogens, modulating immune cell movements and maintaining a unique CNS environment but on the other hand inhibit influx of majority of the available therapeutic drugs[46].

3.2 CSF Dynamics in Neuroinflammatory Disorders and Rationale for CSF-Targeted Drug Delivery

CSF Physiology Changes during neuroinflammatory states including Neurotuberculosis During neuroinflammatory disorders like Neurotuberculosis, microglial activation, astrogliosis and the influx of numerous infiltrating inflammatory cells leads to an accumulation of increased number of cytokines and chemokines including oxidants and other inflammatory products in the CSF thus disturbing the normal environment and flow of CSF[47,48]. Following rupture of the Rich foci, tubercle in case of Neurotuberculosis infects the subarachnoid space, leading to exudation of inflammatory mediators, blockage of CSF flow, Increased intra cranial pressure with the development of hydrocephalus and the subsequent distribution of inflammatory process to entire CNS[49]. It results in further neurological injury and attenuation of the effect of conventional drug therapy by restricting entry of drugs into infected foci[50]. While major progress has been done toward the development of methods to bypass the BBB, the central spinal fluid has been found to offer an available as well as biologically applicable clinical source to treat the illnesses related to central anxious system disease[51]. Instead of a tight barrier which limits the penetration of the nearly all drugs (The barrier-BBB), CSF makes available a straightforward channel to allow medical agents permeate to the brain, meninges and spinal cord. It may assist improve bioavailability as well as CNS bioavailability, maintain continuous drug attention and even less off target impacts when it comes to numerous brain centric illnesses consisting of those with the pathogens in meningo CSF as neurotuberculosis[52,53]. Hence CSF-targeted medication shipment has been recently an effective principle to overcome treatment effectiveness for a variety of neurologic infection as well as a solid ground for constructing futuristic nanocarriers like

eco-friendly synthesized silver nanoparticles that simultaneously overcome the microbial infection, inflammatory neurodegenerative procedure, and the inadequate CNS drug penetration capability[54].

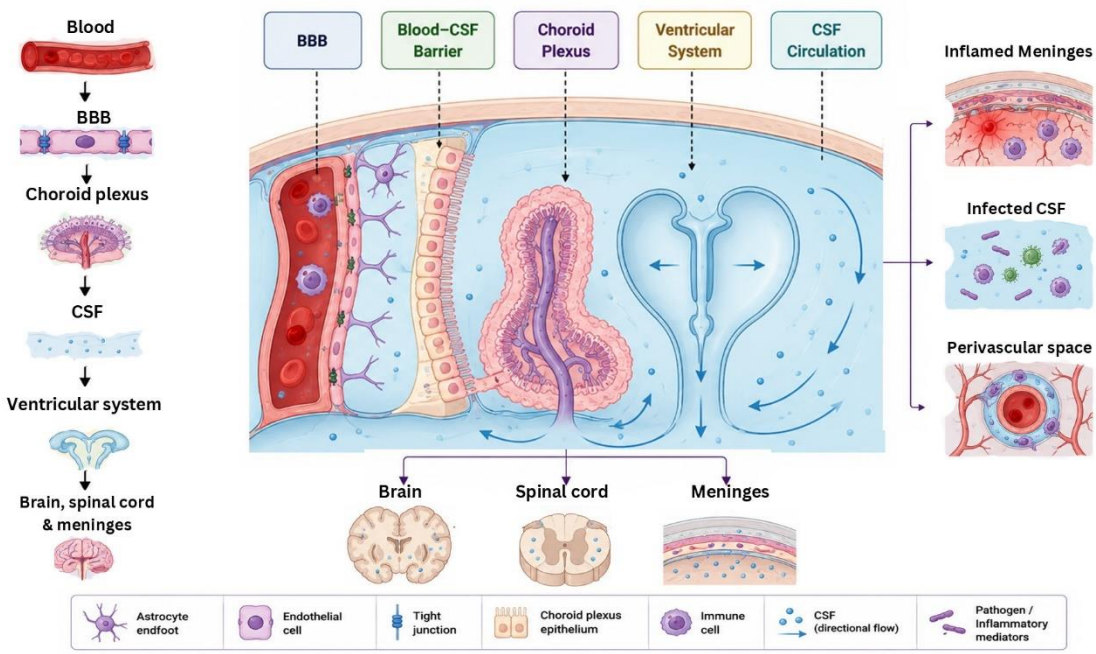


Figure 2. Cerebrospinal fluid as a therapeutic target illustrating transport across the blood–brain barrier and blood–CSF barrier, CSF circulation, and drug distribution to the brain, spinal cord, meninges, and perivascular spaces. Created by the authors using BioRender.com [43,46,53].

4. CURRENT THERAPEUTIC CHALLENGES IN NEURO TUBERCULOSIS

4.1 Limitations of Conventional Anti-Tubercular Therapy and Drug Resistance

Neurotuberculosis is one of the most challenging forms of extrapulmonary tuberculosis because central nervous system (CNS) involves an intricate and not yet entirely clear pathogenic process, and effectiveness of standard Anti tubercular therapy (ATT) against NTB is limited[55]. The conventional ATT (isoniazid, rifampicin, pyrazinamide, ethambutol) significantly decreased mortality but optimum response is not achieved as several drugs that are given in standard ATT do not penetrate effectively the CNS andcerebrospinal fluid (CSF)[56]. Secondly protracted therapy, extending from 9-12 months, leads to suboptimal patients compliances, systemic Toxicity and drugs Associated side Effects. Last as bacterial Clearance occurs, patient develop permanent neurological deficits because of irreversible damage secondary to chronic inflammation mediated effects on neural tissues[57,58]. Another problem is the growing rate of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* MDR/MDRTB strains, which diminish the effectiveness of traditional anti-tuberculosis drug regimens considerably[59]. Acquired resistance can result from natural genetic mutations (spontaneous random mutations), insufficient exposure to anti-tuberculosis drugs and patient's poor compliance or partial treatment and so that bacteria survives & cause reinfection[60]. Furthermore, the survival of *M. Tuberculosis* inside macrophages as intracellular pathogens, particularly in granulomatous environment where drugs do not penetration effectively leads to chronicity, and increased mortality with persistence of bacteria[61].

4.2 Challenges in CNS Drug Delivery and the Need for Targeted Therapeutic Strategies

Further challenges with NTB management include selectively barrier of CNS which inhibit drugs from targeting at site of CNS infected site of infection, such as BBB (blood-brain barrier) and BCSFB (blood-brainCSF barrier) which controls the transport of molecules into the CNS[62]. Only a small variety of available drugs able to reach

adequate levels in either the brain parenchyma and/or CSF, the permeability of BBB usually increases, however it's patchy and insufficient to effectively deal with intracellular bacillus hidden in either granulomas or inflammation sites such as meninges and lesion where bacteria are living, so even effective concentration on plasma don't necessarily correlate the effective concentration on infected sites[63,64]. In addition to limited penetration to the CNS, sustained neuroinflammation, oxidative stress, BBB loss, and abnormalities in CSF movement can restrict the effectiveness of therapy for neurotuberculosis[65]. Effective therapy must therefore incorporate not only antimicrobial capability but also novel delivery systems that are able to traverse the CNS barriers, target the foci of infection and modulate the inflammatory response[66]. The inherent barriers to therapy for neurotuberculosis led to interest in improved methods of drug delivery more recently interest has been directed towards Nanomedicine based solutions, particularly CNS-targeted CSF nanocarriers to increase bioavailability, prolong drug half-life, expand distribution to the CNS and limit systemic toxicity. Here we provide the rationale for investigation of green-synthesized silver NPs as multifunctional nanotherapeutic agents targeting the CSF[67,68].

5. GREEN-SYNTHESIZED SILVER NANOPARTICLES

5.1 Fundamentals of Green Nanotechnology and Plant-Mediated Synthesis of Silver Nanoparticles

Green nanotechnology a better alternative sustainable and economic method for nanomaterials Green nanotechnology have been developed as eco-friendly approach of synthesizing nanoparticles due to reduction in toxic and hazardous chemicals used for nanomaterials production, low energy utilization and use of biomass derived reagents[69]. Instead of chemical and physical based nanomaterials produced used conventional methods the use of nature derived biologically reduced and stabilized plant based nanoparticles produce biologically inert and less harmful nanoparticles. Plant based nanomaterials synthesis by using biological reagents[70]. Among all plant derived agents, the plant mediated synthesis seems a favorable choice for generating nanomaterials due to its ease, economy, scalability and cost-effectiveness, and is an environmentally clean approach to develop nanomaterials[71]. The extracts and products from plant are enriched with natural plant derived active phytochemcial like flavonoids, phenolic compounds, terpenoids, alkaloids, organic acids, proteins and sugars which act as reduce and capping agent on to form silver (Ag) into stable nanoparticles (Ag NPs) and having greater stability , size controlled, surface modified and suitable for Biomedical purposes without toxic chemical agents[72,73].

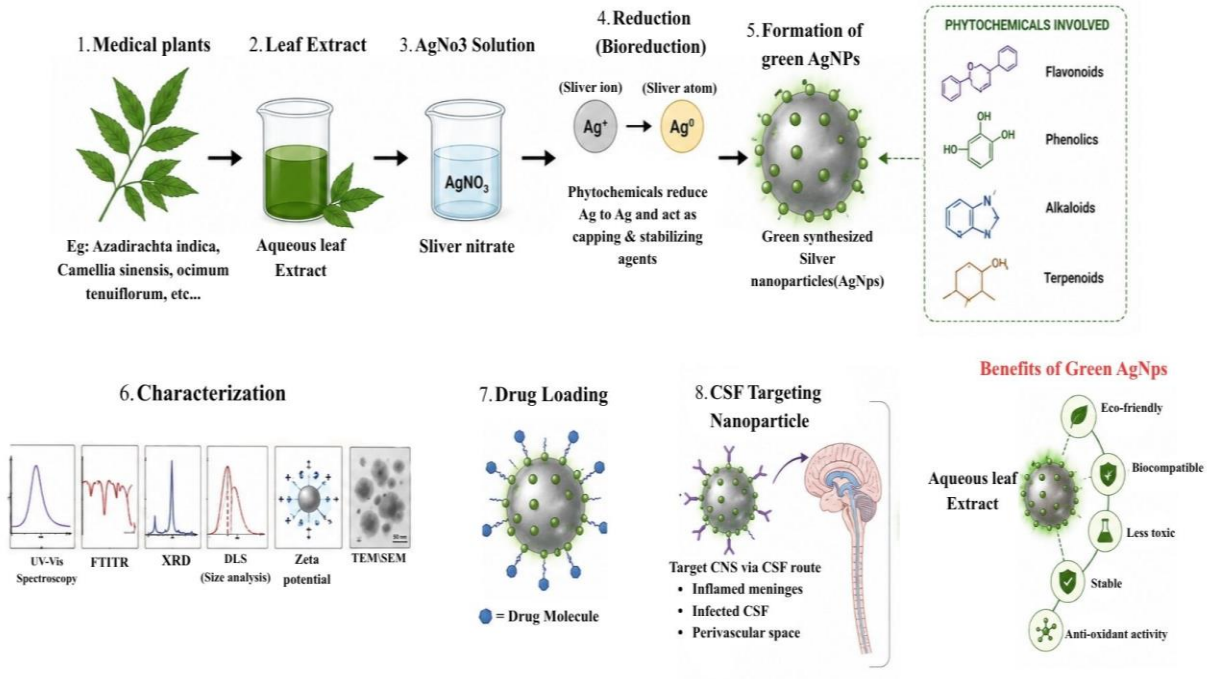


Figure 3. Green synthesis of silver nanoparticles showing plant-mediated reduction of silver ions, nanoparticle formation, characterization, drug loading, and CSF-targeted delivery. Created by the authors using BioRender.com[68,73].

5.2 Physicochemical Characteristics and Biological Advantages of Green-Synthesized AgNPs for CNS Delivery

The therapeutic efficacy of the green-synthesized AgNPs predominantly depends on their physicochemical properties like their particle shape, size, charge density, morphology, crystallinity and surface chemistry that dictate their stability, cellular accumulation and delivery to cells, andbiodistribution in various parts of the body and cellular target[74]. Furthermore these physicochemical properties dictates their drug carrying and loading capability and their interaction and ability to cross biological barrierst such as BBB & BCSFB. Small sized uniform NPs with large surface to volume ratio and with appropriate surface functional group, that remain stable to penetrate in the CNS barriers and can elicit excellent therapeutic effect[75,76]. In addition the presence of the natural phytochemical as capping ligands in green AgNPs increase their solubility, cellular uptake and cellular viability and decrease their self aggregation, and interaction with unwanted surfaces (blood products etc.)[77]. In addition to their favorable physicochemical properties, there are many desirable bioactivities of green-synthesized AgNPs for treatment of neuroinflammatory diseases. As a general class of nanomaterials, AgNPs were identified to have broad spectrum of anti-microbial activities to many pathogenic microorganisms such as *Mycobacterium tuberculosis* and their mechanisms of anti-microbial activity include damaging membrane integrity, generating reactive oxygen species (ROS), inhibiting enzyme activity, interfering with nucleic acid synthesis, etc[78,79]. Furthermore, the plant derived phytochemicals in Green-synthesized AgNPs give it powerful antioxidant activities of scavenging ROS. And anti-inflammatory activity of Green-synthesized AgNPs is attributed to the reduction of ROS and pro-inflammatory cytokine generation and attenuation of the activation of NF-B and NLRP3 inflammasome related signaling pathway[80]. Furthermore, lower cyto-toxicity, better hemocompatibility, superior biological stability, and safer therapeutic profile of Green-synthesized AgNPs against chemically synthesized ones indicated that Green-synthesized AgNPs are efficient multifunctional nanocarriers for CNS-targeted delivery, showing good promise to be employed to treat neurotuberculosis and other neuroinflammatory diseases[81].

Table 2. Physicochemical characteristics and biological advantages of green-synthesized silver nanoparticles for CNS-targeted therapy.

Characteristic	Functional significance	Therapeutic advantage	References
Small particle size	Improves BBB and BCSFB penetration	Enhanced CNS delivery	[74-76]
Uniform morphology	Predictable biodistribution	Improved therapeutic efficiency	[74-76]
High surface-area-to-volume ratio	Increased drug loading	Sustained drug release	[74-76]
Surface phytochemical capping	Stabilization and biocompatibility	Reduced cytotoxicity	[72,73,77]
Surface charge	Influences cellular uptake	Enhanced intracellular delivery	[74-77]
High colloidal stability	Prevents aggregation	Longer circulation time	[72,73,77]

Antimicrobial activity	Inhibits *M. tuberculosis*	Reduced bacterial burden	[78,79]
Anti-inflammatory activity	Suppresses NF-κB and NLRP3 pathways	Reduced neuroinflammation	[80]
Antioxidant activity	Scavenges ROS	Reduced oxidative stress	[73,80]
Neuroprotective activity	Preserves neuronal viability	Improved neurological outcome	[77,81]

6. MECHANISMS OF CSF-TARGETED DELIVERY BY SILVER NANOPARTICLES

6.1 Transport of Silver Nanoparticles Across Central Nervous System Barriers

The effective management of neurological conditions is heavily reliant on the capability of treatment solutions to successfully overcome the impermeable nature of barriers like the blood-brain barrier and the blood cerebrospinal fluid barriers (BCSB). These physiological mechanisms ensure against toxic damage by restricting passage of a majority of antimicrobial drugs and anti-inflamatory substances[82]. In an endeavor to solve this problem, green- synthesized Silver nanoparticles (AgNPs) with nanoscale sizes, variable surface attributes and surface functionalized phytochemicals present a unique solution[83].The delivery of nanostructures across barriers can take place via multiple mechanisms, the choice between which is dominated by specific traits of the formulation, i.e.Passive diffusion (nanoparticles with diameters below 15 nm), receptor mediated transport, receptor non mediated adsorption process, transport by carrier substances and passive transportation by leukocytes (Trojan-horse approach)[84]. Coordinated adsorption on particle surfaces, the use of bioactive phytochemical components lead to better stability and increased biocompatibility of nanoparticles along with lower accumulation by the reticuloendothelialsystem (RET), hence ensuring increased residence and improved transportation into brain. Hence there will increased CNS accumalation and reduced systemic toxicities[85,86].

6.2 Distribution Within the Cerebrospinal Fluid and Cellular Uptake by Neural Cells

Once nanoparticles penetrate the BBB or BCSFB they access the cerebrospinal fluid (CSF), which distribute these particles to various parts of the brain and spinal cord by the ventricular and subarachnoid CSF flow patterns. This diffusion of nanoparticle to various sites of brain helps access the meninges, periventricular regions and sub-cortical region which in turn usually doesn't respond well in systemic administration of drugs[87]. Further the constant and exchange of CSF helps disperse nanoparticles and also prolonged their retention time and efficient interaction with inflamed tissues[88]. In cells, endocytic uptake mechanisms of NPs into neurons, microglia, astrocytes, macrophages and other neural cells include clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and phagocytosis. After entering the cells, they are moved to the cells of intracellular organizations that release drug encapsulated or their natural properties can be manifested, so as to achieve greater internalization[89,90]. Cellular entry has effectively increased antibacterial efficacy against *Mycobacterium tuberculosis* in neurons of host cells, infected macrophages and microglia, as well as regulating inflammation signaling pathways[91]. Finally, phytochemicals existing on green-synthesized NPs increase cellular affinity and non-specific toxicity to the neural tissues while the specifically targeted cells with inflammatory can be interacting with the enhanced affinity NPs[92].

6.3 Controlled Drug Delivery Through the Cerebrospinal Fluid

One the main advantages of AgNPs based drug delivery system includes the sustained and controlled release of drugs inside the CSF. Unlike the typical preparations in which the dosing may require repetitive administration and in which drug concentrations can increase or decrease periodically, AgNPs can retain adequate amount of drugs for prolonged time for the treatment of pathogens orinflammation[93,94]. Controlling drug release property based on varying parameters such as nanocarrier size, topography, surface, nature of bio capping substances, drug nanoparticle conjugation is one of the other reasons why using AgNPs can results in gradual diffusion of the drug and improved drug in to cells, decrease the dosing frequency and lessen adverse effects in other body[95]. Additionally, the green-synthesized AgNPs not only perform as nanocarriers but also have inherently

biological effects that are synergistic to that of therapeutic drugs[96]. Their biological roles include, antibiotic capability, antibacterial effects from dismembering bacterial membranes and blocking bacterial protein and nucleic acid production, and death of bacterial cells induced through generated responsive oxygen species antioxidant and anti-inflammatory capability, antioxidants elimination of harmful responsive oxygen species and anti-inflammatory capability in a manner by inhibiting formation of TNF-, IL-1, IL-6, NF-B signaling and NLRP3 inflammasome[97,98]. Accordingly, CSF-directed AgNPs serve as multipurpose therapeutics that may promote the penetration through blood-CNS obstacles, intracellular drug delivery, sustainable drug release as well as decreasing neuroinflammation and improving therapeutic outcome for neurotuberculosis[99].

7. THERAPEUTIC MECHANISMS OF GREEN-SYNTHESIZED SILVER NANOPARTICLES

7.1 Anti-inflammatory and Antioxidant Mechanisms

Neuroinflammation and oxidative stress form interconnected pathological cascade mechanisms and results in the neuronal injury. AgNPs derived green-synthesized AgNPs showed powerful anti-inflammatory property by managing various inflammatory signaling and limiting exaggerated immunity responses[100]. Different plant phytochemicals that coat surfaces of AgNPs are augmenting bioactivity by controlling core mediators such as NF-kappaB (NF-kappaB), NLRP3 inflammasome, mitogen activated protein kinase (MAPK) and JAK/STAT signaling paths and as such this is associated with lower the expression of pro-inflammatory cytokines such as TNF-alpha (TNF-alpha), IL-1beta, IL-6 and IFN-gamma and restricting activation of microglia and astrocyte cells and resulting in attenuation of chronic neuro-inflammation[101,102]. Moreover, the green-synthesized AgNPs exhibits remarkable antioxidant activity attributed to the biologically active plant extracts, including flavonoids, phenolic compounds, and terpenoids which are considered as free radical scavengers which actively respond toROS (reactive oxygen species) and RNS (reactive nitrogen species), minimizing lipid peroxidation, maintain functioning of mitochondria, prevents damaging the intracellular DNA, lipid and proteins, thus restores redoax balance thereby breaking cascade of inflammation thereby reducing neuronal loss and improves overall therapeutic outcome in patients having neuroinflammatory conditions[103,104].

7.2 Anti-Mycobacterial Activity and Neuroprotective Effects

Green-synthesized AgNPs possess the advantages of large specific surface area and good biocompatibility and are effective against a wide range of pathogens and has been found to be significant in controlling *Mycobacterium tuberculosis*[105]. Multiple complimentary mechanisms are attributed to antimicrobial activity of AgNPs, such as damage the cell wall and membrane of mycobacteria, producing intracellular oxidative stress, inhibition the metabolic pathways of mycobacteria such as interfering with essential metabolic enzymes, disrupting the process of replication of DNA and protein synthesis and inhibiting biofilm formation[106,107]. Multiple mechanisms may be able to efficiently kill bacteria and decrease the possibility to occur resistant. The small size of AgNPs ensures it interacts effectively with both infected and non-infected host cells, such as macrophages and microglia, therefore promotes intracellular killing effects on the intracellular bacilli[108]. The neuroprotective actions of the green-synthesized AgNPs do not stop with their antimicrobial benefits. Their ability to curb inflammatory related injuries to neuronal cells while supporting cellular viability and restoring typical cells viability via lowering oxidant stressors and inflammatory compounds prevent apoptotic changes to neuronal cells, preserves cell connections and function of mitochondria of cells[109]. The phytochemical of the coating increases the compatibly of neuronal tissues to nanomaterial and decreases cytotoxicity to cells. These effects together enable neural tissues against degenerative disorders, facilitate cell-to-cell interaction and preserve the overall neural functionality for restoring from CNS infection[110,111].

7.3 Preservation of Blood–Brain Barrier Integrity

Disruption of blood-brain barrier (BBB) is one of key features of neuroinflammation and neurotuberculosis that not only allows inflammatory cells to infiltrate into the CNS, causing edema and spread of inflammation but also aggravates inflammatory injury[112]. Green-synthesized AgNPs inhibit BBB breakdown by decreasing the activated synthesis of inflammatory cytokines and oxidative stress-mediated injury that contributes to endothelial dysfunction. MMP activation is down-regulated, and the tight junction proteins Claudin,

occludin, and zonula occludens are protected that restores the BBB function and limits vascular permeability[113,114]. Maintenance of BBB function protects the CNS from further invasion of pathogen, infiltration of immune-inflammatory cells and sets up a favorable environment for tissue repair and treatment[115]. All above beneficial effects such as anti-inflammation, antioxidation, reduce load of bacteria, protection of neuron and BBB integrity are combined into the multifunctional nanotherapeutic of green-synthesized AgNPs, that act complementarily to contribute for management of neurotuberculosis and other neuroinflammatory diseases[116].

8. THERAPEUTIC POTENTIAL IN NEUROTUBERCULOSIS

8.1 Targeting *Mycobacterium tuberculosis* and Modulation of Neuroinflammation

Green-synthesized AgNPs hold potential as neurotuberculosis therapeutic due to the possibility of both attacking both *Mycobacterium tuberculosis* in CNS and controlling damaging excessive inflammation at same time[117]. After entering BBB or administration in CSF, AgNPs would localize to the site of inflammation and may even get together with intravcellular tubercle bacili that locate intracellularly inside macrophages, microgliacells orgranulomatuos lesion, where they kill bacillus by acting directly, they damage the bacilli cell wall, increase production of ROS, inhibitm important enzymatic process that involved inthe cellular activity of Mycobacterium interfere with DNA repair and protein synthesizing system and decreases the load of bacillus in the brain[118,119] . In addition to the directly anti-mycobacterial activities, green-synthesized AgNPs can also exert strong immunomodulatory action, down-regulating the inflammation occurring in the central nervous system by preventing NF-B activation and reducing the activation of NLRP3 inflammasome pathway[120]. This is supported by significantly lower levels of major pro-inflammatory cytokines including TNF, IL-1, IL-6 and IFN and mitigated activation of activatedmicroglia, astrocytes, andoxidative stressin theCNS[121]. Hence, AgNPs present a dual action against both bacterial pathogen and inflammatory triggered neuronderangement, which suggests AgNPs could be applied as an anti-tuberculosis agent against neurotuberculosis[122].

8.2 Enhancement of CNS Drug Delivery and Preclinical Progress

One of the major advantage of green-synthesized AgNPs could be to increase drug delivery to the CNS (e.g. It was shown that AgNPs can get the drug in the CNS by targeting the blood-brain barrier)Because the AgNPs are of nano size and have good surface functionality they can overcome the CNS barrier, could deliver efficiently drugs in the cerebral spinal fluid and in intracellular bacteria[123,124]. They help the increased bio-availability, decrease of dosage and toxicity of antituberculous drugs, increase drug effectiveness toward the intracellular and the hard to reach tubercle bacilli. The AgNPs could function also as multifunctional nanocarrier as they have themselves antibiotic, antioxidant and anti-inflammatory effects beside drugs delivery[125]. Both preclinical investigations showed green synthesis Ag NPs had promising activity against *Mycobacterium tuberculosis*, inhibition of neuroinflammation cytokines, alleviating neuroinflammation associated oxidative stress and promotion neuronal survival at low cytotoxicity levels comparing to the NPs derived from chemical methods[126]. Despite most studies are at the preclinical or animal levels currently the data are encouraging enough for their consideration of the next generation nanotherapeutics for neurotuberculosis[127]. However, more studies are essential to optimize Nanoparticle formulation, long-term biosafety assessments and standardization for large-scale synthesis as well as to demonstrate its clinical effects and tolerability via carefully controlled translational or clinical trials[128].

9. SAFETY CONSIDERATIONS AND TRANSLATIONAL CHALLENGES

9.1 Neurotoxicity and Long-Term Biocompatibility of Green-Synthesized Silver Nanoparticles

Even though green-synthesized silver nanoparticles (AgNPs) exhibited a potent therapeutic efficacy against neurotuberculosis, application in clinical settings warrants safety assessment of therapeutic outcomes and evaluation of long-term biocompatibility in the host[129]. A variety of physical and chemical parameters such as size, morphology, charge, concentration, covering, dose, route of exposure, and period of contact of NPS affect biological activities, which can result in the overload of NPS in the central nervous system

(CNS), causing overproduction of reactive oxygen species (ROS), mitochondrial malfunction, calcium homeostasis disturbance, inflammation, and programmed cell death of neuron-neurotoxicity. Thus to attain the best tradeoff between therapeutic advantages and biological disadvantages, NPS properties were optimized to a maximum[130,131]. One of the primary benefits of using plant extracted phytochemistry as green reductant and capping agents (bio molecules) for nanoparticle synthesis compared with traditional chemical approaches includes greater particle stability, lesser aggregation, increased biocompatibility, and less non-specific toxicity[132]. However, the in vivo biodegradation, metabolism, biodistribution, and clearance profile, accumulation of tissues, immunogenicity, and toxic effects following repeated or chronic exposure, are still scanty, therefore thorough in-vivo studies are urgently warranted prior to routine use of green synthesized AgNPs in clinical setup to address the safe dosage, repeat dose toxicity assessment, and overall outcomes of clinical trials[133,134].

9.2 Challenges in Clinical Translation

Even though the initial preclinical studies demonstrated promise, a set of issues that were holding the true therapeutic application (clinical translation) of nanoparticle based on AgNPs were yet prevailing[135]. Poor standardization of green-synthesis methodologies was the leading reason in the limitation as the variation in the plant material used, its constituents, the mode and conditions of the reaction, as well as the purification process can ultimately lead to different sizes of nanoparticles, their morphological appearance, surface features, size, stability and most importantly to varying degrees of bioactivity. This in turn can produce misleading results that do not appear in other study labs[136,137]. Additional translational hurdles are associated with mass production, batch-to-batch uniformity, storage stability, sterilization, optimal formulation, and economical production[138]. Additionally, knowledge about the pharmacokinetic parameters of nanoparticle behavior (biodistribution, interaction with plasma proteins, interaction with immune system, and pathways for clearance) is important to determine future application as drugs in humans[139]. These problems are to be circumvented with rationales, appropriate procedures for standardized fabrication, effective QC as well as appropriate study designs at pre-clinical and clinical stages[140].

9.3 Regulatory Considerations and Future Clinical Implementation

Successful clinical utilization of green-synthesized AgNPs necessitates strict adherence to stringent regulatory guidelines and regulations governing nanomdicines. Regulators demand comprehensive characterization of physicochemical properties of the nano-entity, such as particle size, distribution, morphology, charge, purity, crystallinity, stability, and surface chemistry[141,142]. Regulatory authorities further expect rigorous assessment of the in vivo based parameters such as pharmacokinetic profiles, organ distribution, bio-degradability, toxicity profiles (including immunotoxicity, genotoxicity, etc. of AgNPs), environmental aspects, and other related studies[143]. In addition the manufacturing facilities should also follow regulatory quality management system such as GMB and GLP. Further development also needs Good Laboratory and Manufacturing Practice[144]. Moreover, at the immediate term to facilitate clinical translation, the collaboration among nanotechnologists, drug designers and pharmacists, microbiologists, neurologists, as well as clinicians and regulatory bodies, would be inevitable and necessary[145]. Therefore, harmonizing regulatory guidelines, standardizing green-synthesis procedures, setting up validating standard safety assessment models and accumulating evidence from robust preclinical studies to ensure a safe, efficient, and ultimately clinic ready green-synthesized AgNP based therapy are of paramount importance to effectively tackle neurotuberculosis and neuroinflammation related challenges[146,147].

10. FUTURE PERSPECTIVES

New approaches in nanotechnology, precision medicine, and enhanced drug delivery are poised to redefine the future treatment of neurotuberculosis (NTB). Green-synthesized silver nanoparticles (AgNPs) serve as a remarkable multifunctional nanoplatform that goes beyond general antimicrobial therapy they may offer simultaneous targeted drug delivery, immunomodulatory effects, antioxidant and neuroprotective functionalities, etc[148]. Future research must continue to focus on functionalization of green-synthesized AgNPs with disease targeting molecules like specific antibodies, peptides, aptamers, and other receptors that can selectively target inflammatory tissues of the brain, reactive microglial and infected macroglial cells and cerebrospinal fluid (CSF) compartments and thus achieve maximum therapeutic effects and minimum adverse effects[149]. Integration of NTB responsive nanoparticles with smart responsive mechanisms including stimuli responsive drug delivery systems

based on changing pH, reactive oxygen species (ROS), inflammation induced cytokines, presence of some microbial enzymes and other pathophysiologic events can lead to a localized sustained and site-specific release of drugs within the brain[150]. Combined administration of AgNPs in synergy with anti-Tubercular first line drugs, anti-inflammatory and antioxidant agents, immunomodulators and gene based therapy could further enhance the efficacy by reducing MTBI, mitigating chronic neuroinflammatory response, oxidative injury and enhancing blood-brain barrier integrity and neuronal functional repair respectively[151,152]. Advances in targeted nanomedicine powered by biomarker driven patient selection, AI based design of nanoparticles, computational modelling and personalized medicine approach might allow optimisation of characteristics of nanoparticles and therapeutic strategies tailoring towards specific diseases[153]. But successful translation and application of nanoparticles in clinical scenarios will demand standardisation of green synthesis methods, ease for GMP compliant large-scale production, thorough pharmacokinetics, biodistribution and toxicologic evaluation, long-term clinical trials on multiple sites[154]. All these are the major drivers to define green-synthesized AgNPs as future nanotherapeutics for not only neurotuberculosis (NTB) but for many other CNS infectious diseases and neuroinflammatory conditions[155].

11. CONCLUSION

Neurotuberculosis remains a highly devastating infectious Central nervous system (CNS) diseases, primarily because host defense against *Mycobacterium tuberculosis* is undermined due to an imbalance between bacterial persistence, neuroinflammatory responses, oxidative stress and limited penetration of medications to the CNS via blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) or into the Cerebrospinal Fluid (CSF). These Challenges consequently limit efficacy of conventional anti-tuberculosis therapy and call for urgent next-generation nanomedicines capable of enhancing CNS drug penetration while ameliorating brain inflammation and pathology. Cerebrospinal Fluid (CSF) is selected as a desirable delivery and therapeutic target in CNS because CSF plays critically important physiological and immunological role in maintaining homeostasis in and around brain and spinal cord, which permeates these tissues extensively. As we have shown and proved in this review, that versatile green-synthesized Silver Nanoparticle (AgNPs) and their combinations with conventional drugs have the inherent capabilities required for targeting the CNS, slow release the cargo into the CNS , amplifying the antimicrobial efficiency against *M. Tuberculosis* and targeting inflammatory reactions. More than acting as solely micro-bacterial eliminator, that multifunctional nanoparticle platform has proven capabilities to hit both infectious and host related pathologic process which determine the severity of *M. Tuberculosis* and contribute to more than only suppressing bacterial persistence, rather. While much progress are need toward Long term biosafety, standardard Green-Synthesis and large production of nanomaterials FDA approval Human Trial nevertheless the ever advancing nanotech, nanomaterial engineering, precision health will pave the way toward effective use of nanomedicinies in clinical application. With CSf-target and versatile effects on Neurotuberculosis mediated inflammatory, green-synthesized (AgNPs) provide a novel avenue toward Next generation nanomedicine for Neurotuberculosis by integrating nanotechnlogy brain immunity and CNS drug delivery.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to their institution and faculty members for their support and encouragement during the preparation of this review article. The authors also acknowledge the contributions of the researchers whose published work provided the scientific foundation for this review.

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