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The Potential of Nanobiotechnology in Developing Regenerative Therapies for Ischemic Stroke Patients

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***ABSTRACT** (10 PT)*

Ischemic stroke is a leading cause of disability caused by blocked blood flow to the brain. Conventional treatments such as thrombolysis and thrombectomy are effective but limited by narrow time windows and clinical risks. Nanobiotechnology offers promising alternatives by enabling targeted drug delivery across the blood-brain barrier (BBB). This review discusses the use of nanoparticles—such as TPCD, solid lipid nanoparticles (SLNs), and PLA-PEG-PLA nanomicelles—which show neuroprotective effects by reducing oxidative stress, inflammation, and neuronal damage. These nanoparticles can be designed for passive, active, or stimulus-responsive targeting, increasing drug precision and minimizing side effects. In addition to therapy, nanomaterials improve stroke diagnostics by enhancing biomarker detection (e.g., NSE, NT-proBNP) through advanced biosensors. Some systems also allow for theranostic applications, combining treatment and imaging. Despite their potential, challenges remain in terms of toxicity, long-term safety, and clinical applicability. Further research is essential to translate these innovations into effective stroke therapies.

Keywords : *ischemic stroke, nanobiotechnology, nanoparticle, neuroregeneration, therapy*

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INTRODUCTION

A stroke is the death of brain tissue due to disruption of blood flow, which inhibits the supply of oxygen and nutrients (Vivi *et al.*, 2025). There are two main types of stroke: ischemic stroke, caused by a blockage, and hemorrhagic stroke, caused by a ruptured blood vessel (Prima *et al.*, 2022) with symptoms such as weakness, speech impairment, vision problems, or sudden confusion (Rivier *et al.*, 2025). Ischemic stroke is the most common type of stroke, accounting for about 85% of all cases. It is caused by a blockage in the blood flow to the brain, resulting in the death of nerve cells due to a lack of oxygen and glucose (Dewi & Fitraneti, 2024). Data in Indonesia shows that ischemic stroke is one of the leading causes of death and disability, with a prevalence that has continued to increase over the past five years, reaching 10.9% in 2018 according to Riskesdas data, and most commonly affecting the elderly (Kesuma *et al.*, 2019). Research at Ibnu Sina Hospital in Makassar also shows that ischemic strokes are more common in patients over the age of 66, with major risk factors such as hypertension, atherosclerosis, and the formation of blood clots that block the cerebral arteries, causing irreversible damage to brain tissue (Prayoga & Rasyid, 2022).

Conventional therapy for ischemic stroke usually involves intravenous thrombolytic administration such as alteplase (rt-PA) and mechanical thrombectomy to restore blood flow to the

brain. Administration of rt-PA within the first 4.5 hours after stroke onset, especially within the first 3 hours, has been shown to improve recovery and reduce disability (Tarigan, 2024). Mechanical thrombectomy is effective for occlusion of large vessels within 6 hours, and in certain cases up to 24 hours (Lisnawati *et al.*, 2025).Although effective, both therapies have limitations: rt-PA can cause intracranial bleeding and has certain contraindications, while thrombectomy is limited by facility access and timing (Abdullah *et al.*, 2024). Biotechnology-based regenerative medicine approaches have developed rapidly in recent years, especially in efforts to stimulate the regeneration of nerve tissue damaged by stroke.

One promising treatment approach for ischemic stroke regenerative therapy is nanobiotechnology, which combines nanotechnology with the principles of molecular biology. Nanobiotechnology enables the specific, controlled, and targeted delivery of drugs and biomolecules, including the ability to penetrate the blood-brain barrier (BBB), which has been a major challenge in neurological therapy (Zhu *et al.*, 2024). The use of nanotechnology in neurological therapy for ischemic stroke shows great potential in improving treatment effectiveness through targeted and efficient drug delivery systems. According to a study in Advanced Drug Delivery Reviews, polymer-based nanoparticles can cross the blood-brain barrier (BBB) and deliver neuroprotectants directly to the infarct area, thereby reducing nerve tissue damage (Tian *et al.*, 2021). In addition, research in Materials Advances shows how to use a nanoparticle-based drug delivery system specifically designed to increase penetration into the brain and target ischemic areas specifically (Yuan *et al*., 2021).This literature review aims to examine the latest developments in the use of nanobiotechnology in ischemic stroke regenerative therapy, particularly innovations in nanoparticles, nano delivery systems, and nano-based scaffolds for nerve tissue regeneration. This study also discusses clinical potential and challenges, such as toxicity, stability, and the effectiveness of drug delivery through the blood-brain barrier (BBB).

RESEARCH METHODS

The writing of this article employs a literature review method with a descriptive qualitative approach, aiming to examine the development and potential of nanobiotechnology in regenerative therapy for stroke patients. The literature collection process was carried out using major databases, including Google Scholar, PMC, ScienceDirect, and CellPress.The literature search strategy applied a combination of keywords, namely "nanobiotechnology OR nanotechnology," "nanoparticles AND biotechnology," "ischemic stroke," "nanoparticle therapy," and "neurosystem." The search was conducted in both English and Indonesian languages and limited to publications from 2020 to 2025 to ensure that the information reviewed remains relevant and reflects the latest advancements in this field. The articles included in this study were selected based on specific inclusion criteria, namely that the articles must address ischemic stroke and involve research utilizing or developing nanoparticle technology within the context of stroke therapy. Furthermore, only research articles were included. The exclusion criteria consisted of articles discussing diseases other than ischemic stroke and publications categorized as reviews or other non-research forms.

RESULTS AND DISCUSSION

The search results yielded six articles that met the inclusion and exclusion criteria for this review.

Table 1. **Related Articles The Use of Nanoparticles in the Treatment and Diagnosis of Ischemic Stroke**

No.	Article Title	Types of Nanoparticles	The Effect of Nanoparticles on Ischemic Stroke	Source
1.	*Targeted Treatment of Ischemic Stroke by Bioactive Nanoparticle-Derived Reactive Oxygen Species-Responsive and Inflammation-Resolving Nanotherapies*	TPCD *nanoparticles*	Reduces ROS, reduces inflammation, improves BBB function	(Yuan *et al.*, 2021)
2.	*Melatonin Delivered in Solid Lipid Nanoparticles Ameliorated its Neuroprotective Effects Ii Cerebral Ischemia*	*Solid Lipid Nanoparticles* (SLNs)	Enhances the neuroprotective effects of melatonin, reduces oxidative stress and inflammation, improves neurological function	(Sohail *et al.*, 2023)
3.	*Triblock Copolymer Nanomicelles Loaded with Curcumin Attenuates Inflammation via Inhibiting the NF-κB Pathway in the Rat Model of Cerebral Ischemia*	PLA-PEG-PLA *nanomicelle*	Decreases the expression of NF-κB, TNF-α, IL-1β, and IL-6; reduces nerve tissue damage	(Li *et al.*, 2021)
4.	*Nanotechnology in Stroke: New Trails with Smaller Scales*	Multifungsi (trombolitik + antioksidan)	Overcoming reperfusion injury, expanding the stroke treatment window	(Toljan *et al.*, 2023)
5.	*Enzyme-free Multicolor Biosensor Based on Cu2+-Modified Carbon Nitride Nanosheets and gold Nanobipyramids for Sensitive Detection of Neuron Specific Enolase*	Au NBPs + g-C_3N_4 *nanosheets*	Detection of NSE biomarkers with high sensitivity and multicolor output	(Lin *et al.*, 2019)
6.	*Ultrasensitive Ratiometric Electrochemical Immunoassay of N-terminal pro-B-Type Natriuretic Peptide Based on Three-Dimensional* PtCoNi *Hollow Multi-Branches/Ferrocene-Grafted-Ionic Liquid and* Co–N–C *Nanosheets*	PtCoNi 3D *hollow structure* + Co–N–C *nanosheets*	Rapid and sensitive detection of NT-proBNP biomarkers for stroke diagnosis	(Chen *et al.*, 2021)

Ischemic stroke occurs due to blockage of cerebral blood vessels by plaque or thrombus, causing disruption of blood supply, hypoxia, impaired ATP production, and excitotoxicity through activation of NMDAR receptors (Karki & Manandhar, 2024; Salaudeen *et al.*, 2024). In addition, the release of DAMPs triggers inflammation and further damage through the activation of microglia and the release of proinflammatory cytokines such as TNF-α and IL-1β (Maida *et al.*, 2024). Conventional therapies such as tPA have several challenges, ranging from being limited by a narrow time window and the risk of bleeding (Ahmed *et al.*, 2024), to being ineffective in restoring nerve function. Therefore, a new approach is needed that is safer and capable of promoting neuroregeneration (Yang *et al.*, 2021).

The Role of Nanobiotechnology in Ischemic Stroke Therapy

One study showed that nanoparticles can be modified to penetrate the blood–brain barrier (BBB) and specifically deliver drugs to brain regions affected by stroke (Lv *et al.*, 2022), thereby increasing drug concentration at the target site and minimizing side effects. Nanobiotechnology itself is a science that combines nanotechnology and biotechnology for biomedical applications, such as specific moleculer detection and targeted drug delivery (Khoerunnisa *et al.*, 2025).

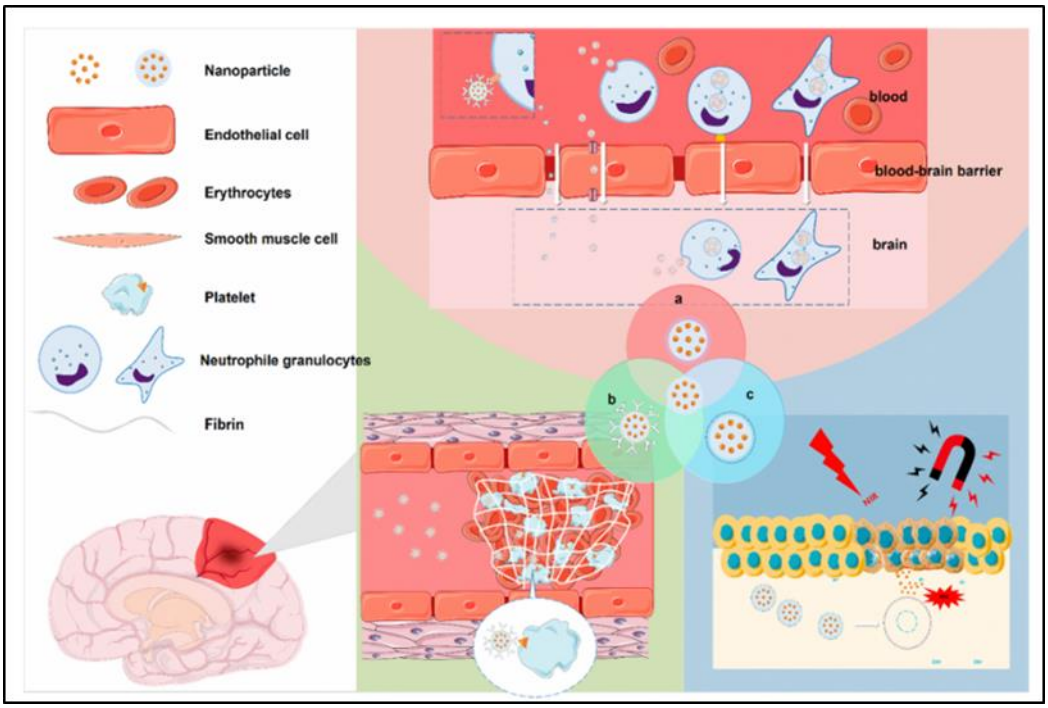

Figure 1. Schematic diagram of targeted NPs in ischemic stroke treatment. (a) NPs targeted to overcome the BBB. (b) NPs targeted for diagnosis and treatment of thrombosis. (c) NPs targeting ischemic tissue (Li *et al.*, 2023).

Drug delivery mechanisms for stroke therapy can be passive, active, or responsive to specific stimuli, such as magnetic fields or changes in the microenvironment of the brain (Xiang *et al.*, 2021). Magnetic nanoparticles, for example, can be directed to the location of a blood clot and release thrombolytic drugs in a controlled manner (Shen *et al.*, 2021), while other nanoparticles can carry anti-inflammatory agents to reduce tissue damage (Ren *et al.*, 2024). There are three main strategies in the use of nanoparticles: (1) Passive targeting, where nanoparticles are modified to remain in the blood circulation longer; (2) Active targeting, by adding active ligands to the surface of nanoparticles so that they can recognize and bind to specific targets in the brain, such as certain proteins in blood-brain barrier (BBB) endothelial cells; and (3) Stimulus-responsive targeting, where nanoparticles are designed to release drugs in response to certain stimuli in the brain environment, such as changes in pH, enzymes, or magnetic fields. For example, magnetic nanoparticles can be directed to the location of a blood clot using an external magnetic field, then release thrombolytic drugs locally to destroy the clot more effectively and safely. In addition, nanoparticles can also carry anti-inflammatory or neuroprotective agents to protect brain tissue around the infarct area (Li *et al.*, 2023).

foundation in the development of more specific and multifunctional ischemic stroke therapies. In addition to therapy, nanoparticle systems are also used in diagnosis and brain tissue protection. Nanomaterials help improve the sensitivity of biomarker detection such as GFAP, S100B, and MMP-9 (Dagonnier *et al.*, 2021). Lin *et al.* (2019), developed a multicolor biosensor based on Au NBPs to accurately detect NSE **(Table 1)**. Chen *et al.* (2021), designed PtCoNi and Co–N–C-based electrochemical immunosensors to detect NT-proBNP, which contributes to the rapid and sensitive monitoring of stroke patients' cardiovascular conditions **(Table 1)**.

Nanoparticles as a Solution for Ischemic Stroke Therapy Through BBB (Blood-Brain Barrier) Targeting

Nanobiotechnology-based approaches are now increasingly being developed as an additional therapeutic strategy for ischemic stroke, with a focus on the ability of nanoparticles to target the blood-brain barrier (BBB) (Thangudu *et al.*, 2020). Some types of nanomaterials not only function as drug carriers, but also have direct therapeutic effects that support brain tissue recovery (Dong *et al.*, 2020). One study conducted at the Third Military Medical University (Army Medical University), Chongqing, China showed that TPCD nanoparticles that are responsive to oxidative stress are able to reduce ROS production, reduce inflammation, and improve blood-brain barrier (BBB) function in a mouse model with ischemic stroke (Yuan *et al.*, 2021). BBB damage is one of the main consequences of ischemic stroke, occurring both during blockage and when blood flow returns (reperfusion). This damage causes leakage that allows harmful molecules to enter brain tissue. Although risky, this condition opens up opportunities to utilize nanoparticles as a more efficient drug delivery system to the brain (Gao *et al.*, 2023). Meanwhile, research by Toljan *et al.* (2023), emphasizes the importance of designing nanoparticles that can carry both thrombolytic agents and antioxidants, thereby addressing the risk of reperfusion injury and expanding the therapeutic windowi **(Table 1)**. Ji *et al.* added that more than 98% of small molecule drugs cannot naturally penetrate the BBB, requiring nanoparticle engineering that enables selective and specific penetration into ischemic tissue. Systems such as tPA-DPNs and SHp-RBC-NP have been designed to prolong drug circulation time, improve stability, and reduce systemic toxicity by directing the therapeutic load directly to the affected area of the brain (Ji *et al.*, 2024).

A similar approach was developed by Paris et al., who used RGD peptides to help nanoparticles adhere better to the walls of cerebral blood vessels (endothelial cells), allowing the drugs carried by the nanoparticles to more easily enter and work in the area affected by stroke. In addition, these nanoparticles can also be activated by light (through photothermal and photodynamic effects) to help accelerate tissue recovery (Paris *et al.*, 2020). Research by Nong *et al.* (2024), also shows that the use of lipid nanoparticles targeted at the blood-brain barrier (BBB) can increase the effectiveness of neuroprotective therapies such as Ferrostatin-1, which significantly strengthens protection against brain damage caused by ischemic stroke through increased drug distribution in the target area. In line with BBB targeting efforts, Sohail *et al.* (2023), developed solid lipid nanoparticles (SLNs) containing melatonin (MLT-SLNs) to improve the bioavailability and neuroprotective effects of melatonin. In an ischemic stroke mouse model, MLT-SLNs showed improved neurological recovery, reduced infarct size, and decreased oxidative stress and inflammation compared to regular melatonin, through activation of the NRf2/HO-1 pathway and suppression of TNF-α and NF-κB expression **(Table 1)**. Similar findings were also reported by Li *et al.* (2021), who designed nanomicelles from PLA-PEG-PLA triblock copolymers (NC) containing curcumin and evaluated their anti-inflammatory effects in a mouse model with cerebral ischemia or reperfusion injury (I/R). The results showed that NC significantly reduced the expression of NF-κB protein and inflammatory cytokine levels such as TNF-α, IL-1β, and IL-6, while also reducing oxidative stress and nerve tissue damage, thus demonstrating strong potential as a neuroprotective agent in ischemic stroke therapy **(Table 1)**.

In addition, nanoparticle- and nanoconjugate-based approaches have also been used specifically to treat strokes caused by large blockages (ELVO). Encapsulating tPA in nanoparticles for therapeutic purposes may be a safer and more targeted method, reducing the risk of bleeding, accelerating recanalization, protecting brain tissue from reperfusion injury, and extending the window of opportunity for drug administration (Draxler *et al.*, 2019). Various nanoparticle platforms have also been modified with specific ligands or antibodies on their surfaces to increase affinity for receptors that are overexpressed in areas of the brain affected by ischemia, such as transferrin receptors (TfR) and integrins. This approach improves targeting efficiency to brain tissue and avoids non-specific distribution to other organs (Thomsen *et al.*, 2022; Zhao *et al.*, 2022). In addition, the combination of nanoparticle delivery technology with active biomolecules such as siRNA, neuroprotective peptides, or growth factors opens up opportunities to accelerate the process of neuroregeneration and reduce secondary damage after stroke (Bernardo *et al.*, 2021). Advances in nanoparticle design now enable more programmed drug release control through responses to specific stimuli in the brain environment, such as changes in pH, enzymes, temperature, or free radical levels. This system is called stimulus-

responsive nanoparticles, which are capable of releasing their therapeutic payload only when they reach ischemic areas, thereby reducing toxicity to healthy tissue (Wu *et al.*, 2024). In addition to their therapeutic function, a number of studies have also shown that nanoparticles can act as theranostic agents, combining therapy and diagnosis. This system enables early detection of ischemic areas and real-time monitoring of treatment effectiveness through the labeling of nanoparticles with imaging agents, such as fluorescent agents or MRI contrast agents (Lapusan *et al.*, 2024).

Although experimental studies have demonstrated the success of nanoparticles in drug delivery and brain tissue regeneration, their long-term effectiveness and clinical safety remain unknown. The complexity of interactions with biological systems and the potential toxicity influenced by particle size, shape, charge, and solubility pose challenges that need to be further investigated.We would like to express our gratitude to our supervisors and all those who have contributed to the preparation of this literature review.

CONCLUSION

Nanobiotechnology has great potential in ischemic stroke regenerative therapy through precise drug delivery, BBB penetration, and reduction of inflammation and oxidative stress. The use of nanoparticles such as TPCD, SLNs, and curcumin nanomicelles has been shown to enhance neuroprotective effects and nerve tissue repair. This technology also supports stroke diagnosis through the detection of more sensitive biomarkers. However, challenges such as toxicity, stability, and long-term effectiveness still need to be studied before it can be applied clinically.

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