허혈성 뇌졸중에서 신경 보호 및 실시간 활성산소(ROS) 모니터링을 위한 치료-진단 융합형 구리-프러시안 블루 나노자임

아닉 쿠말 칼 [1], 라제쉬 마두빌라쿠 [1], 홍용근 [1,2,3*]

[1] 인제대학교 일반대학원 디지털항노화헬스케어학, [2] 인제대학교 일반대학원 재활과학, [3] 의생명보건대학 물리치료학과, 인제대학교, 대한민국

Theranostic Cu-Prussian Blue nanozyme for neuroprotection and real-time ROS monitoring in ischemic stroke

Anik Kumar Kar[1], Rajesh Madhuvilakku[1], Yonggeun Hong[1,2,3*]

[1]Department of Digital Anti-aging Healthcare, Graduate School of Inje University, [2]Department of Rehabilitation Science, Graduate School of Inje University, [3]Department of Physical Therapy, College of Biomedical Sciences & Health, Inje University, Gimhae 50834, Korea

Abstract

Ischemic stroke remains a major cause of mortality and long-term disability worldwide, largely driven by oxidative stress and excessive reactive oxygen species (ROS) generation following cerebral ischemia-reperfusion injury. In this study, we evaluated the neuroprotective potential of mesoporous Copper-Prussian Blue nanoparticles (Meso Cu-PB NPs), a potent ROS scavenging nanozyme, in both in vitro and in vivo models of ischemic stroke. In SH-SY5Y cells, Meso Cu-PB NPs exhibited no cytotoxicity up to 40 μg/mL (10, 20 and 40 μg/mL) and effectively protected against $CoCl_2$ induced hypoxic injury in a concentration-dependent manner. In a rat middle cerebral artery occlusion/reperfusion (MCAo/R) model, intranasal administration of Cu-PB NPs immediately after reperfusion significantly reduced infarct volume, improved neurological function, and enhanced locomotor recovery, with higher doses (10, 20 and 50 mg/kg) showing the most pronounced effects. Golgi-cox staining further demonstrated restoration of neuronal density and dendritic complexity, suggesting enhanced neuronal remodeling and plasticity. Building upon these therapeutic findings, a Cu-PB NPs based wearable sensor device is designed to enable real-time electrocatalytic monitoring of ROS in body fluids (e.g., interstitial fluid). This platform aims to provide continuous assessment of oxidative stress dynamics and support data-driven intervention strategies for stroke management. Collectively, this study highlights the potent neuroprotective efficacy of Meso Cu-PB NPs and introduces a next-generation theranostic platform that integrates nanozyme-based therapy with real-time oxidative biosensing to enable targeted neuroprotection in ischemic stroke.

Keywords: Ischemic stroke, Reactive oxygen species (ROS), Mesoporous Copper-Prussian Blue nanoparticles, Neuroprotection, Real-time ROS monitoring

1. Research background

Ischemic stroke, caused by reduced cerebral blood flow, leads to neuronal death and is the second leading cause of death globally by DALYs (Lin et al., 2023). From 1990-2021, stroke incidence rose 70%, mortality 44%, and disability 32%, costing approximately US$890 billion annually and projected to double by 2050 (Feigin et al., 2025). In South Korea, 8,992 new cases occurred in 2021, 98.5% ischemic, totaling 97,326 cases between 2008-2021, with ischemic stroke causing near about 0.88 trillion KRW in productivity loss (Park et al., 2024; Cha et al., 2018). Reperfusion therapies like tPA and thrombectomy are the only established therapeutic approach till now in the stroke research (Li et al., 2022). Re-establishment of blood flow to the brain causes cerebral ischemia reperfusion injury which leads to a series of pathological changes such as oxidative stress, apoptosis, ferroptosis, parthanatos, neuroinflammation, blood brain barrier breakdown which ends with death of neural cells. (Zhang et al., 2024). Among them oxidative stress plays a vital role after the ischemia reperfusion injury by producing reactive oxygen species (ROS) and reactive nitrogen species (RNS) which overpowers the endogenous scavenging activity and play as an important mediator for cerebral injury (Xue et al., 2017). This unavoidable reperfusion injury is the crucial steps in stroke treatment and becoming the prime target for the treatment of ischemic stroke.

Current approaches primarily utilizing various nanoparticle types such as polymeric nanoparticles, liposomes, cerium oxide nanoparticles, and carbon-based nanomaterials to enhance bioavailability and reduce stroke lesions (He et al., 2021). While nanotechnology offers promising avenues for ischemic stroke therapy, existing nanoparticle-based treatments still present limitations. While nanotechnologies hold considerable promise for treating ischemic stroke, current nanoparticle-based therapies encounter notable drawbacks. A primary concern is their potential neurotoxicity, posing significant safety challenges for brain applications. Beyond this critical health aspect, other general limitations include difficulties with nanoparticle aggregation and stability. (Ji et al., 2024). While, mesoporous-copper–Prussian blue nanoparticles (Meso-Cu-Pb NPs), a novel hybrid nanomaterial with superior and synergistic ROS scavenging capabilities. Prussian blue nanoparticles (PBNPs) are already recognized for their excellent biosafety, FDA approval as an antidote which suggest favorably low intrinsic neurotoxicity (He et al., 2021) and robust multi-enzyme mimetic activities, including catalase and superoxide dismutase-like functions, which effectively scavenge ROS in stroke models(Liu et al., 2023) Crucially, the integration of copper ions ($Cu^{2+)}$ into this framework is anticipated to provide a synergistic enhancement in catalytic efficiency, as Cu^{2+} independently exhibits notable catalase-like behavior due to its redox cycling ability

(Kong et al., 2023) This combined catalytic power is expected to offer a more comprehensive and potent reduction of reactive oxygen species compared to single-component nanoparticle systems, directly addressing the multifaceted oxidative stress characteristic of cerebral ischemia-reperfusion injury. Furthermore, this project proposed intranasal delivery of Meso Cu-PB NPs offers a distinct advantage by bypassing the formidable blood-brain barrier, a major impediment for approximately 98% of small-molecule drugs and almost all large-molecule drugs (Jones et al., 2007), facilitating direct and efficient delivery of the therapeutic agent to the ischemic brain while minimizing systemic exposure and potential side effects (Bors et al. 2019). This innovative blend of a highly efficient, dual-action hybrid nanomaterial and a non-invasive intranasal delivery of Meso-Cu-Pb NPs offers a distinct advantage by directly targeting the brain, a strategy that fundamentally differentiates it from many current nanoparticle-based ROS scavenger approaches in ischemic stroke.

Reactive oxygen species (ROS) are central biomarkers of oxidative stress and cellular redox balance, with critical implications in both physiological signaling and pathological damage. The ability to detect and differentiate multiple ROS species, along with key redox partners such as reduced glutathione (GSH), is essential for advancing diagnostic and therapeutic strategies in diseases linked to oxidative dysregulation. Advances in wearable biosensing have enabled real-time, non-invasive tracking of clinically relevant molecules such as glucose and hydrogen peroxide via electrochemical detection in interstitial fluid (Liu et al., 2023). Building on these frameworks, Wang et al. (2024) developed a microfluidic patch (iCares) for continuous monitoring of ROS in wound exudate, and Singh et al., (2023) introduced a microneedle-enabled enzymatic sensor for in situ H_2O_2 detection in plant tissues—demonstrating translational potential for wearable ROS sensing in human clinical care. Together, these studies support the feasibility of a dual-platform innovation: 1) Therapeutic approach by using Meso Cu-PB NPs as ROS scavenger for ischemic stroke treatment (2) a novel, minimally invasive, wearable electrochemical sensor for real-time H_2O_2 monitoring in post-stroke patients-addressing both systemic redox profiling and continuous oxidative stress surveillance at the point of care.

2. Research methods

2.1 Synthesis of mesoporous copper Prussian blue nanozymes (Meso-CuPB nanozyme): The techniques for synthesizing mesoporous Cu-PB nanozymes are summarized from our prior study (Madhuvilakku et al, 2023) as follows:

Step 1: Synthesis of Prussian Blue Microcubes (PBMCs): 131.72 mg of $K_4[Fe(CN)_6]\cdot 3H_2O$ and 3 g of PVP were dissolved in 40 mL DI water containing 0.01 M HCl under stirring for 30 min. The solution was heated at 80°C for 20 h, and the resulting PBMCs were collected by centrifugation (13,000 rpm, 20 min), washed with ethanol and DI water, and dried at 25°C for 24 h.

Step 2: Formation of Mesoporous PBMCs (Meso-PBMCs): 20 mg of PBMCs and 100 mg of PVP were dispersed in 20 mL of 1 M HCl and stirred for 30 min. The mixture was hydrothermally treated at 140°C for 12 h, then centrifuged (13,000 rpm, 20 min), washed, and dried at 25°C for 24 h.

Step 3: Copper Incorporation (Meso-CuPB NPs): 20 mg of Meso-PBMCs, 10 mg of $Cu(NO_3)_2\cdot H_2O$, and 100 mg of PVP were dispersed in 20 mL DI water and stirred for 3 h. Then, 50 mg of $K_4[Fe(CN)_6]$ was added, and the reaction was aged at 80°C for 20 h. The final Meso-CuPB nanozymes were collected by centrifugation, washed with ethanol and DI water, and dried at 25°C.

2.2 Cell culture:

SH-SY5Y cells were maintained in modified eagle medium supplemented with 10% fatal bovine serum and 1% antibiotics (Penicillin, streptomycin) at 37°C in a humidified incubator with 5% CO_2. The media was replaced every 2-3 days. Cells were passaged when they reached approximately 80% confluency.

2.3 Cell Viability Assay:

Cell viability was assessed using the MTT assay SH-SY5Y cells (1×10^4 cells/well) were seeded in 96-well plates and incubated for 24 h at 37°C, followed by treatment with varying concentrations of Cu-Prussian Blue nanozymes (10-160 µg/mL) for another 24 h. For the oxygen-glucose deprivation model, cells were exposed to 300 µM $CoCl_2$ for 24 h (Zhang et al., 2019), then treated with Cu-PB NPs (10-40 µg/mL). Absorbance was measured at 540 nm using a microplate reader.

2.4 Establishment of the transient middle cerebral artery occlusion (tMCAo) model:

Transient cerebral ischemia was induced using the intraluminal suture method (Lee et al., 2014). Rats were anesthetized with 3% isoflurane (30% O_2, 70% N_2O) via mechanical ventilation (Harvard Apparatus, USA). Following a midline neck incision, the CCA, ECA, and ICA were exposed, and the STA and OA were cauterized. A silicone-coated monofilament (Doccol Corp., USA) was inserted through the ECA into the ICA (~18 mm) to occlude the MCA for 90 min, then withdrawn to allow reperfusion. The incision was sutured, and rats were housed individually post-surgery.

2.5 Experimental groups:

Rats were randomly divided into eight groups: Sham, MCAo/R, 1mg/kg Cu-Pb, 2 mg/kg Cu-Pb, 5 mg/kg Cu-Pb, 10 mg/kg Cu-Pb, 20 mg/kg Cu-Pb, 50 mg/kg Cu-Pb. In the Sham group, only a skin incision was made without inducing ischemia. The MCAo/R group underwent transient middle cerebral artery occlusion (tMCAo), followed by intranasal administration of normal saline at the time of reperfusion. For the treatment groups, Cu-PB NPs were intranasally administered at the time of reperfusion in their respective doses.

2.6 Measurement of infarct volume:

Brain infarct volume was assessed 24 h after tMCAo using 2% TTC. Brains were harvested, rinsed with PBS, and coronally sectioned at 2 mm thickness (+4 mm to −6 mm) using a rat brain matrix. Slices were incubated in 2% TTC at 37°C for 15 min, and infarct areas were analyzed using ImageJ. Infarct volume (%) was calculated by using the following formula: Percentage of the lesioned volume (%) = (Volume of the contralateral hemisphere- volume of the non-infarcted tissue in the ipsilateral hemisphere) / Volume of the contralateral hemisphere × 100%.

2.7 Neurological behavioral deficit assessment:

To assess the motor and sensory nerve impairment, we performed modified neurological severity score (mNSS) behavioral test 24 hours after the tMCAo surgery (Lee et el, 2014). The scoring scale varies from 0 (absence) to 18 (severe).

2.8 Open field test:

Locomotor activity was assessed 24 h after MCAo. Rats were placed in the center of an open field (1 m × 1 m) for 10 min in a light- and noise-controlled room. Movement was recorded by an overhead camera, and total distance traveled (cm) was analyzed using automated tracking software.

2.9 Golgi-cox staining and Sholl analysis:

Ipsilateral brain tissue was collected 24 h after MCAo and processed

using the FD Rapid GolgiStain™ Kit. Samples were immersed in Solutions A and B for 2 weeks, followed by Solution C for 1 week. Brains were sectioned at 100 µm using a vibratome, mounted on gelatin-coated slides, and air-dried overnight. Sections were then sequentially treated with distilled water, Solutions D and E, dehydrated with graded ethanol (50–100%), cleared in xylene, and coverslipped with permount. Neuronal images were captured using an Olympus microscope, and dendritic complexity was quantified by Sholl analysis in ImageJ.

2.10 Wearable electrochemical sensor patch for real-time H_2O_2 monitoring

A flexible, multilayered wearable biosensor patch is designed for real-time detection of hydrogen peroxide (H_2O_2) in interstitial fluid (ISF) following ischemia-reperfusion brain injury in rats.

Device Structure and Function:

The patch adheres to the skin and integrates:

- Microneedle array: Polyurethane microneedles (600-800 µm height, 20-50 µm tip, 200-300 µm base) fabricated by soft lithography enable painless, minimally invasive ISF extraction.
- Electrode layer: A three-electrode configuration (working, reference, and counter electrodes) detects H_2O_2 via electrochemical reactions. The working electrode is modified with Cu-Prussian Blue (Cu-PB), providing high catalytic activity and stability. The reference electrode (Ag/AgCl) maintains potential, and the counter electrode (carbon) completes the circuit.
- Capillary-active and hydrogel interface: Ensures uniform ISF contact, hydration, and stable signal transmission without complex microfluidics.
- Nafion membrane: Acts as a selective barrier, allowing H_2O_2 diffusion while blocking interfering species and stabilizing the sensing surface.
- Potentiostat circuit: Applies controlled potential (+0.3–0.6 V vs Ag/AgCl) to drive H_2O_2 redox reactions and converts resulting current into digital signals proportional to H_2O_2 concentration.
- Microcontroller: Digitizes, filters, and processes signals, converting them into quantitative concentration data.
- Bluetooth Low Energy (BLE) module: Enables real-time wireless transmission of data to external devices.
- Power source: A thin, flexible lithium battery powers all components for up to 72 h continuous operation.

This integrated system enables continuous, non-invasive, real-time monitoring of oxidative stress through ISF H_2O_2 levels in rodents model of stroke.

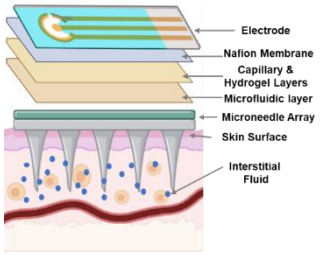

Figure 1: Proposed design of real time ROS monitoring sensor patch

2.11 Statistical analysis:

All data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using t-test (unpaired two tailed) and one-way ANOVA followed by Tukey's post hoc test to determine significance, using GraphPad Prism software. Statistical significance was defined as a p-value below 0.05.

3. Results

3.1 Cytotoxic effect of Cu-PB NPs on SH-SY5Y cells:

To evaluate the potential cytotoxicity of Cu-PB nanoparticles, SH-SY5Y cells were treated with different concentrations 10, 20, 40, 80,160 µg/mL of Cu-Pb NPs for 24 h, and cell viability was assessed using the MTT assay. As shown in Figure 2A, Cu-PB nanoparticles exhibited no significant cytotoxic effect up to 40 µg/mL compared with the healthy control group. However, a gradual decrease in cell viability was observed at higher concentrations (80 µg/mL and 160 µg/mL), suggesting that Cu-PB nanoparticles are biocompatible and safe at concentrations below 40 µg/mL for subsequent experiments. Thus 10, 20 and 40 µg/mL concentration is further used to check the neuroprotective effects of Cu-Pb NPs on hypoxic condition.

3.2 Cu-PB nanoparticles protect SH-SY5Y cells against $CoCl_2$ induced hypoxic condition

To investigate the neuroprotective potential of Cu-PB nanoparticles under hypoxic stress, SH-SY5Y cells were exposed to 300 µM $CoCl_2$ for 24 h to mimic oxygen-glucose deprivation, followed by treatment with Cu-PB nanoparticles (10, 20, and 40 µg/mL). As shown in Figure 2B, $CoCl_2$ treatment markedly reduced cell viability compared with the healthy control ($p < 0.001$). Treatment with Cu-PB nanoparticles markedly improved cell survival in a concentration-dependent manner, indicating that Cu-PB effectively mitigates $CoCl_2$-induced cytotoxicity and provides neuroprotection to SH-SY5Y cells.

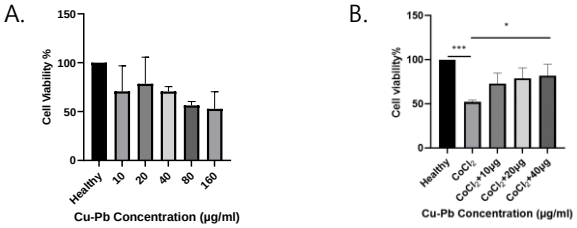

Figure 2: A) Cytotoxicity of Cu-PB NPs in SH-SY5Y cells. B) Neuroprotective roles of Cu-Pb NPs in SH-SY5Y cells against $CoCl_2$ stimulated hypoxia condition.

3.3 Meso-Cu-Pb NPs treatment attenuates the ischemia reperfusion injury:

Cu-PB NPs (1-50 mg/kg) were administered intranasally at reperfusion following 90 min of MCAo. The Sham group received only a skin incision, and the MCAo/R group received saline. After 24 h, brains were collected for infarct volume measurement using 2% TTC staining. The MCAo/R group showed a marked increase in infarction compared to Sham, while Cu-PB NPs treatment dose-dependently reduced infarct volume. Significant reductions were observed at higher doses (10, 20, and 50 mg/kg), whereas lower doses (1 and 2 mg/kg) showed modest effects (Fig. 3A, B).

We performed the Modified neurological severity scale (mNSS) to assess the neurological behavioral deficit. MCAo/R groups showed significant increase of neurological behavioral deficit compare to sham group. But with the treatment of Meso Cu-PB NPs showed significantly improvement of neurological function compare to MCAo/R group indicating neuroprotective effect of meso Cu-Pb NPs. (Fig. 3C)

Open field test assessed locomotor activity after ischemic stroke. The MCAo/R group showed markedly reduced mobility, indicated by shorter travel distance. Low doses (1, 2, and 5 mg/kg) of Cu–PB NPs showed no significant improvement, whereas 10 mg/kg treatment improved mobility. Higher doses (20 and 50 mg/kg) significantly

enhanced locomotor activity compared to the MCAo/R group (Fig. 3D).

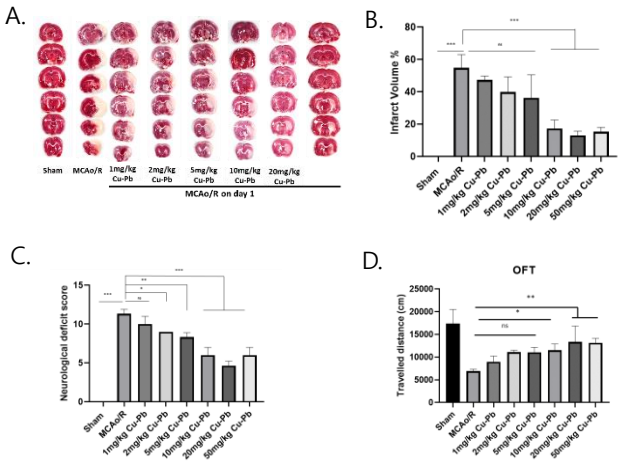

Figure 3: Meso Cu-Pb NPs treatment attenuates cerebral infarction and neurological dysfunction in MCAo/R rats. (A) Representative images of TTC stained brain sections 24 h after MCAo/R. (B) The percentage of infarct volume was calculated by image J software and statistically analyzed, n=3. (C) Quantification of neurological deficit score, n=3. (D) Representation of the total travelled distance (cm) in open field test.

3.4. Assessment of dendritic remodeling and neural density by Golgi-Cox staining:

Golgi staining was performed to measure the neuronal plasticity across the different treatment groups (Fig. 4) In the MCAo/R group showed the loss of dendritic intersection and neuronal density compared to the sham group. Which is restored by the different treatment groups of Cu-PB NPs. Moderate to higher dosage of treatment demonstrates the increase of dendritic intersection and neuronal density. This indicate that therapy with Cu-PB NPs was able to notably improve the dendritic remodeling and neural plasticity in the injured brain.

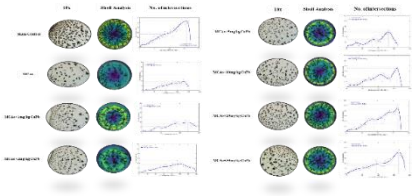

Figure 4: Golgi-cox staining and Sholl analysis provided quantitative assessment of dendritic intersection and neural density following MCAo and treatment with Cu-PB.

4. Acknowledgments

This study was an outcome of the “Gyeongsangnam-do Regional Innovation System & Education (RISE-202502990001 to YH)” Project, supported by the Ministry of Education and Gyeongsangnam-do, Republic of Korea.

5. References

1. Bors, L. A., & Erdő, F. (2019). Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. *Scientia Pharmaceutica*, *87*(1), 6.

2. Cha, Y. J. (2018). The economic burden of stroke based on South Korea’s national health insurance claims database. *International journal of health policy and management*, *7*(10), 904.

3. Feigin, V. L., Brainin, M., Norrving, B., Martins, S. O., Pandian, J., Lindsay, P., ... & Rautalin, I. (2025). World Stroke Organization: Global Stroke Fact Sheet 2025. *International Journal of Stroke*, 17474930241308142.

4.He, W., Zhang, Z., & Sha, X. (2021). Nanoparticles-mediated emerging approaches for effective treatment of ischemic stroke. *Biomaterials*, *277*, 121111.

5. Ji, P., Xu, Q., Li, J., Wang, Z., Mao, W., & Yan, P. (2024). Advances in nanoparticle-based therapeutics for ischemic stroke: Enhancing drug delivery and efficacy. *Biomedicine & Pharmacotherapy*, *180*, 117564.

6. Jones, A. R., & Shusta, E. V. (2007). Blood–brain barrier transport of therapeutics via receptor-mediation. *Pharmaceutical research*, *24*, 1759-1771.

7. Kong, J., Zou, R., Chu, R., Hu, N., Liu, J., Sun, Y., ... & Wang, Y. (2023). An ultrasmall Cu/Cu2O nanoparticle-based diselenide-bridged nanoplatform mediating reactive oxygen species scavenging and neuronal membrane enhancement for targeted therapy of ischemic stroke. *ACS nano*, *18*(5), 4140-4158.

8. Lee, S., Lee, M., Hong, Y., Won, J., Lee, Y., Kang, S. G., ... & Hong, Y. (2014). Middle cerebral artery occlusion methods in rat versus mouse models of transient focal cerebral ischemic stroke. *Neural regeneration research*, *9*(7), 757-758.

9. Li, X., Han, Z., Wang, T., Ma, C., Li, H., Lei, H., ... & Chen, G. (2022). Cerium oxide nanoparticles with antioxidative neurorestoration for ischemic stroke. *Biomaterials*, *291*, 121904

10. Lin, W., Zhao, X. Y., Cheng, J. W., Li, L. T., Jiang, Q., Zhang, Y. X., & Han, F. (2023). Signaling pathways in brain ischemia: Mechanisms and therapeutic implications. *Pharmacology & Therapeutics*, 108541

11. Liu, Y., Yang, L., & Cui, Y. (2023). Transdermal amperometric biosensors for continuous glucose monitoring in diabetes. *Talanta*, *253*, 124033.

12. Madhuvilakku, R., Hong, Y., Nila, I. S., Villagra Moran, V. M., Subramanian, P., Khan, Z. A., ... & You, S. G. (2023). Quantification of neuronal cell-released hydrogen peroxide using 3D mesoporous copper-enriched prussian blue microcubes nanozymes: a colorimetric approach in real time and anticancer effect. *ACS Applied Materials & Interfaces*, *15*(48), 55466-55485.

13. Park, T. H., Cho, Y. J., Park, J. M., Lee, K., Lee, M., Lee, J., ... & Bae, H. J. (2024). Contemporary statistics of acute ischemic stroke and transient ischemic attack in 2021: insights from the CRCS-K-NIH registry. *Journal of Korean Medical Science*, *39*(34).

14. Singh, N., Zhang, Q., Xu, W., Whitham, S. A., & Dong, L. (2025). A Biohydrogel-Enabled Microneedle Sensor for In Situ Monitoring of Reactive Oxygen Species in Plants. *ACS sensors*, *10*(3), 1797-1810.

15. Wang, C., Fan, K., Sani, E. S., Lasalde-Ramírez, J. A., Heng, W., Min, J., Solomon, S. A., Wang, M., Li, J., Han, H., Kim, G., Shin, S., Seder, A., Shih, C.-D., Armstrong, D. G., & Gao, W. (2024). A microfluidic wearable device for wound exudate management and analysis in human chronic wounds. *Science Translational Medicine*, 16(726), eadt0882.

16. Xue, Y., Qu, Z., Fu, J., Zhen, J., Wang, W., Cai, Y., & Wang, W. (2017). The protective effect of astaxanthin on learning and memory deficits and oxidative stress in a mouse model of repeated cerebral ischemia/reperfusion. *Brain research bulletin*, *131*, 221-228.

17. Zhang, M., Liu, Q., Meng, H., Duan, H., Liu, X., Wu, J., ... & Yuan, J. (2024). Ischemia-reperfusion injury: molecular mechanisms and therapeutic targets. *Signal transduction and targeted therapy*, *9*(1), 12.

18. Zhang, M., Liu, Q., Meng, H., Duan, H., Liu, X., Wu, J., ... & Yuan, J. (2024). Ischemia-reperfusion injury: molecular mechanisms and therapeutic targets. *Signal transduction and targeted therapy*, *9*(1), 12.

19.Zhang, K., Tu, M., Gao, W., Cai, X., Song, F., Chen, Z., ... & Tian, M. (2019). Hollow prussian blue nanozymes drive neuroprotection against ischemic stroke via attenuating oxidative stress, counteracting inflammation, and suppressing cell apoptosis. *Nano letters*, *19*(5), 2812-2823.