ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(10): 6965-6968 (2026)
©Biomedical Informatics (2026)

BIOINFORMATION
Discovery at the interface of physical and biological sciences
BIOMEDICAL INFORMATICS
www.bioinformation.net
Volume 22(10)
Review

Received October 1, 2026; Revised October 31, 2026; Accepted October 31, 2026, Published October 31, 2026
DOI: 10.6026/973206300226965

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478
2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Declaration on official E-mail:
The corresponding author declares that lifetime official e-mail from their institution is not available for all authors

License statement:
This is an Open Access article which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. This is distributed under the terms of the Creative Commons Attribution License

Comments from readers:
Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

Disclaimer:
Bioinformation provides a platform for scholarly communication of data and information to create knowledge in the Biological/ Biomedical domain after adequate peer/editorial reviews and editing entertaining revisions where required. The views and opinions expressed are those of the author(s) and do not reflect the views or opinions of Bioinformation and (or) its publisher Biomedical Informatics. Biomedical Informatics remains neutral and allows authors to specify their address and affiliation details including territory where required.

Edited by P Kangueane
Citation: Singla *et al.* Bioinformation 22(10): 6965-6968 (2026)

Neuroprotective interventions in *in vitro* models of hypoxic-ischaemic injury: A review

Rashmi Singla[1], Arsalan Moinuddin[2]*, Ashish Goel[2] & Deepak Goel[3]

[1]Department of Pharmacology, Shri Guru Ram Rai Institute of Medical & Health Sciences, SGRR University, Dehradun, India; [2]Department of Physiology, Shri Guru Ram Rai Institute of Medical & Health Sciences, SGRR University, Dehradun, India; [3]Department of Neurology, Himalayan Institute of Medical Sciences, SRHU, Dehradun, India; *Corresponding author

Affiliation URL:
https://www.sgrrmc.com/
https://srhu.edu.in/medical-sciences/

Author contact:
Rashmi Singla - E-mail: singlarashmi@gmail.com
Arsalan Moinuddin - E-mail: drarsalan.moinuddin@gmail.com

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(10): 6965-6968 (2026)
©Biomedical Informatics (2026)

Ashish Goel - E-mail: drashishgoel2012@gmail.com
Deepak Goel - E-mail: goeld007in@yahoo.co.in

Abstract:
Ischaemic-reperfusion injury after stroke involves oxidative stress, mitochondrial dysfunction and regulated cell death, creating a need for effective neuroprotective targets. Therefore, it is of interest to examine the recent evidence from 2024 to August 2026 on Nrf2-related neuroprotective interventions, with emphasis on SH-SY5Y oxygen-glucose deprivation/reoxygenation models. Recent studies indicate that Nrf2 activation may reduce oxidative stress, preserve mitochondrial function and regulate apoptosis, autophagy, mitophagy and ferroptosis through pathways involving Keap1-Nrf2, Nrf2/HO-1 and Nrf2/GPX4 signalling. Nrf2 therefore represents an important experimental target for neuroprotection, although validation in standardized and more human-relevant models is required before clinical translation.

Keywords: Nrf2, SH-SY5Y, oxygen-glucose deprivation or reoxygenation, neuroprotection, ischaemia-reperfusion, ferroptosis

Background:
Ischaemic stroke continues to impose a major global burden of mortality and neurological disability **[1].** Reperfusion by thrombolysis or mechanical thrombectomy is essential but restored blood flow can contribute to secondary reperfusion injury **[2].** Cerebral ischaemia-reperfusion injury involves oxidative stress, mitochondrial dysfunction and regulated cell-death pathways **[3].** Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulator of antioxidant and cytoprotective responses during cerebral ischaemic injury **[4].** Nrf2 activation has also been linked with reduced ferroptosis and inflammatory injury after cerebral ischaemia **[5].** Recent experimental evidence suggests that Nrf2 activation may reduce oxidative stress and preserve mitochondrial function during reperfusion injury **[6].** Human SH-SY5Y cells exposed to oxygen-glucose deprivation followed by reoxygenation provide an *in vitro* model for studying neuronal injury **[7].** This model has also been associated with ferroptosis and mitochondrial dysfunction, supporting its use in mechanistic neuroprotection studies **[8].** Cellular responses may vary with reoxygenation duration, highlighting protocol-dependent differences in SH-SY5Y OGD/R models **[9].** Therefore, it is of interest to review the recent Nrf2-related neuroprotective interventions in *in vitro* models of hypoxic-ischaemic injury, with emphasis on SH-SY5Y OGD/R models.

Literature search and scope:
Search terms included oxygen-glucose deprivation, OGD/R, SH-SY5Y, neuroprotection, Nrf2, NRF2, Keap1, oxidative stress and ferroptosis. Recent original studies examining Nrf2-related neuroprotective mechanisms were prioritized. Reference lists of relevant articles and recent reviews were also examined. The evidence was synthesized according to the major mechanisms of neuroprotection. Recent studies discussed in this review are summarized in **Table 1**. They mainly evaluated oxidative stress, mitochondrial dysfunction, apoptosis, autophagy, mitophagy and ferroptosis in SH-SY5Y OGD/R models.

Table 1: Recent studies on Nrf2-related neuroprotection in SH-SY5Y OGD/R models

Intervention	*in vitro* model	Nrf2-related mechanism	Main findings	References
Kellerin	SH-SY5Y, OGD/R	Promoted Akt-dependent Nrf2 nuclear translocation; Akt/Nrf2 inhibition weakened protection	Reduced mitochondrial ROS and ferroptosis and improved cell survival	**[11]**
Indobufen	SH-SY5Y, 3 h OGD + 18 h reoxygenation	Increased NRF2 and suppressed ATG5; NRF2 knockdown weakened protection	Increased viability and reduced oxidative stress, apoptosis and excessive autophagy	**[12]**
Epicatechin	Senescent SH-SY5Y, OGD/R	Activated Nrf2/HO-1 signalling; Nrf2 silencing reversed protection	Improved cell survival and antioxidant defence and reduced ROS, MDA and apoptosis	**[10]**
NBP–TMP triazole hybrid, mainly compound 8a	SH-SY5Y, 3.5 h OGD + 12 h reoxygenation	Bound KEAP1 and promoted NRF2 dissociation and nuclear translocation; ML385 weakened protection	Improved viability and mitochondrial function and reduced LDH release, ROS and lipid peroxidation	**[16]**
Cpd.51, Nrf2 activator	SH-SY5Y, OGD/R	Interacted with Keap1 BTB domain and modulated DHRS3–Nrf2 signalling; Nrf2 knockdown attenuated protection	Improved viability, GSH, ATP and mitochondrial function and reduced oxidative injury	**[17]**
Molecular hydrogen (H_2)	SH-SY5Y, 5 h OGD + 12 h reoxygenation	Activated Nrf2/HO-1 and PINK1/Parkin-mediated mitophagy; ML385 reversed protection	Improved viability and mitochondrial function and reduced oxidative stress and apoptosis	**[15]**
Imperatorin-loaded neutrophil-membrane	SH-SY5Y, OGD/R + 24 h reoxygenation	Modulated Nrf2/ARE/Keap1 signalling; ML385 reduced the	Improved cell survival and Nrf2/HO-1 signalling and reduced	**[18]**

biomimetic nanoparticles		protective response	oxidative injury	
Molecular hydrogen (H_2)	SH-SY5Y, OGD/R	Activated Nrf2/GPX4/HO-1 signalling; ML385 abolished protection	Improved viability and mitochondrial membrane potential and reduced apoptosis, oxidative stress and ferroptosis	**[13]**

Nrf2-mediated antioxidant neuroprotection:
Oxidative stress is an important component of neuronal injury during OGD or R. Epicatechin was evaluated in senescent SH-SY5Y cells and increased Nrf2 or HO-1 signalling. It also reduced ROS, MDA and apoptosis while improving cellular survival. Nrf2 silencing reversed these effects and supported functional involvement of the pathway **[10].** The senescence-associated model may provide additional relevance to ageing. However, senescent SH-SY5Y cells cannot reproduce the complex cellular changes occurring in the ageing human brain.

Nrf2 signalling and regulated cell death:
Nrf2-related protection extends beyond classical antioxidant activity. Kellerin promoted Akt-dependent Nrf2 nuclear translocation and reduced mitochondrial ROS and ferroptotic injury. Inhibition of Akt/Nrf2 signalling weakened the protective response **[11].** Indobufen showed a different downstream mechanism. It increased NRF2 activity while suppressing ATG5-related excessive autophagy. This was associated with improved cell viability and reduced oxidative stress and apoptosis. NRF2 knockdown weakened the protective effect **[12].** Molecular hydrogen also influenced ferroptotic injury. It activated the Nrf2/GPX4/HO-1 pathway and improved mitochondrial membrane potential. Oxidative stress, apoptosis and ferroptosis were reduced, while ML385 abolished the protective response **[13].** These findings support interaction between Nrf2 and different forms of regulated cell injury. Ferroptosis involves iron-dependent lipid peroxidation and disruption of antioxidant defence and has been increasingly implicated in neuronal injury after cerebral ischaemia **[14].**

Mitochondrial protection and mitophagy:
Mitochondrial dysfunction contributes to oxidative stress, energy failure and apoptosis during OGD or R injury. Molecular hydrogen improved cellular viability and mitochondrial function in SH-SY5Y cells. The response involved Nrf2 or HO-1 signalling together with PINK1 or Parkin-mediated mitophagy. ML385 reversed the protective effects, supporting Nrf2-dependent regulation of mitochondrial quality control **[15].** Mitophagy may help remove damaged mitochondria before further oxidative injury occurs. However, evidence for this mechanism remains limited and requires confirmation in additional experimental models.

Direct targeting of Keap1-Nrf2 signalling:
Recent studies have moved from indirect Nrf2 activation toward more direct targeting of Keap1-Nrf2 signalling. NBP-TMP triazole hybrid compound 8a interacted with KEAP1 and promoted NRF2 dissociation and nuclear translocation. It improved mitochondrial function and reduced ROS, lipid peroxidation and cellular injury. ML385 weakened its protective effect **[16].** Cpd.51 represented another target-directed approach. The compound interacted with the Keap1 BTB domain and influenced DHRS3-Nrf2 signalling. It improved cellular viability, GSH, ATP and mitochondrial function. Nrf2 knockdown attenuated the protective response **[17].** These studies provide stronger mechanistic evidence than increased Nrf2 expression alone. Direct pathway interaction together with functional reversal helps support a specific role of Nrf2 in neuroprotection.

Emerging therapeutic and delivery approaches:
Imperatorin loaded neutrophil membrane biomimetic nanoparticles represented a different therapeutic strategy. The intervention improved SH-SY5Y cell survival and enhanced Nrf2 or HO-1-related signalling. ML385 substantially reduced the protective cellular response **[18].** The formulation also showed targeted accumulation in ischaemic brain tissue in the *in vivo* component of the study. Nanotechnology-based approaches may improve drug delivery across the blood-brain barrier, although formulation complexity and clinical translation remain important challenges **[19].**

Translational relevance and limitations:
The available evidence is predominantly based on SH-SY5Y cells. This model provides a reproducible system for studying neuronal injury but remains a neuroblastoma-derived cell line. It cannot reproduce interactions among neurons, astrocytes, microglia, endothelial cells and other components of the neurovascular unit. Recent developments in human *in vitro* stroke modelling support the use of multicellular, three-dimensional and neurovascular-unit models. Such approaches may provide greater biological and translational relevance **[20].** Experimental heterogeneity is another important limitation. OGD duration, reoxygenation period, intervention concentration and treatment timing differed between studies. These differences make direct comparison between interventions difficult. Most interventions remain at an early experimental stage. Effective concentrations in cell culture cannot be assumed to represent clinically achievable exposure. Nrf2-dependent cellular protection also does not establish blood-brain barrier penetration, pharmacokinetics, therapeutic window or clinical efficacy.

Future directions:
Future studies should use more standardized OGD or R protocols and clearly report intervention concentration and treatment timing. Direct comparison between promising Nrf2-targeted interventions may improve understanding of their relative mechanisms. Independent replication is also required

for newer interventions. Human-derived neurons, multicellular models and three-dimensional systems may provide greater translational relevance. Clinically achievable concentrations and treatment windows should also be examined.

Conclusion:

Nrf2-related signalling represents a common target across recent neuroprotective interventions in SH-SY5Y OGD/R models. Its effects involve antioxidant defence, mitochondrial preservation and regulation of apoptosis, autophagy, mitophagy and ferroptosis. Mechanistic evidence is strongest when Nrf2 dependence is confirmed by inhibition, gene silencing or direct Keap1-Nrf2 modulation, but more human-relevant models are required before clinical translation.

References:

[1] https://pubmed.ncbi.nlm.nih.gov/39304265/
[2] Awasthi VA *et al. Vascul Pharmacol.* 2024 **156**:107413. [PMID: 39059676]
[3] Saini SK & Singh D. *Mitochondrion.* 2024 **77**:101883. [PMID: 38631511]
[4] Fadoul G *et al. CNS Neurosci Ther.* 2024 **30**:e14462. [PMID: 37715557]
[5] Fan W *et al. Sci Rep.* 2024 **14**:5300. [PMID: 38438409]
[6] Lan X *et al. Redox Biol.* 2024 **77**:103406. [PMID: 39454290]
[7] Cortez IM *et al. Antioxidants (Basel).* 2024 **13**:705. [PMID: 38929144]
[8] Yu S *et al. J Integr Neurosci.* 2024 **23**:14. [PMID: 38287843]
[9] Bermejo IS *et al. Antioxidants (Basel).* 2024 **13**:946. [PMID: 39199193]
[10] Jiang C *et al. Food Sci Nutr.* 2024 **12**:6521. [PMID: 39554346]
[11] Mi Y *et al. Phytomedicine.* 2024 **128**:155406. [PMID: 38520834]
[12] Wang Y *et al. J Pharm Pharmacol.* 2024 **76**:842. [PMID: 38600790]
[13] Wang ZK *et al. Sci Rep.* 2026. [DOI: 10.1038/s41598-026-67710-8]
[14] Tian X *et al. Cell Mol Neurobiol.* 2024 **44**:25. [PMID: 38393376]
[15] Wang Z *et al. J Stroke Cerebrovasc Dis.* 2026 **35**:108645. [PMID: 42049119]
[16] Li G *et al. Redox Biol.* 2025 **86**:103835. [PMID: 40850191]
[17] Sun X *et al. Theranostics.* 2026 **16**:5713. [PMID: 41993611]
[18] Chen F *et al. Int J Nanomedicine.* 2026 **21**:592970. [PMID: 42305693]
[19] Peng B *et al. Bioact Mater.* 2024 **43**:145. [PMID: 39386225]
[20] Pang B *et al. Exp Neurol.* 2024 **381**:114942. [PMID: 39222766]

Caveat Emptor is applicable among the literate community where required and possible. The publisher, its journal, editors and the internal/external reviewers take adequate steps to check, evaluate, correct, edit, revise and improve content where possible and required.