e-ISSN: 2807-7970
doi: 10.20473/aksona.v5i2.70359

AKSONA

Volume 5 Number 2, July 2025

Cerebellar Purkinje Cells and GABA Neurotransmission in the Diabetic Rodent Models: A Systematic Review

Viskasari P Kalanjati[1^], Rayhan B Mahdi[2^], Dwi Martha Nur Aditya[3]
[1] Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2] Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3] Department of Anatomy and Histology, Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia

^ Equal first autor

Article info

Article History:
Received Feb 27, 2025
Revised Apr 21, 2025
Accepted May 7, 2025
Published Jul 31, 2025

Keywords:
Cerebellar Purkinje cells
Diabetes Mellitus
GABA
Oxidative stres

ABSTRACT

Introduction: Hyperglycemia-induced neurotoxicity has been linked to the cerebellum, specifically the impairment of Purkinje cells; its relation to GABA neurotransmission has yet to be cleared. **Objective:** We conducted an updated review on the mechanism of hyperglycemia-induced impairment of cerebellar Purkinje cells in a rodent diabetic model. **Methods:** A modified ScR-PRISMA flow diagram was applied as the screening tool. All English-language research articles published between 2014 and 2024 that containing the purposed topics and were indexed in PubMed and Medline were included. These articles were then critically appraised using the JBI checklist to minimize potential bias. The final inclusion of 8 articles was included for analysis and discussion, together with additional retrieved articles. **Results:** Hyperglycemic-induced subjects demonstrated a marked reduction in Purkinje and granular cell populations, accompanied by several morphological impairments. Alterations were observed in GABAergic inhibitory neurotransmission, including receptors and GABA synthesis, compared to controls. These findings are consistent with observed deficits in motor coordination and cerebellar function. **Conclusion:** Hyperglycemia produces adverse effects on the function and survival of Purkinje cells in the cerebellum. Impaired GABAergic neurotransmission might result as parts of oxidative stress and inflammation induced by hyperglycemia in the cerebellar cells. Taken altogether, these results in motor impairment and cognitive dysfunction.

Corresponding Author
Viskasari P Kalanjati
Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
email: viskasari-p-k@fk.unair.ac.id

Available at https://e-journal.unair.ac.id/index.php/aksona

INTRODUCTION

Hyperglycemia, commonly seen in diabetes, is a pathological condition characterized by elevated blood glucose levels. Chronic hyperglycemia can have detrimental effects on various organ systems, including the central nervous system (CNS). One area that has been implicated in hyperglycemia-induced neurodegeneration is the cerebellum, particularly the Purkinje cells, which are essential for motor coordination and cognitive function.[1] The excitatory signals to the Purkinje cells originate from the parallel fibers, which are the axonal extensions of granule cellsthat receive excitatory inputs from the mossy fibers. Other inputs come from the climbing fibers of the inferior olive, while the inhibitory input provided by the stellate and basket cells, which are known as molecular layer interneurons. The only output of the cerebellar cortices is via the axons of the Purkinje cells, which project to the deep cerebellar nuclei.[2]

Recent studies have highlighted the disruption of GABAergic neurotransmission in the cerebellum as a key factor in the pathophysiology of hyperglycemia-induced motor deficits.[3,4]

OBJECTIVE

In this review, we aimed to examine the effects of hyperglycemia on gamma-aminobutyric acid (GABA) neurotransmission in rat cerebellar Purkinje cells, identify potential research gaps, and outline future directions for investigating therapeutic strategies to mitigate related damage.

METHODS

The Joanna Briggs Institute (JBI) critical appraisal and review methodology was employed to identify and analyze studies investigating the effects of hyperglycemia on Purkinje cells.[5] A systematic search of online databases (PubMed and Medline)[6] was conducted for studies published between 2014 and 2024. Inclusion criteria included original research articles focusing on hyperglycemia, Purkinje cells, and GABAergic signaling in rodent models. Studies involving olther species or article types were excluded. All included studies were screened for relevance and quality. A modified PRISMA-ScR was used for screening process.[6]

This review included English-language articles indexed in PubMed and Medline. The PubMed Advanced Search Builder was used as the filter tool.[7] Searching terms used were found in the abstract and/or the title, i.e. 'hyperglycemia' AND 'Purkinje'. Additional searches were conducted using terms such as 'cerebellar' OR 'cerebellum', AND 'GABA (gamma-aminobutyric acid)', as shown in the PRISMA flow diagram (Figure 1).

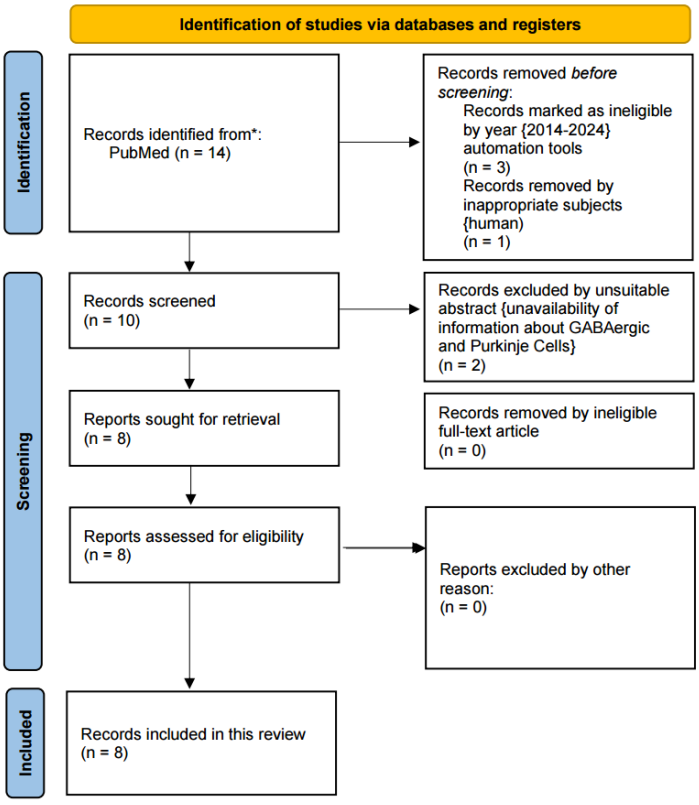

Figure 1. PRISMA flow diagram

RESULTS

The initial screening produced 14 articles. We found more articles about GABAergic neurotransmission in the Purkinje layer of diabetic rodent models through further searches, and we added these to our discussion. Figure 1 illustrates the details of the flow. We summarized the results and detailed the key findings from the included articles in Table 1.

Table 1. Summary of the final findings (n = 8)

Authors	Title	DOI	Key findings
Abdel Fattah S, Waly H, El-enein AA, kamel A, Labib H.[8]	Mesenchymal stem cells versus curcumin in enhancing the alterations in the cerebellar cortex of streptozocin-induced diabetic albino rats. The role of GFAP, PLC and α-synuclein	https://doi.org/10.1016/j.jchemneu.2020.101842	Diabetic rats: Showed significant alterations in cerebellar layers, including abnormal cell organization, vacuolation, and loss of Purkinje cells. Biochemical changes: Increased glial fibrillary acidic protein (GFAP) reactivity, elevated malondialdehyde (MDA) levels, and lower superoxide dismutase (SOD) and glutathione (GSH) levels. Decreased phospholipase C (PLC) and increased α-synuclein levels.
Bak DH, Zhang E, Yi MH, Kim DK, Lim K, Kim JJ, et al.[9]	High ω3-polyunsaturated fatty acids in fat-1 mice prevent streptozotocin-induced Purkinje cell degeneration through BDNF-mediated autophagy	https://doi.org/10.1038/srep15465	STZ-treated fat-1 mice: Did not develop hyperglycemia, motor deficits, or Purkinje cell loss. Autophagic markers: STZ-treated wild-type mice showed increased expression of autophagy-realted proteins LC3-I, LC3-II, Beclin-1, and p62. In STZ-treated fat-1 mice, the expression levels were even higher levels, except p62. BDNF signaling: Increased BDNF expression in Purkinje cells, with no changes in TrkB, but increased phosphorylation of Akt and CREB in fat-1 mice. Protection and therapeutic potential: STZ-treated fat-1 mice were protected from Purkinje cell loss and showed enhanced autophagic flux activity and BDNF signaling. These effects may support Purkinje cell survival and offer potential therapeutic targets for diabetic neuropathy-related motor deficits.
Forero-Vivas ME, Hernández-Cruz A.[10]	Increased firing frequency of spontaneous action potentials in cerebellar Purkinje neurons of db/db mice results from altered auto-rhythmicity and diminished GABAergic tonic inhibition	https://doi.org/10.4149/gpb_2013056	GABAergic inhibition: Blocking GABAergic tonic inhibition with bicuculline changes the firing pattern in wild-type mice but not in db/db mice, indicating that db/db neurons receive weaker GABAergic inhibitory input. Intrinsic firing properties: The intrinsic firing properties of Pukinje neurons (PNs) differ between wild-type and db/db mice . Tonic firing of PNs: Provides a persistent signal to downstream cerebellar targets.
Yang S, Xia C, Li S, Du L, Zhang L, Hu Y.[11]	Mitochondrial dysfunction driven by the LRRK2-	https://doi.org/10.1038/cddis.2014.184	Hyperglycemia and inflammation: The cerebellum of 24-week STZ

Table 1 continued. Summary of the final findings (n = 8)

Authors	Title	DOI	Key findings
	mediated pathway is associated with loss of Purkinje cells and motor coordination deficits in diabetic rat model		diabetic rats exhibited increased levels of proinflammatory cytokines and chemokines. Purkinje cell degeneration: Characterized by axon terminal swellings, impaired autophagosome formation, reduced LC3-II/LC3-I and Lamp2, and accumulation of p62 puncta. LRRK2 pathway: Higher expression of LRRK2-mediated hyperphosphorylation of tau and increased mitochondrial dynamin-like protein (mito-DLP1) in 24-week STZ-diabetic rats. Mitochondrial dysfunction: Overexpression of LRRK2 induces mitochondrial fragmentation and a reduction in protein degradation rates. Motor deficits: Coordinated motor deficits in 24-week STZ-diabetic rates were confirmed through rotarod test. LRRK2-mediated pathway: Induces mitochondrial dysfunction and loss of cerebellar Purkinje neurons, potentially contributing to motor coordination deficits in diabetic neuropathy.
Santoso P, Simatupang A, Fajria A, Rahayu R, Jannatan R.[12]	Andaliman (*Zanthoxylum acanthopodium* DC.) fruit ethanolic extract exerts attenuative effect on hyperglycemia, sensory and motoric function's disorders in alloxan-induced diabetic mice	https://doi.org/10.5455/javar.2023.j716	Sensory and motor balance: Improved paw sensitivity and motor balance. Cerebellar histopathology: Reduced degeneration of Purkinje cells. Oxidative stress: Lower MDA levels in blood and brain tissue.
Kara A, Unal D, Simsek N, Yucel A, Yucel N, Selli J.[13]	Ultra-structural changes and apoptotic activity in cerebellum of post-menopausal-diabetic rats: a histochemical and ultra-structural study	https://doi.org/10.3109/09513590.2013.864270	Degeneration: Degenerative changes in Purkinje cell membranes were observed in both ovariectomy and ovariectomy-diabetic groups, including swollen organelles, degenerated mitochondria, edema formation, and vacuolization. Apoptotic activity: Increased in the ovariectomy and ovariectomy-diabetic groups compared to the control group. Estradiol and insulin deficiency: Affects the cerebellar cortex, supporting the hypothesis of neuronal damage in post-menopausal diabetics.
Seke Etet PF, Farahna M, Satti GMH, Bushara YM, El-Tahir A, Hamza MA, et al.[14]	Garcinia kola seeds may prevent cognitive and motor dysfunctions in a type 1 diabetes mellitus rat model partly by mitigating neuroinfllammation	https://doi.org/10.1515/jcim-2016-0167	Inflammation markers: Increased expressions of TNF, iba1 (CD68), and GFAP, along with decreased neuronal density in motor cortex, medial septal nucleus, and cerebellar Purkinje/granular cell layers

Table 1 continued. Summary of the final findings (n = 8)

Authors	Title	DOI	Key findings
			in diabetic controls, but not in treated animals. Neuroinflammation and neuronal loss: Mediated T1DM-like functional alterations.

Table 1 demonstrates that the reviewed studies consistently revealed Purkinje cell degeneration, dysfunction, and altered neurotransmitter dynamics under hyperglycemic conditions.

Key findings include:

1. GABAergic dysfunction:
   Several studies observed altered GABAergic neurotransmission, contributing to motor coordination and cognitive deficits.[11,15]
2. Oxidative stress:
   Increased oxidative stress was reported to exacerbate cellular damage in Purkinje cells.[12,15]
3. Neuroinflammation:
   Hyperglycemic conditions were found to increase pro-inflammatory citokines expression, compromising the integrity of Purkinje cells.[11,15]
4. Mitochondrial dysfunction and calcium dysregulation:
   Mitochondrial dysfunction, along with calcium dysregulation were identified as major factors contributing to Purkinje cell loss.[11,12]
5. Interventions:
   Various interventions to dampen these adverse effects. Such as antioxidant and anti-inflammatory treatments, showed promise in mitigating hyperglycemia-induced damage.[12,14]

DISCUSSION

Pathophysiology of hyperglycemia in the brain

The relationship between hyperglycemia and the central nervous system, particularly with respect to the Purkinje layer of the cerebellum, is an essential field of neurobiological investigation. The cerebellum plays a vital role in motor control and balance, and its Purkinje cells are critical for processing motor signals. Elevated blood glucose levels, as seen in hyperglycemia, disrupt normal cellular processes, triggering oxidative stress and inflammation that can damage these neural cells. As the connection between glucose metabolism and neurological disorders continues to grow, it is crucial to understand how hyperglycemia impacts Purkinje cells. This review focused on the mechanisms by which hyperglycemia affects the Purkinje layer, with potential consequences for motor function and neurodegenerative conditions. These insights are crucial for developing targeted treatments for disorders associated with hyperglycemia.[14,16]

Chronic hyperglycemia induces a series of cellular and molecular changes that compromise brain function. One of the primary mechanisms by which hyperglycemia affects neuronal function is oxidative stress. Elevated glucose levels increase the production of reactive oxygen species (ROS), which lead to cellular damage in various brain regions, including the cerebellum.[17] An increase in Purkinje cell apoptosis has also been reported following the induction of hyperglycemia.[16]

Morphological and functional changes in Purkinje cells

The combined effects of oxidative stress, inflammation, mitochondrial dysfunction, and calcium dysregulation result in significant changes in Purkinje cell morphology and function. Purkinje cells experience increased apoptosis, reduced numbers, and changes in their dendritic architecture, all of which impair synaptic connectivity and neuronal signaling. These structural changes contribute to the motor coordination and cognitive deficits associated with cerebellar dysfunction in diabetic conditions.[13,17] Moreover, calcium dysregulation furhter exacerbates the functional decline of Purkinje cells.[13] Impaired autophagy has also been implicated in their pathology under hyperglycemic conditions, further diminishing cell survival and function.[16,18] In Purkinje cells, oxidative stress contributes to mitochondrial dysfunction, calcium dysregulation, and inflammation, which impair cellular function and survival. Furthermore, hyperglycemia alters the blood-brain barrier permeability, exacerbating the inflammatory response and facilitating the entry of immune cells into the brain, which further exacerbates neuronal damage.[16,18]

Pathophysiological changes in Purkinje cells

The pathological effects of hyperglycemia on Purkinje cells involve several processes:

1. Oxidative stress

Elevated blood glucose levels lead to the overproduction of ROS, resulting in oxidative damage to cellular structures like lipids, proteins, and DNA. This damage is further compounded by mitochondrial dysfunction, which plays a critical role in neuronal survival. Mitochondrial impairment under hyperglycemic conditions contributes to neuronal apoptosis and increased cell vulnerability.[1]

2. Inflammation

Hyperglycemia activates inflammatory pathways, particularly through the stimulation of microglia and astrocytes. Pro-inflammatory cytokines including TNF-α and IL-6, are released by these cells, causing further damage to neurons and exacerbate Purkinje cell loss. Moreover, disruption of the blood-brain barrier allows harmful substances to reach the cerebellum, thereby intensifying the neuroinflammatory response.[19]

3. Calcium dysregulation

Calcium homeostasis is essential for neuronal signaling and function. Hyperglycemia disrupts calcium channels and transporters, leading to intracellular calcium overload. This overload triggers excitotoxicity and activates apoptotic pathways, resulting in Purkinje cell death. Calcium dysregulation has been shown as a critical factor in hyperglycemia-induced neuronal damage.[10]

4. Impaired neurotransmission

Impaired neurotransmission can manifest as reduced GABAergic signaling, disrupted synaptic plasticity, and decreased motor coordination. All of these impairments are correlated with increased neuronal apoptosis in the Purkinje cells, which alters the synapse to and from this lamina, including those connected to the pons and cortical cerebrum via the corticopontocerebellar tract. This pathway primarily regulates motor coordination and is also involve in the cognitive functions that depend on GABAergic neurotransmission.[10]

GABAergic dysfunction in Purkinje cells

GABA (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the central nervous system (CNS) and plays a crucial role in regulating neuronal excitability and maintaining balance within neural circuits. The GABAρ subunits belong to the ionotropic GABA-A receptor family, which has 19 identified genes encoding an equal number of distinct proteins: α1–α6, β1–β3, γ1–γ3, δ, ε, Θ, π, and ρ1–ρ3. GABA-A receptors are pentameric heterocomplexes, typically composed of α1β2γ2 subunits, which regulate chloride (Cl^-) channel upon activation. Other configurations may include δ, ρ, or ε subunits, each contributing unique functional and pharmacological characteristics. GABAρ subunits can also assemble into homopentameric receptors with a high affinity for GABA (EC50: 1–5 μM) and a low desensitization rate, making them well-suited for tonic transmission. These subunits are mainly found in the retina, where they regulate glutamatergic output in bipolar neurons, but they are also present in other regions of the CNS, like the striatum, hippocampus, and cerebellum, although their precise functions in these areas remain unclear.[20]

GABAρ subunits have been involved in both tonic (extrasynaptic) and phasic (synaptic) transmission in cerebellar Purkinje neurons. GABAρ are also expressed by a significant proportion of ependymoglial cells (EGCs), which are specialized, ciliated glial fibrillary acidic protein positive (GFAP+) cells that facilitate cerebrospinal fluid flow in the fourth ventricle. GABA-activated ion currents in these cells are resistant to pentobarbital and partially inhibited by the GABA-A antagonist bicuculline. This suggests that glial-origin cells, such as EGCs and astrocytes, possess a diverse range of ionotropic GABA receptors that incorporate GABAρ subunits, although their precise functional role remains unknown.[20]

In the cerebellum, Purkinje cells receive GABAergic input from inhibitory interneurons and send GABAergic projections to the deep cerebellar nuclei. Hyperglycemia has been shown to disrupt GABAergic neurotransmission, leading to altered synaptic function and impaired motor coordination. Studies have demonstrated that prolonged hyperglycemia can reduce the expression of GABA receptors, decrease GABA synthesis, and impair GABAergic signaling, all of which contribute to the motor deficits observed in diabetic animals. These changes in GABAergic function are believed to be caused by oxidative stress, altered calcium homeostasis, and the activation of inflammatory pathways that affect the GABAergic system at multiple levels.

Effects of hyperglycemia on Purkinje cell function

Purkinje cells are a critical component of the cerebellum, and their dysfunction is associated with impaired motor coordination, balance, and cognitive processing. Hyperglycemia-induced damage to Purkinje cells has been shown to cause dendritic atrophy, synaptic loss, and decreased firing activity.[21,22] This is accompanied by deficits in motor coordination, including gait disturbances and tremors, which are prevalent in diabetic rodents. The exact mechanisms by which hyperglycemia leads to Purkinje cell damage remain complex and multifactorial, involving a combination of metabolic disturbances, inflammatory responses, and GABAergic dysfunction. In particular, the disruption of GABAergic signaling in Purkinje cells plays a key role in motor deficits, as GABAergic

inhibition is necessary for maintaining proper cerebellar function and coordinating movement.

Strategies to mitigate hyperglycemia-induced Purkinje cell damage

The importance of Purkinje cells in motor coordination and the detrimental effects of hyperglycemia on cerebellar function make it necessary to explore therapeutic strategies aimed at protecting these cells from damage.[8] Current diabetic treatments generally focus on blood glucose control, but these interventions are often insufficient to prevent neurodegeneration and motor dysfunction. Potential therapeutic interventions in reducing oxiadative stress and inflammation in Purkinje cells include the use of antioxidants, anti-inflammatory agents, and calcium homeostasis modualtors.[19] Several studies have reported the potential of specific agents to mitigate the negative effects of hyperglycemia on cerebellar Purkinje cells. For example, compounds such as *Irvingia gabonensis* have shown potential in alleviating these effects, providing a potential therapeutic avenue for restoring cerebellar function in hyperglycemic conditions.

Furthermore, targeting GABAergic dysfunction directly through the use of GABA receptor modulators or agents that enhance GABA synthesis may offer a promising strategy for restoring normal cerebellar function and improving motor coordination in diabetic animals.[23]

Future Directions and Research Gaps

The effects of hyperglycemia on Purkinje cells in the cerebellum present several research opportunities that could significantly enhanc our comprehension of diabetic neuropathy and motor coordination deficits. Although there is mounting evidence on the detrimental effects of hyperglycemia on the brain, further research is needed to explore the precise molecular mechanisms and identify potential therapeutic interventions.[3,16]

1. Exploration of early biomarkers for hyperglycemia-induced damage

One of the key areas for future research is the identification of early biomarkers that can detect hyperglycemia-induced damage to Purkinje cells before the onset of irreversible changes. Early diagnosis is crucial to prevent the progression of neuronal injury and preserve motor function. Research could focus on the role of specific proteins, microRNAs, and metabolites as potential biomarkers for Purkinje cell dysfunction under hyperglycemic conditions.[24]

2. Targeted therapies to protect Purkinje cells

Current therapeutic strategies targeting hyperglycemia-induced neuronal damage are still limited, with most treatments focusing on blood glucose control. Future research should focus on developing targeted therapies to protect Purkinje cells from oxidative stress, inflammation, and excitotoxicity. This could include exploring the use of antioxidants, anti-inflammatory agents, and calcium channel blockers as potential therapeutic options to mitigate neuronal damage.

3. Investigating the role of GABAergic dysfunction

This review study highlights the important role of GABAergic dysfunction in the pathophysiology of hyperglycemia-induced Purkinje cell damage; still, the exact mechanisms by which hyperglycemia alters GABAergic neurotransmission remain underexplored. Investigating the molecular pathways that disrupt GABA receptor function, GABA synthesis, and GABAergic signaling in Purkinje cells could provide new insights into potential therapeutic targets aimed at restoring normal cerebellar function.[4]

4. Animal models for studying long-term hyperglycemia

Most existing animal studies on hyperglycemia-induced neuronal damage in Purkinje cells focus on short-term models. However, the chronic effects of long-term hyperglycemia, as seen in type 2 diabetes, may lead to more complex and persistent alterations to cerebellar function. Long-term animal models that closely replicate the pathophysiology of chronic hyperglycemia in humans are crucial for understanding the progressive nature of cerebellar dysfunction and for testing the efficacy of new therapies.[25]

5. Role of other brain regions in hyperglycemia-induced motor deficits

This review study has focused on the cerebellum; however, other brain regions involved in motor coordination, such as the basal ganglia and motor cortex, may also be affected by hyperglycemia. Future research should investigate the impacts of hyperglycemia on these regions and their interactions with the cerebellum, as this could provide a more comprehensive knowledge of motor coordination deficits in diabetes.[19]

6. Clinical translational studies

In the end, further clinical studies are needed to examine the translation of findings from animal models to human conditions. Although animal models have provided valuable insights into the effects of hyperglycemia on Purkinje cells, human studies are necessary to ascertain the relevance of these findings in clinical settings. Clinical trials exploring potential therapeutic interventions, such as antioxidant treatments, GABAergic modulators, or diabetes management strategies, could provide valuable insights

into the most effective ways to protect cerebellar function in individuals with hyperglycemia or diabetes.[16]

Furthermore, addressing gaps in current research, such as investigating early biomarkers, developing specific therapeutics, and validating findings in clinical settings, will be essential to improving outcomes for individuals with hyperglycemia and diabetes.[16,17] A limited numbers of databases were reviewed, and only publications from the last decade in English were included. Therefore, the results must be taken wisely. Future research should continue to investigate the complex relationship between hyperglycemia and Purkinje cell dysfunction, with the goal of providing novel therapeutic strategies to reduce the impact of hyperglycemia on the brain and restore motor and cognitive function.[2,15]

CONCLUSION

Hyperglycemia profoundly impairs the function and survival of Purkinje cells in the cerebellum, leading to motor deficits and cognitive dysfunction. The underlying pathophysiological processes include oxidative stress, inflammation, calcium dysregulation, and GABAergic dysfunction. Understanding the molecular pathways involved in hyperglycemia-induced neuronal damage is critical for the development of targeted therapies aimed at protecting Purkinje cells and preserving cerebellar function.

Acknowledgement
The authors would like to thank the Faculty of Medicine, Universitas Airlangga, Surabaya.

Conflict of Interest
Authors declared there are no conflict of interest in this research.

Funding
The author declares that there was no support or competing financial interest in this research.

Author Contributions
VPK contributed to formulating ideas, screening articles, and developing manuscripts. RBM and DMNA contributed to screening articles and checking the quality of the records.

REFERENCES

1. Gupta M, Pandey S, Rumman M, Singh B, Mahdi AA. Molecular mechanisms underlying hyperglycemia associated cognitive decline. *IBRO Neurosci Rep*. 2023; 14:57–63; doi: 10.1016/j.ibneur.2022.12. 006
2. Kalanjati VP, Dewi AK, Santoso MWA. Quantitative study on human cerebellar cortex from anatomy cadaver preparations. *Int J Morphol*. 2017; 35(1):167–71; doi: 10.4067/S0717-95022017000100027
3. Perovic M, Pavlovic D, Palmer Z, Udo MSB, Citadin CT, Rodgers KM, et al. Modulation of GABAergic system as a therapeutic option in stroke. *Exp Neurol*. 2025; 384:115050; doi: 10.1016/j.expneurol. 2024.11 5050
4. Tang X, Jaenisch R, Sur M. The role of GABAergic signalling in neurodevelopmental disorders. *Nat Rev Neurosci*. 2021; 22(5):290–307; doi: 10.1038/s41583-021-00443-x
5. Joanna Briggs Institute. Critical Appraisal Tools. 2023. [Web page]
6. Prisma Group. PRISMA Flow Diagram. 2020. [Web page]
7. National Library of Medicine. Accelerating biomedical discovery and data-powered health. 2024. [Web page]
8. Abdel Fattah S, Waly H, El-enein AA, Kamel A, Labib H. Mesenchymal stem cells versus curcumin in enhancing the alterations in the cerebellar cortex of streptozocin-induced diabetic albino rats. The role of GFAP, PLC and α-synuclein. *J Chem Neuroanat*. 2020; 109:101842; doi: 10.1016/j.jchemneu.2020.101842
9. Bak DH, Zhang E, Yi MH, Kim DY, Lim K, Kim JJ, et al. High ω3-polyunsaturated fatty acids in fat-1 mice prevent streptozotocin-induced Purkinje cell degeneration through BDNF-mediated autophagy. *Sci Rep*. 2015; 5(1):15465; doi: 10.1038/srep15465
10. Forero-Vivas ME, Hernández-Cruz A. Increased firing frequency of spontaneous action potentials in cerebellar Purkinje neurons of db/db mice results from altered auto-rhythmicity and diminished GABAergic tonic inhibition. *Gen Physiol Biophys*. 2014; 33(1):29–41; doi: 10.4149/gpb_2013056
11. Yang S, Xia C, Li S, Du L, Zhang L, Hu Y. Mitochondrial dysfunction driven by the LRRK2-mediated pathway is associated with loss of Purkinje cells and motor coordination deficits in diabetic rat model. *Cell Death Dis*. 2014; 5(5):e1217–e1217; doi: 10.1038/cddis.2014.184
12. Santoso P, Simatupang A, Fajria A, Rahayu R, Jannatan R. Andaliman (Zanthoxylum acanthopodium DC.) fruit ethanolic extract exerts attenuative effect on hyperglycemia, sensory and motoric function's disorders in alloxan-induced diabetic mice. *J Adv Vet Anim Res*. 2023; 10(4):608-19; doi: 10.5455/javar.2023.j716
13. Kara A, Unal D, Simsek N, Yucel A, Yucel N, Selli J. Ultra-structural changes and apoptotic activity in cerebellum of post-menopausal-diabetic rats: A histochemical and ultra-structural study. *Gynecol Endocrinol*. 2014; 30(3):226–31; doi: 10.3109/09513590.2013.864270
14. Seke Etet PF, Farahna M, Satti GMH, Bushara YM, El-Tahir A, Hamza MA, et al. Garcinia kola seeds may prevent cognitive and motor dysfunctions in a type 1 diabetes mellitus rat model partly by mitigating neuroinflammation. *J Complement Integr Med*. 2017; 14(3); doi: 10.1515/jcim-2016-0167
15. Solmaz V, Köse Özlece H, Eroglu HA, Aktuğ H, Erbaş O, Taşkıran D. Accumulation of α -Synuclein in cerebellar purkinje cells of diabetic rats and its potential relationship with inflammation and oxidative stress markers. *Neurol Res Int*. 2017; 2017(1):1–6; doi: 10.1155/2017/ 5952149
16. Lee H, Kim MJ, Lee IK, Hong CW, Jeon JH. Impact of hyperglycemia on immune cell function: A comprehensive review. *Diabetol Int*. 2024; 15(4):745–60; doi: 10.1007/s13340-024-00741-6
17. González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. *Int J Mol Sci*. 2023; 24(11):9352; doi: 10.3390/ijms24119352
18. Hwang ES, Song SB. Impaired autophagic flux in glucose-deprived cells: An outcome of lysosomal acidification failure exacerbated by mitophagy dysfunction. *Mol Cells*. 2023; 46(11):655–63. doi: 10.14348/molcells.2023.0121

19. Arcambal A, Taïlé J, Rondeau P, Viranaïcken W, Meilhac O, Gonthier M-P. Hyperglycemia modulates redox, inflammatory and vasoactive markers through specific signaling pathways in cerebral endothelial cells: Insights on insulin protective action. *Free Radic Biol Med*. 2019; 130:59–70. doi: 10.1016/j.freeradbiomed.2018.10.430
20. Pétriz A, Reyes-Haro D, González-González MA, Miledi R, Martínez-Torres A. GABAρ subunits confer a bicuculline-insensitive component to GFAP+ cells of cerebellum. *Proc Natl Acad Sci*. 2014; 111(49):17522–7; doi: 10.1073/pnas.1419632111
21. Cook AA, Fields E, Watt AJ. Losing the beat: Contribution of purkinje cell firing dysfunction to disease, and its reversal. *Neuroscience* 2021; 462:247–61; doi: 10.1016/j.neuroscience.2020.06.008
22. Nishiyama H, Nishiyama N, Zemelman BV. Loss of purkinje cells in the developing cerebellum strengthens the cerebellothalamic synapses. 2023; doi: 10.1101/2023.11.01.564864
23. Calvo-Flores Guzmán B, Vinnakota C, Govindpani K, Waldvogel HJ, Faull RLM, Kwakowsky A. The GABAergic system as a therapeutic target for Alzheimer's disease. *J Neurochem*. 2018; 146(6):649–69; doi: 10.1111/jnc.14345
24. Bodaghi A, Fattahi N, Ramazani A. Biomarkers: Promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. *Heliyon*. 2023; 9(2):e13323; doi: 10.1016/j.heliyon.2023.e13323
25. Chaudhary R, Nawaz A, Khattak Z, Butt MA, Fouillaud M, Dufossé L, et al. Microbial bio-control agents: A comprehensive analysis on sustainable pest management in agriculture. *J Agric Food Res*. 2024; 18:101421; doi: 10.1016/j.jafr.2024.101421