SYSTEMATIC REVIEW

# Effects of Secretomes on Neuroglia in Central Nervous System (CNS): A Systematic Review

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**ABSTRACT**

**Background:** Glial cells or neuroglia are important non-neuronal components of the central nervous system (CNS), accounting for approximately 50% of its cellular composition. In addition, there are different types of neuroglia, including oligodendrocytes, astrocytes, and microglia, each with its distinct function. Several studies have shown that secretomes containing secretions from stem cells can modulate neuronal cells and neuroglia. Therefore, this study aimed to systematically review the effects of secretomes on neuroglia in CNS. **Methods:** The study used the Cochrane Handbook for Systematic Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic literature search was conducted on 11 electronic medical databases, followed by an assessment of quality and the risk of bias. **Results:** A total of 337 articles were obtained from the systematic literature search, with only 12 meeting the inclusion criteria. The results of the risk of bias assessment showed that most of the articles were in the low-risk category. Secretomes has been shown to exert beneficial effects on oligodendrocytes (2 studies), astrocytes (4 studies), and microglia (3 studies), with additional studies highlighting its dual impact on oligodendrocytes and astrocytes (2 studies), and one study demonstrating its therapeutic potential across all three glial cell types. **Discussion:** Secretomes positively modulate neuroglia because these cells contain growth factors, cytokines, chemoattractants, and extracellular vesicles, which carry microRNA and proteins. **Conclusion:** Secretomes had positive effects on neuroglia in CNS. Further studies are still needed to examine specific secretome components and molecular examination of neuroglia.
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**Keywords:** Brain, CNS, Conditioned Media, Glial Cells, Neuroglia, Secretomes

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## 1. Background

Glial cells or neuroglia are essential non-neuronal central nervous system (CNS) components. Although neuroglia are often considered as supporting cells, recent studies have highligthed their pleiotropic and dynamic roles in brain function and development. The main types of neuroglia include astrocytes, which provide structural support and regulate the blood-brain barrier, and oligodendrocytes, responsible for the myelination of axons. Other types include microglia, which act as immune cells, and ependymal cells, which are involved in the production of cerebrospinal fluid. These cells facilitate neural communication, maintain homeostasis, and participate in neuroregeneration processes. Despite their importance, studies related to the effects of stem cells therapy and secretomes on neuroglia remain limited [1,2].

Stem cells are essential components of neurorestorative therapy, which helps to reduce morbidity and mortality in neurological disorders [3–5]. These components are unspecialized cells that can differentiate into any cell in an organism and have high regenerative potential. However, stem cell-based therapy has several limitations, such as the need for special transport media, the risk of rejection effects from the body's immunity (incompatibility), and the risk of cell migration (embolism) and tumorigenicity. This current study proposes the use of secretomes, a conditioned media from stem cells, as a more affordable and compatible alternative. Secretomes can modulate angiogenesis, neurogenesis, the inflammatory system, and immune response, along with the ability to reduce

cell death. Consequently, these cells have the potential to be an effective therapeutic option for cells with limited regeneration capacity, such as neurons and neuroglia [4,5,14,15,6–13]. Ribeiro CA et al. (2011) and Salgado AJ et al. (2010) showed that secretomes had a positive effect on neuroglia in CNS [16,17]. Although the effects on these cells have been extensively studied, there is no systematic review on this topic. Therefore, this study aims to systematically review the effects of secretomes on neuroglia in CNS.

## 2. Method

This systematic review's protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420250652989. This study was conducted based on the Cochrane Handbook and the Guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18–21].

### 2.1 Inclusion and Exclusion Criteria

Inclusion criteria:

1. Publication type:
   Full-text articles reporting the effects of secretomes on neuroglia in CNS.
   Experimental studies (clinical trials)
2. Articles published in English and Indonesian.
3. Articles published between January 2000 and December 2024.
4. This study used humans, animals, and cells as subjects.
5. The purpose, methodology, and results of the study must discuss the relationship between the effects of secretomes on neuroglia in CNS.

Exclusion criteria:

1. Study respondents: in silico
2. Publication type was an observational study or review
3. There were confounding variables related to the effects of secretomes on neuroglia in CNS.

### 2.2 Literature Search

A systematic literature search was conducted in the following electronic medical databases, such as ClinicalKey, Cochrane Library, EBSCOhost, Emerald Insight, Europe PMC, Google Scholar, JSTOR, ProQuest, PubMed, ScienceDirect, and Springer Link; restricted to publications identified between January and February 2025. The search was carried out using the following keywords for the title and abstract, namely (secretomes OR conditioned media OR extracellular vesicle OR exosome OR paracrine) AND (neuroglia OR glial cell OR astrocyte OR oligodendrocyte OR microglia OR ependymal cell OR radial glial cell) AND (central nervous system OR brain OR spinal cord). References of included studies were assessed to avoid missing published articles. Grey literature and non-peer-reviewed studies were excluded to ensure the inclusion of only high-quality, peer-reviewed evidence, thereby enhancing the reliability and scientific rigor of the review.

### 2.3 Data Analysis

Articles were selected for assessment after two authors (YA and DT) checked the keywords from electronic medical databases. The results of the literature search were discussed with a third author (R), and any discrepancies in the results were discussed to maintain reliability and minimize subjective bias using a methodology that had been previously established and agreed upon by all reviewers. Furthermore, the selected full articles were independently evaluated by three authors to confirm the results (DS, EM, CS). Data from the included articles were provided in a summary table, which contained the key points of each study, including first author and year, study design, sample, secretomes characteristics, and results.

### 2.4 Study Quality Assessment (Risk of Bias)

The lead author evaluated each included article's quality and risk of bias and discussed it with other authors. Version 2 of the Cochrane risk-of-bias tool (RoB 2) was used to evaluate randomized controlled trial studies with the interpretation known as high risk or some concerns or low risk [19,22].

## 3. Result

### 3.1 Studies' Selection for Systematic Review

Figure 1 showed the PRISMA flow diagram. Initially, 337 peer-reviewed articles were retrieved from electronic medical databases. After removing duplicates, 185 studies were left for abstract and title screening. Those that did not meet the inclusion and exclusion criteria were not evaluated. The fourteen studies were assessed for eligibility, and twelve studies underwent qualitative synthesis (systematic review).

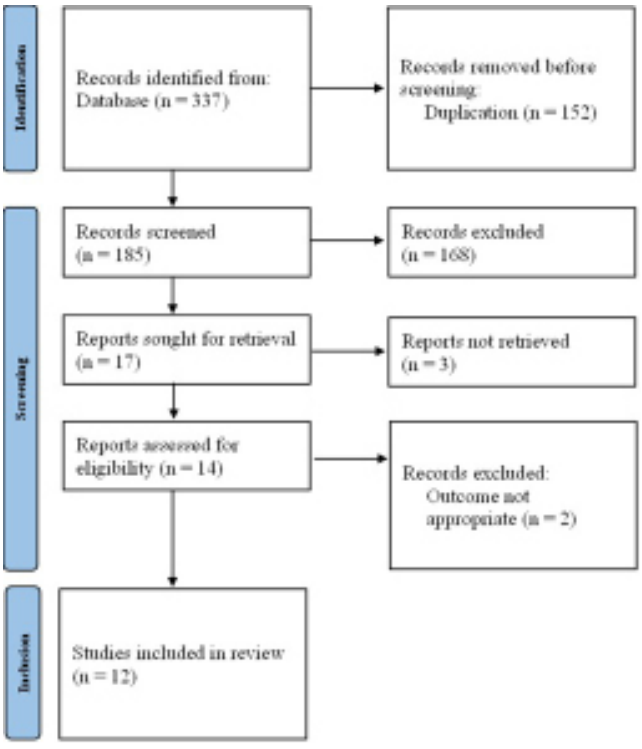


**Figure 1: PRISMA flow diagram**

### 3.2 Assessment of Study Validity (Quality and Risk of Bias Assessment)

All articles included were related to the effects of secretomes on neuroglia in CNS. Figure 2 showed the results of ROB 2 assessment, which found that all studies were low-risk.

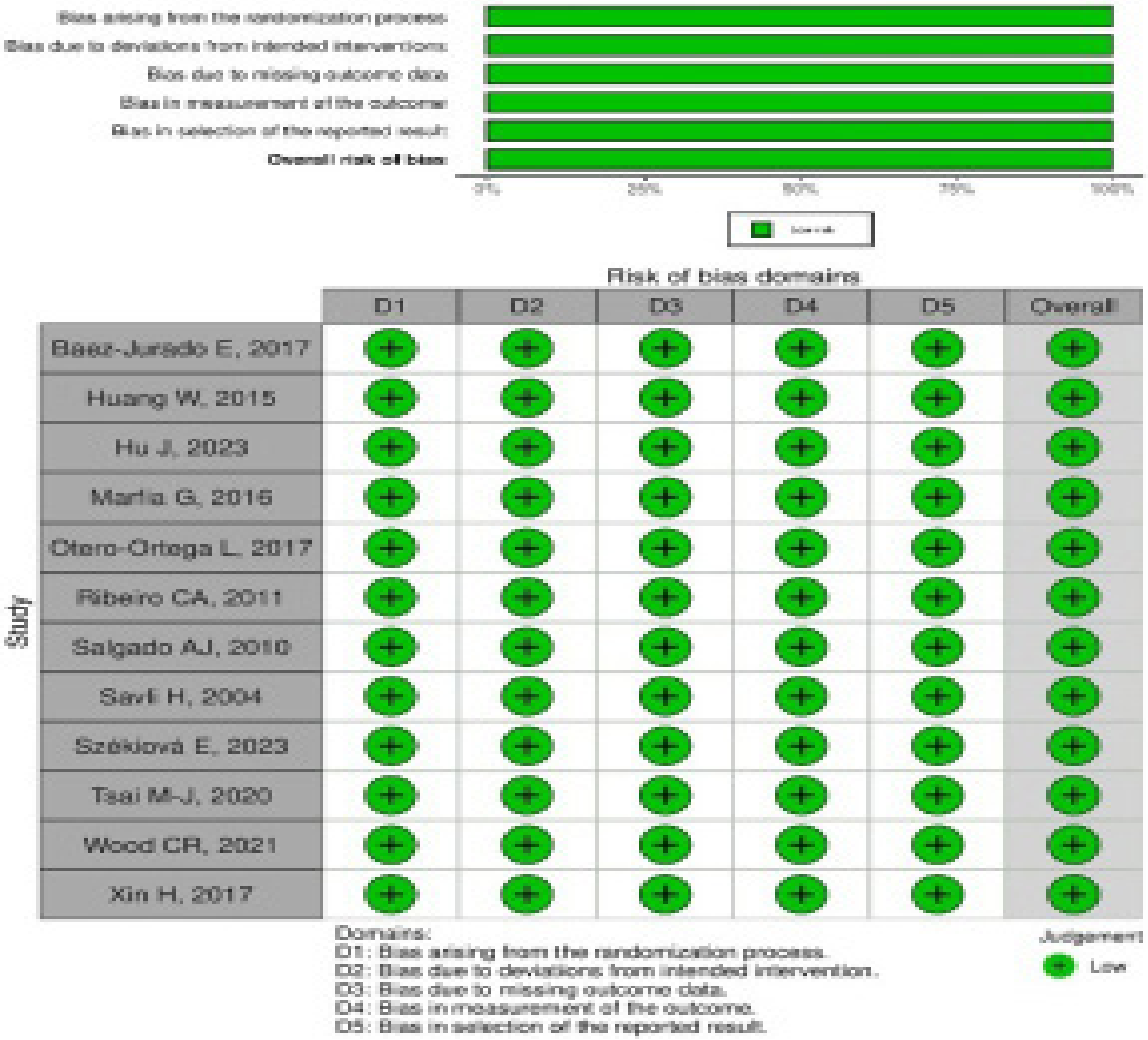


**Figure 2: ROB 2**

### 3.3 Study Characteristics

Study characteristics for the included studies were presented in Table 1. All studies showed that secretomes positively affected neuroglia in CNS. Twelve studies have investigated the effects of secretome on glial cells, revealing its potential in modulating neuroinflammation and supporting neural repair. Two studies focused on oligodendrocytes, showing benefits for myelination and cell survival; four studies examined astrocytes, highlighting effects on activation, neuroprotection, and cytokine regulation; and three studies explored microglia, suggesting a role in modulating polarization and reducing pro-inflammatory signaling. Additionally, two studies addressed the dual impact on oligodendrocytes and astrocytes, while one study evaluated secretome's influence across all three glial types, underscoring its broad therapeutic potential in central nervous system disorders.

**Table I: Study Characteristics**

| No. | First author, country, year | Study Design | Sample | Secretomes characteristics | Results |
|---|---|---|---|---|---|
| 1. | Baez-Jurado E, 2017[23] | RCT | Scratch assay (control and treatment groups) on human astrocyte cell culture. | Secretomes from mesenchymal stem cells (human adipose tissue) with 5, 10, and 15% concentrations. | Secretomes (dose-response) increased viability, reduced nuclear fragmentation, maintained mitochondrial membrane polarity, and increased astrocyte migration (morphological changes and increased polarity index) significantly (p<0.05). |
| 2. | Huang W, 2015[24] | RCT | Astrocyte cell culture from Wistar rats with OGD. | Paracrine factors from rat bone marrow stem cells for 1 day. | Paracrine factors from stem cells significantly decreased astrocyte apoptosis, increased astrocyte metabolic activity, and decreased GFAP overexpression (p<0.05) in ischemic stroke cases. |
| 3. | Hu J, 2023[25] | RCT | Glial cell culture from Sprague-Dawley rat brain tissue (control and treatment groups). | Fibroblast secretomes at a concentration of 25% for 4-5 days. | Fibroblast secretomes significantly increased the yield (Iba-1 positive cells) and purity of microglia and significantly reduced the total glia culture time (p<0.05). Microglia obtained from secretomes group showed longer branched morphology than the control group (p<0.05). |
| 4. | Marfia G, 2016[26] | RCT | Microglia cell culture. | Secretomes from human adipose stem cells for 2 days. | Secretomes inhibited LPS-induced microglia activation (including CD68 expression, pro-inflammatory cytokine/IL-17 secretion, microglia proliferation, and migration) and significantly increased the levels of anti-inflammatory cytokine (IL-10) in LPS-induced microglia (p<0.05). |
| 5. | Otero-Ortega L, 2017[27] | RCT | Subcortical brain tissue of Sprague-Dawley rats with stroke (control and treatment groups), examination on day 7. | Extracellular vesicles 100 µg intravenously (from rat adipose tissue) on day 1. | Extracellular vesicles significantly increased oligodendrogenesis (p<0.05) [increased CNP-ase, A2B5, and MOG] in stroke cases. |
| 6. | Ribeiro CA, 2011[17] | RCT | Culture from cortical glial cells of Wistar rats (control and treatment groups; treatment 1: secretomes conditioning for 1 day, treatment 2: secretomes conditioning for 2 days, treatment 3: secretomes conditioning for 3 days, treatment 4: secretomes conditioning for 4 days). | Secretomes from mesenchymal stem cells (from bone marrow) for 9 days. | Secretomes increased the viability of glial cells (p<0.05). Secretomes increased the expression of astrocytes (GFAP), oligodendrocytes (O4), and microglia (CD11b) (p<0.05). |
| 7. | Salgado AJ, 2010[16] | RCT | Culture from cortical glial cells of Wistar rats (control and treatment groups; treatment 1: secretomes conditioning for 1 day, treatment 2: secretomes conditioning for 2 days, treatment 3: secretomes conditioning for 3 days). | Secretomes from mesenchymal stem cells (human umbilical cord) for 14 days. | Secretomes increased the viability and proliferation of glial cells (p<0.05). Secretomes increased the expression of astrocytes (GFAP) and oligodendrocytes (O4) (p<0.05) |
| 8. | Savli H, 2004[28] | RCT | Culture from striatal glial cells (control and treatment groups). | Secretomes from microglia (from striatum and cortex of Sprague-Dawley rat pups) for 2 days. | Secretomes increased BDNF gene expression from striatal astrocytes (1.33 times). |
| 9. | Szйkiov6 E, 2023[29] | RCT | Culture from rat spinal cord slices (control and treatment groups, treatment 1: secretomes conditioning for 1 day, treatment 2: secretomes conditioning for 2 days, treatment 3: secretomes conditioning for 3 days). | Secretomes from mesenchymal stem cells (rat bone marrow) for 1, 2, and 3 days. | Secretomes significantly increased the migration of astrocytes (GFAP positive cells) and the density of oligodendrocytes (RIP positive cells), specifically in treatment group 3 (p<0.05). |
| 10. | Tsai M-J, 2020[30] | RCT | In vitro: Culture from the cerebrocortical area of Sprague-Dawley rat embryos (control and treatment groups).<br>In vivo: Brain tissue of rats with stroke/MCAO (control and treatment groups), examined 1 week after occlusion. | Secretomes from mesenchymal stem cells (from mouse bone marrow).<br>In vitro: 4 µl with 40-fold concentration for 3 days.<br>In vivo: 200 µl with 40-fold concentration given IV at 2 hours, 1st day and 2nd day. | Secretomes increased the expression of oligodendrocytes (RIP-IR) insignificantly and reduced microglia infiltration significantly (ED-1) (p<0.05) in ischemic stroke cases. |

CONTINUE

**Table I: Study Characteristics. (CONT.)**

| No. | First author, country, year | Study Design | Sample | Secretomes characteristics | Results |
|---|---|---|---|---|---|
| 11. | Wood CR, 2021[31] | RCT | Cultures from spinal cord slices of CD1 rats (control and treatment groups). | Secretomes of mesenchymal stem cells (from dog inguinal fat pad) over 3 days. | Secretomes increased the expression of astrocytes (GFAP) and the length of astrocytes significantly ($p<0.05$) and increased NG2 antibodies insignificantly. |
| 12. | Xin H, 2017[32] | RCT | Brain tissue of Wistar rats experiencing stroke/MCAO (control and treatment groups), examination on day 28. | Extracellular vesicles (exosomes) 100 µg (containing miR 17-92-cluster) intravenously (from rats bone marrow) day 1. | Exosomes significantly ($p<0.05$) increased oligodendrogenesis [increased oligodendrocyte progenitor cells (BrdU and NG2 positive staining) and mature oligodendrocytes (BrdU and MBP positive staining)] in ischemic stroke cases. |

**Description:**
**BDNF: brain-derived neurotrophic factor**
**BrdU: bromodeoxyuridine**
**CD11b: cluster of differentiation molecule 11b**
**CNP-ase: 2′,3′-cyclic nucleotide 3′-phosphodiesterase**
**GFAP: glial fibrillary acidic protein**
**Iba-1: ionized calcium-binding adaptor molecule 1**
**LPS: lipopolisakarida**
**MBP: myelin basic protein**
**MOG: mature oligodendrocyte**
**NG2: neural/glial antigen 2**
**O4: oligodendrocyte Marker O4**
**OGD: oxygen-glucose deprivation**
**p: probability**
**RIP-IR: RIP-immunoreactive**

## 4. Discussion

Stem cells are unspecialized cells capable of differentiating into various cell types in the body and possess regenerative properties. They are categorized into totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells. Among these, mesenchymal stem cells (MSCs) are the most commonly used due to their ability to differentiate into multiple tissue types such as nerve, blood vessel, adipose, and bone tissues. Consequently, secretomes derived from MSCs are widely utilized in research owing to their low risk and ease of availability [4,10–14,23–25]. MSCs release a variety of bioactive molecules, including cytokines, chemokines, anti-inflammatory factors, growth factors, and proteins encapsulated within extracellular vesicles. These collective secretions are referred to as secretomes or conditioned media. Secretomes play several biological roles, including immunomodulation and anti-inflammatory activity. Furthermore, they exhibit neurotrophic, neuroprotective, anti-apoptotic, pro-angiogenic, and regenerative properties [4,10–13].

The composition of secretomes varies depending on changes in the microenvironment [4,26]. Growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF); cytokines such as IL-10 and transforming growth factor-beta (TGF-β); chemoattractants such as monocyte chemoattractant protein-1 (MCP-1); and extracellular vesicles (carrying microRNAs and proteins) are major components of secretomes that have effects on neuroglia [4,9,11,26–32]. Studies from Ribeiro CA et al. (2011) and Salgado AJ et al. (2010) reported that secretomes increased the viability and proliferation of neuroglial cells in cultures from the cortex of experimental rats [16,17]. Furthermore, a study by Szйkiovб E et al. (2023) demonstrated that secretomes conditioned for three days contained the highest concentrations of neurotrophins (NGF and VEGF), which positively affected neuroglia and exhibited the broadest spectrum of proteins and bioactive substances in proteomic analysis [33].

Oligodendrocytes, a major type of neuroglial cells in CNS, play an important role in myelination, axon protection, and providing metabolic support to neurons. Dysfunction of oligodendrocyte cells can cause and worsen various diseases of the nervous system, including neurovascular diseases such as stroke, neurodegenerative diseases, multiple sclerosis, leukodystrophy, schizophrenia, and autism spectrum disorders [2,34–39]. Five studies included in this review reported beneficial effects of secretomes on oligodendrocytes in the CNS. These effects include the promotion of oligodendrogenesis, marked by increased expression of oligodendrocyte progenitor cells and mature oligodendrocytes. The mechanism is believed to involve paracrine signaling mediated by bioactive components in the secretomes, such as growth factors, extracellular vesicles, and exosomes [16,17,33,40–42].

Astrocytes are essential neuroglial cells in the CNS that play a key role in maintaining neuronal homeostasis, supporting neuronal function, and responding to injury.

Recent studies have shown that astrocytes actively participate in synaptic transmission and plasticity by regulating the extracellular environment, modulating neurotransmitter levels, and maintaining ionic balance. Additionally, they form complex networks with neurons and other glial cells and communicate through the release of gliotransmitters such as glutamate and ATP, which influence neuronal excitability and synaptic strength. Astrocytes also contribute to the integrity of the blood-brain barrier and provide metabolic support to neurons, especially during periods of increased demand. Moreover, they exert neuroprotective functions by reducing oxidative stress and inflammation, implicating them in the pathology of conditions such as stroke, Alzheimer's disease, and multiple sclerosis [2,34,43–50] . The role of secretomes on astrocyte cells has been reported in seven studies, including their effect in regulating the number of astrocyte cells (reducing excessive astrocyte cell expression), thereby preventing excessive astrogliosis and glial scar formation. The mechanism by which secretomes regulate astrocytes involves the paracrine action of bioactive factors secreted by stem cells including cytokines, chemokines, growth factors, and immunomodulatory molecules. These components reduce inflammation and oxidative stress, suppress excessive astrocyte activation, and promote tissue repair through factors such as TGF-β and VEGF [4,9,31–33,51–54,11,16,17,26–30]. The study conducted by Huang W et al. (2015) also reported that the positive effects of secretomes on astrocyte cells occured through the inhibition of p38 MAPK and JNK activation, specifically in supressing p53 and STAT 1 (which are the mediators of cell response to external stimuli/stress-activated protein kinase) [52]. According to Savli H et al. (2004), glial cells play a positive role (mutual relationship) as indicated by the presence of secretomes microglia that could increase astrocyte cell expression in CNS [53].

Microglia are the primary immune cells of CNS, accounting for approximately 10% of all cells in the brain, and play a critical role in maintaining homeostasis, supporting neuronal health, and responding to injury. These highly dynamic cells continuously monitor their environment through an extensive process and respond rapidly to changes in neuronal activity and local pathology. Microglia are involved in several key functions, including phagocytosis of dead cells, excess synapses, and protein aggregates, thereby contributing to synaptic pruning and overall brain development. These cells also secrete a variety of cytokines and neurotrophic factors that modulate neuroinflammation and promote tissue repair after injury. However, microglia activation has a dual effect, suggesting that excessive activation can lead to neuroinflammation that contributes to neurodegenerative diseases such as alzheimer's and parkinson's disease as well as neurovascular diseases such as stroke and other neurological disorders [2,34,49,50,55–59]. A total of four studies in this systematic review discussed that secretomes maintain microglia function and suppressed microglia activity that could harm CNS through secretomes components such as growth factors [17,42,60,61]. Secretomes modulate microglia by promoting a shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype via the TLR4/NF-κB/PI3K/Akt pathway, suppressing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) while enhancing IL-10, TGF-β, and VEGF, and regulating apoptosis through caspase cascades and Bax/Bcl-2 modulation [61–63]. A study by Marfia G et al. (2016) also reported that secretomes-inhibited microglial activation was induced by lipopolysaccharide (LPS) through modulation of sphingosine 1 phosphate/S1P signals. S1P is one of the regulatory signals that played a role in the activation of immune cells (including microglia) and the neurogenesis process [61].

This systematic review included twelve full-text primary studies examining the effects of secretomes on neuroglial cells within the central nervous system. A number of limitations were identified among the included studies, including substantial heterogeneity in secretome type, dosage, frequency, and duration, as well as a predominance of in vitro models, which may limit translational applicability. Future studies should focus on addressing these limitations by incorporating standardized protocols for secretome preparation and administration, conducting in vivo and clinical investigations, and elucidating the specific bioactive components responsible for the observed effects. Additionally, further research should explore the impact of secretomes on neuroglial responses in defined neurological conditions, examine neuroglia at the molecular/cellular level, and expand the scope to include underexplored glial populations such as ependymal cells.

## 5. Conclusion

In conclusion, secretomes positively affect neuroglia in CNS. Further studies are needed regarding the standardization of secretomes and specific examinations in secretomes components and neuroglia components.

## REFERENCES

1. Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. Science. 2018;362(6411):181–185. doi: 10.1126/science.aat0473.
2. Rasband MN. Glial Contributions to Neural Function and Disease. Mol Cell Proteomics. 2016;15(2):355–361. doi: 10.1074/mcp.R115.053744.
3. Aninditha T, Harris S, Wiratman W. Buku Ajar Neurologi Edisi Kedua. 2022. Jakarta. Departemen Neurologi FK UI.
4. Cunningham CJ, Redondo-castro E, Allan SM.

The therapeutic potential of the mesenchymal stem cell secretome in ischaemic stroke. J Cereb Blood Flow Metab. 2018;38(8):1276–1292. doi: 10.1177/0271678X18776802.
5. Behzadifard M, Aboutaleb N, Dolatshahi M, Khorramizadeh M. Neuroprotective Effects of Conditioned Medium of Mesenchymal Stem Cells (MSC - CM ) as a Therapy for Ischemic Stroke Recovery : A Systematic Review. Neurochem Res. 2023;48(5):1280–1292. doi: 10.1007/s11064-022-03848-x.
6. Taei AA, Nasoohi S, Hassanzadeh G, Kadivar M, Dargahi L, Farahmandfar M. Enhancement of angiogenesis and neurogenesis by intracerebroventricular injection of secretome from human embryonic stem cell-derived mesenchymal stem cells in ischemic stroke model. Biomed Pharmacother. 2021;140:1–13. doi: 10.1016/j.biopha.2021.111709.
7. Chouaib B, Haack-sшrensen M, Chaubron F, Cuisinier F. Towards the Standardization of Mesenchymal Stem Cell Secretome-Derived Product Manufacturing for Tissue Regeneration. Int J Mol Sci. 2023;24:1–15. doi: 10.3390/ijms241612594.
8. Gwam C, Mohammed N, Ma X. Stem cell secretome , regeneration, and clinical translation: a narrative review. Ann Transl Med. 2021;9(6):1–11. doi: 10.21037/atm-20-5030.
9. Pinho AG, Cibr JR, Silva NA, Monteiro S, Salgado J. Cell Secretome : Basic Insights and Therapeutic Opportunities for CNS Disorders. Pharmaceutical. 2020;13(31):1–18. doi: 10.3390/ph13020031.
10. Alwjwaj M, Kadir RRA, Bayraktutan U. The secretome of endothelial progenitor cells : a potential therapeutic strategy for ischemic stroke. Neural Regen Res. 2021;16(8):1483–1489. doi: 10.4103/1673-5374.303012.
11. Foo JB, Looi QH, Chong PP, Hassan NH, Yeo GEC, Ng CY, et al. Comparing the Therapeutic Potential of Stem Cells and their Secretory Products in Regenerative Medicine. Stem Cells Int. 2021;2021:1–30. doi: 10.1155/2021/2616807.
12. Gonzбlez-gonzбlez A, Garcна-sбnchez D, Dotta M, Rodrнguez-rey JC, Pйrez- FM, Gonzбlez-gonzбlez A, et al. Mesenchymal stem cells secretome: The cornerstone of cell-free regenerative medicine. World J Stem Cells. 2020;12(12):1529–1553. doi: 10.4252/wjsc.v12.i12.1529.
13. Lin L, Du L. The role of secreted factors in stem cells-mediated immune regulation. Cell Immunol. 2018;326:24–32. doi: 10.1016/j.cellimm.2017.07.010.
14. Putra A. Basic Molecular Stem Cells. 2019. Semarang. Unissula Press.
15. Li W, Shi L, Hu B, Hong Y, Zhang H, Li X, et al. Mesenchymal Stem Cell-Based Therapy for Stroke: Current Understanding and Challenges. Front Cell Neurosci. 2021;5(2):1–12. doi: 10.3389/fncel.2021.628940.
16. Salgado AJ, Fraga JS, Mesquita AR, Neves NM, Reis RL, Sousa N. Role of human umbilical cord mesenchymal progenitors conditioned media in neuronal/glial cell densities, viability, and proliferation. Stem Cells Dev. 2010;19(7):1067–1074. doi: 10.1089/scd.2009.0279.
17. Ribeiro CA, Salgado AJ, Fraga JS, Silva NA, Reis RL, Sousa N. The secretome of bone marrow mesenchymal stem cells-conditioned media varies with time and drives a distinct effect on mature neurons and glial cells (primary cultures). J Tissue Eng Regen Med. 2011;5:668–672. doi: 10.1002/term.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:1–9. doi: 10.1136/bmj.n71.
19. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of intervention 6.4. 2023. United Kingdom. John Wiley and Sons.
20. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration : updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:1–36. doi: 10.1136/bmj.n160.
21. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. BMJ. 2020;368:1–6. doi: 10.1136/bmj.l6890.
22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:1–8. doi: 10.1136/bmj.l4898.
23. Zakrzewski W, Dobrzynski M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther. 2019;10(68):1–22. doi: 10.1541/ieejfms.128.329.
24. Undale A, Westendorf JJ, Yaszemski MJ, Khosla S. Mesenchymal Stem Cells for Bone Repair and Metabolic Bone Diseases. Mayo Clin Proc. 2009;84(10):893–902. doi: 10.1007/978-94-007-6716-4_13.
25. Li X, Zhang D, Yu Y, Wang L, Zhao M. Umbilical cord-derived mesenchymal stem cell secretome promotes skin regeneration and rejuvenation: From mechanism to therapeutics. Cell Prolif. 2024;57(4):1–16. doi: 10.1111/cpr.13586.
26. Han Y, Yang J, Fang J, Zhou Y, Candi E, Wang J, et al. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduct Target Ther. 2022;7(1):1–19. doi: 10.1038/s41392-022-00932-0.
27. Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-fernandez R. Mesenchymal Stem Cell Secretome : Toward

Cell-Free Therapeutic Strategies in Regenerative Medicine. Int J Mole. 2017;18(1852):1–24. doi: 10.3390/ijms18091852.
28. Puyhunen S, Er S, Domanskyi A, Airavaara M. Effects of neurotrophic factors in glial cells in the central nervous system: Expression and properties in neurodegeneration and injury. Front Physiol. 2019;10(APR):1–20. doi: 10.3389/fphys.2019.00486.
29. Rhatomy S, Pawitan JA, Kurniawati T, Fiolin J, Dilogo IH. Allogeneic umbilical cord mesenchymal stem cell conditioned medium (secretome) for treating posterior cruciate ligament rupture: a prospective single-arm study. Eur J Orthop Surg Traumatol. 2023;33(3):669–675. doi: 10.1007/s00590-022-03278-z.
30. Katahira Y, Murakami F, Inoue S, Miyakawa S, Sakamoto E, Furusaka Y, et al. Protective effects of conditioned media of immortalized stem cells from human exfoliated deciduous teeth on pressure ulcer formation. Front Immunol. 2023;13(January):1–18. doi: 10.3389/fimmu.2022.1010700.
31. da Silva AV, Serrenho I, Araьjo B, Carvalho AM, Baltazar G. Secretome as a Tool to Treat Neurological Conditions: Are We Ready? Int J Mol Sci. 2023;24(22):1–30. doi: 10.3390/ijms242216544.
32. Ferrini F, Juбrez EH, Merighi A. Does mesenchymal stem cell's secretome affect spinal sensory circuits? Implication for pain therapies. Neural Regen Res. 2025;20(1):181–183. doi: 10.4103/nrr.nrr-d-23-01967.
33. Szйkiovб E, Michalovб Z, Bla ko J, Mucha R, Slovinskб L, Kello M, et al. Characterisation of mesenchymal stem cells conditioned media obtained at different conditioning times: their effect on glial cells in in vitro scratch model. Growth Factors. 2023;41(2):57–70. doi: 10.1080/08977194.2023.2182145.
34. Rahman MM, Islam MR, Yamin M, Islam MM, Sarker MT, Meem AFK, et al. Emerging Role of Neuron-Glia in Neurological Disorders: At a Glance. Oxid Med Cell Longev. 2022;2022:1–27. doi: 10.1155/2022/3201644.
35. Chapman TW, Kamen Y, Piedra ET, Hill RA. Oligodendrocyte Maturation Alters the Cell Death Mechanisms That Cause Demyelination. J Neurosci. 2024;44(13):1–15. doi: 10.1523/JNEUROSCI.1794-23.2024.
36. Foerster S, Floriddia EM, van Bruggen D, Kukanja P, Hervй B, Cheng S, et al. Developmental origin of oligodendrocytes determines their function in the adult brain. Nat Neurosci. 2024;27(8):1545–1554. doi: 10.1038/s41593-024-01666-8.
37. Kuhn S, Gritti L, Crooks D, Dombrowski Y. Oligodendrocytes in Development, Myelin Generation and Beyond. Cells. 2019;8(1424):1–23. doi: 10.1016/j.coms.2016.10.001.
38. Michalski JP, Kothary R. Oligodendrocytes in a nutshell. Front Cell Neurosci. 2015;9(september):1–11. doi: 10.3389/fncel.2015.00340.
39. Bradl M, Lassmann H. Oligodendrocytes: Biology and pathology. Acta Neuropathol. 2010;119(1):37–53. doi: 10.1007/s00401-009-0601-5.
40. Otero-Ortega L, Laso-Garcна F, Del Carmen Gymez-De Frutos M, Rodrнguez-Frutos B, Pascual-Guerra J, Fuentes B, et al. White matter repair after extracellular vesicles administration in an experimental animal model of subcortical stroke. Sci Rep. 2017;7(3):1–11. doi: 10.1038/srep44433.
41. Xin H, Katakowski M, Wang F, Qian J-Y, Liu XS, Ali MM, et al. MiR-17-92 cluster in exosomes enhance neuroplasticity and functional recovery after stroke in rats. Stroke. 2017;48(3):747–753. doi: 10.1002/hep.30150.Ductular.
42. Tsai MJ, Liou DY, Chu YC, Chen Y, Huang MC, Huang WC, et al. Minocycline exhibits synergism with conditioned medium of bone marrow mesenchymal stem cells against ischemic stroke. J Tissue Eng Regen Med. 2021;15(3):279–292. doi: 10.1002/term.3171.
43. Escalada P, Ezkurdia A, Ramнrez MJ, Solas M. Essential Role of Astrocytes in Learning and Memory. Int J Mol Sci. 2024;25(3):1–15. doi: 10.3390/ijms25031899.
44. Guillamyn-Vivancos T, Gymez-Pinedo U, Matнas-Guiu J. Astrocytes in neurodegenerative diseases (I): Function and molecular description. Neurologia. 2015;30(2):119–129. doi: 10.1016/j.nrl.2012.12.007.
45. Theparambil SM, Kopach O, Braga A, Nizari S, Hosford PS, Sagi-Kiss V, et al. Adenosine signalling to astrocytes coordinates brain metabolism and function. Nature. 2024;632(8023):139–146. doi: 10.1038/s41586-024-07611-w.
46. Valles SL, Singh SK, Campos-Campos J, Colmena C, Campo-Palacio I, Alvarez-Gamez K, et al. Functions of Astrocytes under Normal Conditions and after a Brain Disease. Int J Mol Sci. 2023;24(9). doi:10.3390/ijms24098434 doi: 10.3390/ijms24098434.
47. Gradisnik L, Velnar T. Astrocytes in the central nervous system and their functions in health and disease: A review. World J Clin Cases. 2023;11(15):3385–3394. doi: 10.12998/wjcc.v11.i15.3385.
48. Verkhratsky A, Butt A, Li B, Illes P, Zorec R, Semyanov A, et al. Astrocytes in human central nervous system diseases: a frontier for new therapies. Signal Transduct Target Ther. 2023;8(1):1–37. doi: 10.1038/s41392-023-01628-9.
49. Garland EF, Hartnell IJ, Boche D. Microglia and Astrocyte Function and Communication: What Do We Know in Humans? Front Neurosci. 2022;16(February):1–21. doi: 10.3389/fnins.2022.824888.
50. Perez-Catalan NA, Doe CQ, Ackerman SD. The

role of astrocyte-mediated plasticity in neural circuit development and function. Neural Dev. 2021;16(1):1–14. doi: 10.1186/s13064-020-00151-9.

51. Baez-Jurado E, Hidalgo-Lanussa O, Guio-Vega G, Ashraf GM, Echeverria V, Aliev G, et al. Conditioned Medium of Human Adipose Mesenchymal Stem Cells Increases Wound Closure and Protects Human Astrocytes Following Scratch Assay In Vitro. Mol Neurobiol. 2017;55(6):5377–5392. doi: 10.1007/s12035-017-0771-4.
52. Huang W, Lv B, Zeng H, Shi D, Liu Y, Chen F, et al. Paracrine Factors Secreted by MSCs Promote Astrocyte Survival Associated With GFAP Downregulation After Ischemic Stroke via p38 MAPK and JNK. J Cell Physiol. 2015;230(10):2461–2475. doi: 10.1002/jcp.24981.
53. Savli H, Gulkac MD, Esen N. The effect of stimulated microglia conditioned media on BDNF gene expression of striatal astrocytes: Quantification by real-time PCR. Int J Neurosci. 2004;114(12):1601–1612. doi: 10.1080/00207450490476138.
54. Wood CR, Ju6rez EH, Ferrini F, Myint P, Innes J, Lossi L, et al. Mesenchymal stem cell conditioned medium increases glial reactivity and decreases neuronal survival in spinal cord slice cultures. Biochem Biophys Reports. 2021;26(December):1–8. doi: 10.1016/j.bbrep.2021.100976.
55. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther. 2023;8(1):1–37. doi: 10.1038/s41392-023-01588-0.
56. Mendiola AS, Yan Z, Dixit K, Johnson JR, Bouhaddou M, Meyer-Franke A, et al. Defining blood-induced microglia functions in neurodegeneration through multiomic profiling. Nat Immunol. 2023;24(7):1173–1187. doi: 10.1038/s41590-023-01522-0.
57. Alekseeva OS, Kirik O V., Gilerovich EG, Korzhevskii DE. Microglia of the Brain: Origin, Structure, Functions. J Evol Biochem Physiol. 2019;55(4):257–268. doi: 10.1134/s002209301904001x.
58. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. Annu Rev Immunol. 2017;35:441–468. doi: 10.1146/annurev-immunol-051116-052358.
59. Wake H, Fields RD. Physiological Function of Microglia. Neuron Glia Biol. 2011;7(1):1–3. doi: 10.1017/S1740925X12000166.Physiological.
60. Hu J, Wang P, Wang Z, Xu Y, Peng W, Chen X, et al. Fibroblast-Conditioned Media Enhance the Yield of Microglia Isolated from Mixed Glial Cultures. Cell Mol Neurobiol. 2023;43(1):395–408. doi: 10.1007/s10571-022-01193-9.
61. Marfia G, Navone SE, Hadi LA, Paroni M, Berno V, Beretta M, et al. The Adipose Mesenchymal Stem Cell Secretome Inhibits Inflammatory Responses of Microglia: Evidence for an Involvement of Sphingosine-1-Phosphate Signalling. Stem Cells Dev. 2016;25(14):1095–1107. doi: 10.1089/scd.2015.0268.
62. Cuitavi J, Duart-Abadia P, Sanchez J, S6nchez-Lypez CM, Lorente JD, Marcilla A, et al. Activated microglia secretome and proinflammatory cytokines increase neuronal mu-opioid receptor signalling and expression. Biochem Pharmacol. 2024;230:116608. doi: https://doi.org/10.1016/j.bcp.2024.116608.
63. Műzes G, Sipos F. Mesenchymal Stem Cell-Derived Secretome: A Potential Therapeutic Option for Autoimmune and Immune-Mediated Inflammatory Diseases. Cells. 2022;11:1–23. doi: 10.3390/cells11152300.