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The impact of minocycline in inhibiting glial scar formation in rats with traumatic brain injury: A mini scoping review

Donny Wisnu Wardhana [1,2]*, Husnul Khotimah [3], Tommy Alfandy Nazwar [2] and Nurdiana Nurdiana [3]

[1] Doctoral Program in Medical Sciences, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2] Department of Surgery, Faculty of Medicine, Universitas Brawijaya/Saiful Anwar General Hospital, Malang, Indonesia.
[3] Department of Pharmacology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
* Correspondence: donnywisnuw@ub.ac.id; Tel.: +6281334350055

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ABSTRACT: Minocycline, a second-generation tetracycline derivative, is proven to inhibit glial scar formation in several neurological diseases. However, studies associating micocycline in traumatic brain injury (TBI) is very limited. This review aims to determine the role of minocycline in inhibiting glial scar or astrogliosis formation in TBI animal models. This scoping review includes original studies in PubMed, Science Direct, and Google Scholar databases published between 1 January 2012 to 31 December 2022, in full text, involving rodent research, and written in English. Two authors who followed the Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines, conducted the assessment independently. Of 2687 studies, 13 studies are reviewed. Two studies describe the benefits of minocycline in inhibiting glial scar formation in TBI, while 11 studies show that minocycline inhibits glial scar formation in diseases other than TBI. An explanation of the signaling pathways and cells involved in the mechanism of glial scar inhibition by minocycline can be found in ten articles, of which four observe the role of microglial cells, four observe the role of astrocyte cells, and two do not explain the mechanism. Research on the impact of minocycline in inhibiting glial scar formation in rats with TBI is limited. The results of this review support early research on the role of minocycline in inhibiting glial scar or astrogliosis in TBI, and similar studies in several other CNS diseases support this. However, the mechanism of minocycline's inhibitory pathway to glial scarring remains unclear.

Keywords: Minocycline; Glial scar; Central nervous system disease; Traumatic brain injury; Rats

1.0 INTRODUCTION

Traumatic brain injury (TBI) is brain damage caused by mechanical forces external to the brain. It can result in temporary or permanent impairments in cognitive, physical, and social brain functions, as well as mild to severe loss of consciousness (coma), which may persist for extended periods and, in severe cases, lead to death (Galgano et al., 2017). Galgano reported that the number of deaths caused by TBI has decreased because of advancements in driving safety technology, enhanced

trauma management, and improved treatment technology. With an increasing number of TBI and decreasing death rates, more people are living with disabilities after TBI. Findings from Ahmed et al. (2017) indicate an annual rise of approximately 100,000 cases of new disabilities due to TBI and long-term consequences in about 2.5 million to 6.5 million people. Furthermore, data presented by James et al. (2019) explain that TBI causes 8.1 million people to live with disability.

One of the causes of prolonged disability following TBI is the creation of a glial scar, which hinders axonal regeneration and counteracts TBI recovery. The formation of glial scar after central nervous system (CNS) trauma (either in the brain or spinal cord) varies based on (1) the type of trauma, namely penetration trauma, contusion, or diffuse trauma (such as in cases of diffuse axonal injury); (2) the severity of the trauma; (3) the duration of time elapsed between the injury and biopsy or autopsy; and (4) the distance of the tissue examined from the site of injury/trauma. According to the study by Wardhana et al. (2023), moderate TBI with small focal lesions can lead to persistent cognitive impairments due to glial scar formation. Glial cells, specifically reactive astrocytes resulting from TBI, form dense glial scars in the perilesional area, which inhibits brain recovery in later phases (Ng & Lee, 2019). This condition is exacerbated by the inadequate intrinsic ability of nerve cells in the CNS to repair injured axons, ultimately leading to regenerative failure (Leibinger et al., 2013).

Currently, there is extensive research on compounds and drugs that are suspected to have neuroprotective effects. Minocycline, a second-generation tetracycline derivative, is one of the compounds that has been extensively studied. It has been shown to have anti-inflammatory, antiapoptotic and antioxidant effects in previous preclinical studies (Meythaler et al., 2019). It has been recommended by the US Food and Drug Administration (FDA-approved) for use in humans and is available at an affordable price (Meythaler et al., 2019). Its neuroprotective properties have been demonstrated in experimental and clinical studies for neurodegenerative disease as well as TBI (Xu et al., 2012), ischemic stroke (Cai et al., 2010; Erning & Segura, 2020), spinal cord injury (Pourkhodadad et al., 2018; Squair et al., 2018), and Alzheimer's disease (Sadick & Liddelow, 2019).

In the case of TBI, studies on the efficacy of minocycline as a neuroprotectant have shown positive effects on therapeutic targets, including neurons, microglia, and oligodendrocytes, leading to clinical improvements (Meythaler et al., 2019). On the other hand, research on the effects of minocycline on astrocyte cells and glial scar development is limited. Astrocytes are the most common type of glial cells and are well-known for their involvement in the cascade of secondary brain damage (Meythaler et al., 2019; Zhou et al., 2020). Therefore, this scoping review aims to determine the role of minocycline in inhibiting the formation of glial scar or astrogliosis in TBI experimental animals.

2.0 METHODS

2.1 Study Design

Minocycline has been shown to inhibit glial scar development in several disorders such as hydrocephalus (Xu et al., 2012), ischemia stroke (Erning & Segura, 2020), spinal cord injury (Pourkhodadad et al., 2018; Squair et al., 2018), and Alzheimer's disease (Sadick & Liddelow, 2019). There are equivalent findings in a few TBI cases. This scoping review aims to compile and share the results of previous studies associating application of minocycline in TBI cases. In addition to discussing the association between minocycline and glial scar in disorders other than brain damage, this review presents the findings of a literature search focusing on the role of minocycline in inhibiting glial scar formation in TBI animal models. This scoping review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018).

2.2 Search Strategy

The keywords used to identify relevant literature were selected based on the population, concept, and context framework and developed in consultation with academic librarians. Each keyword that had been determined in population, concept, and context was entered into each database using the "AND" operator to retrieve pertinent literature.

Population: The population examined in this review comprises all rodents with TBI. Initially, using the keywords (rat OR mice OR rodent) AND ((traumatic brain injury) OR (brain injury) OR TBI) yielded few results. After consulting with academic librarians, the search terms were adjusted to ((traumatic brain injury) OR (brain injury) OR TBI). This modification effectively excluded studies involving subjects other than rats or rodents from the review process.

Concept: The concept of interest is "minocycline" because this review would identify articles that

evaluated the role of minocycline in inhibiting astrogliosis or glial scar formation in TBI cases. This review does not limit the dose, duration of treatment, injection method, and form of utilization of minocycline either as a single drug or in combination.

Context: The context of this review is the inhibition of astrogliosis, or glial scar characterized by a decrease in GFAP expression as an astrocyte marker. This review did not limit the signalling pathways utilized in inhibiting glial scarring.

2.3 Type of Sources

This review considered original research that had been reviewed in the form of quantitative, qualitative, or mixed methods studies.

2.4 Eligibility Criteria

The article's eligibility criteria are based on predetermined inclusion and exclusion criteria. The inclusion criteria include: (1) primary research study; (2) full text available; (3) published between 1 January 2012 and 31 December 2022; (4) research involving rodent subjects; and (5) English language. The exclusion criteria for this review were studies with topics that did not directly discuss minocycline and glial scar, keywords that were not addressed in the core of the study, studies that did not contain all the keywords searched, and research on human subjects.

2.5 Selection Process

The literature review was conducted from 1 – 30 January 2023, using PubMed, Science Direct, and Google Scholar databases. These databases were selected for their comprehensive collection of literature relevant to the review topic. The initial search focused on TBI cases, with the intention to expand to other diseases if insufficient articles discussing minocycline's role in inhibiting glial scar in TBI were found.

Literature from the three databases was compiled and organized using Microsoft Excel and Mendeley. Duplicate entries were eliminated through title screening, followed by sorting based on inclusion criteria by reviewing titles and abstracts. Articles passing the initial screening underwent full-text examination to assess their relevance to the established inclusion and exclusion criteria. Data collection from relevant literature was performed independently by two authors, with a third author resolving any discrepancies. The methodology and findings were documented according to PRISMA-ScR guidelines (**Figure 1**).

2.6 Data Mapping

Data mapping was conducted through detailed article reading by all authors during working meetings. The mapped data included the reference and disease/condition, dosage, route, frequency of minocycline administration, and glial scar formation or astrogliosis. Additionally, information was provided on the research results of each article that demonstrated the role of minocycline in inhibiting glial scar formation or astrogliosis. Key information from each article was compiled in a table for the reader's convenience (**Table 1**). This streamlined summary of the available research on TBI cases laid the groundwork for further investigation into this topic. Following the tabulated results, a narrative summary elaborates on the most significant findings from each set of data extractions and their relation to the research objectives.

3.0 RESULTS

3.1 Article Search Results

The article search process involved three stages: identification, screening, and feasibility evaluation. The identification phase began with a search for relevant publications in three databases, resulting in 2,687 articles published between 1 January 2012 and 31 December 2022. All identified article titles were summarized in Microsoft Excel and sorted alphabetically to identify duplicates, resulting in 488 articles being excluded due to duplication. Subsequently, 2,199 articles were screened based on title and abstract to assess their relevance to the predefined inclusion criteria. Among them, 817 articles met the inclusion criteria, while 1382 articles did not, primarily due to being review articles, lacking abstract/results, and not in English.

Of the 817 articles that passed the screening process, 804 were found not to match the review topic upon full-text review. Meanwhile, two articles were found relevant to the research question related to the role of minocycline in inhibiting glial scar formation in TBI diseases. However, these articles lacked comprehensive information to thoroughly discuss the mechanism of minocycline's role in inhibiting glial scar formation. Consequently, researchers expanded the search to include articles on minocycline's role in inhibiting glial scar formation in other diseases. This extended search yielded 11 additional relevant articles, resulting in 13 articles reviewed (**Figure 1**).

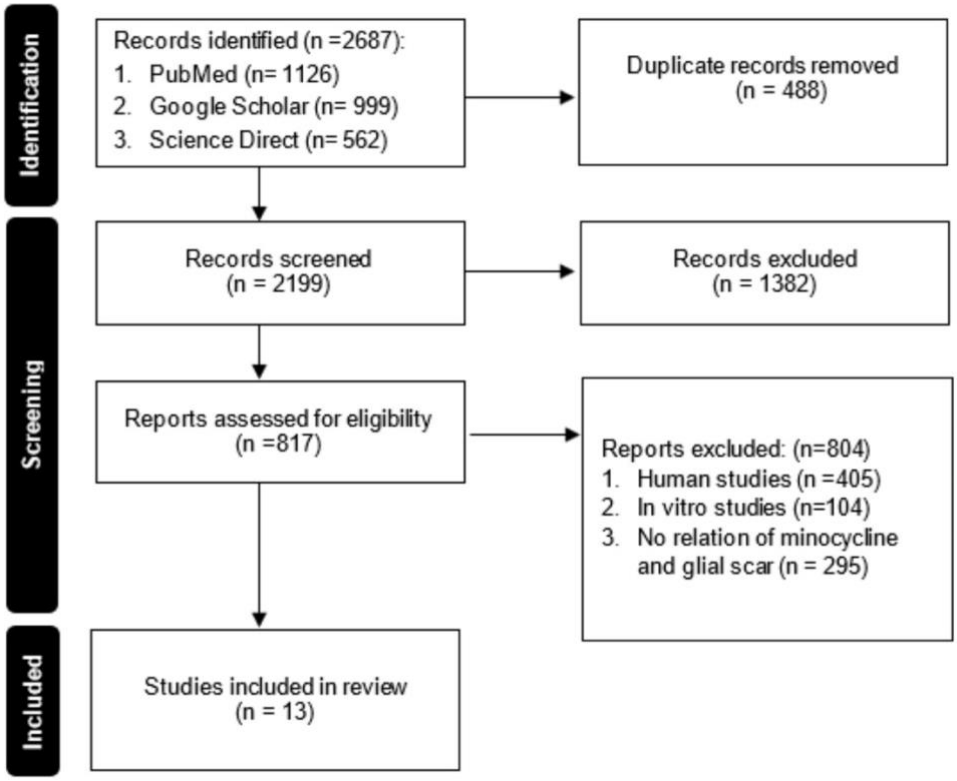

Figure 1: PRISMA-SCR flow chart of the study selection process

3.2 Article Eligibility Results

Thirteen studies were pertinent to this investigation, and their findings supported the assertion that minocycline can inhibit glial scar formation and astrogliosis. Minocycline's effectiveness in inhibiting glial scarring after brain damage was discussed in only two papers (Lam et al., 2013; Shinozaki et al., 2017). Additional studies have identified minocycline's role in inhibiting glial scar formation in various diseases, including obesity (Hsuchou et al., 2012), hydrocephalus (Xu et al., 2012), postoperative cognitive dysfunction (Jin et al., 2013), bone cancer pain (Song et al., 2016), chronic cannula implantation in the rat brain (Hayn et al., 2017), Sandhoff disease (Ogawa et al., 2017), spinal cord injury (SCI) (Pourkhodadad et al., 2018; Squair et al., 2018), prion disease (Shah et al., 2019), neurodegenerative diseases (Ji et al., 2017), and epilepsy (Sano et al., 2021). However, while several studies discussed minocycline's role in glial scar formation, the number of studies on each disease remains limited and not thoroughly explored (**Table 1**).

The drug of interest in this review is minocycline, either reported as single drug use in ten studies (Hayn et al., 2017; Hsuchou et al., 2012; Ji et al., 2020; Jin et al., 2013; Lam et al., 2013; Sano et al., 2021; Shinozaki et al., 2017; Song et al., 2016; Squair et al., 2018; Xu et al., 2012) or a combination of minocycline and other drugs, in three studies (Ogawa et al., 2017; Pourkhodadad et al., 2018; Shah et al., 2019). Seven out of ten articles that used minocycline as a single treatment explicitly demonstrated the inhibition of astrogliosis, while three others concluded the inhibition of Glial Fibrillary Acidic Protein (GFAP), a marker of glial scar formation. The administration of minocycline alone or in combination with FK506 (an immunosuppressive drug) was shown to suppress astrogliosis (Ogawa et al., 2017), while Shah and colleagues (2019) concluded that minocycline + FK506 alone could inhibit astrogliosis during the asymptomatic phase. Another study utilizing an Olfactory Ensheathing Cells (OEC) graft combined with minocycline or minocycline administration alone, showed a reduction in functional deficits and astrogliosis in spinal tissue (Pourkhodadad et al., 2018) (**Table 1**).

Most examined studies (11 out of 13) employed mg/kg dosage units, while nM and g/l were also utilized. The dosage variation within this unit ranged from 25 to 90 mg/kg body weight, with the most commonly used doses being 25 mg/kg (Lam et al., 2013; Sano et al., 2021;

Shah et al., 2019) and 45 mg/kg (Jin et al., 2013; Squair et al., 2018; Xu et al., 2012), which demonstrated an inhibitory effect on astrogliosis. In 11 studies, minocycline was administered intraperitoneally, while this information was not included in the remaining two articles. Among the 13 reviewed articles, eight described the frequency of minocycline administration, while the remaining five did not provide this information. Six out of the eight articles administered minocycline once per day, while the other two administered it twice per day. Regarding the duration of minocycline administration, nine studies provided this information with varying results, ranging from a minimum duration of two days to a maximum duration of thirty days. Among these 11 studies, the most selected duration of minocycline administration was seven days (Lam et al., 2013; Ogawa et al., 2017; Xu et al., 2012).

In this review, ten studies explained the signalling pathways and cells involved in inhibiting astrogliosis or glial scar by minocycline, but three other studies did not explain the mechanism. Of the ten studies, two articles lack explaination on the mechanism of glial scar inhibition by minocycline, four studies explained that inhibition of astrogliosis or glial scar occurred through microglia cells (Lam et al., 2013; Ogawa et al., 2017; Sano et al., 2021; Shah et al., 2019), and four others explained the inhibition of glial scar through astrocyte cells (Jin et al., 2013; Pourkhodadad et al., 2018; Song et al., 2016; Xu et al., 2012). In Song et al. (2016), the inhibition of astrogliosis through astrocyte cells was explained in more detail through the nuclear factor kappa B (NF-KB) p65 signalling pathway.

Table 1: Compilation of article search results

Reference	Disease / condition	Type of medication (Dose, Route, Frequency)	Formation of glial scar / astrogliosis	Result
Hsuchou et al. (2012)	Obesity	Minocycline - 200 nM	(+) Signal line: NA	Minocycline cotreatment completely abolished reactive astrogliosis.
Xu et al. (2012)	Hydrocephalus	Minocycline - 45 mg/kg/day - Intraperitoneal - 1x/day, for 7 days	(+) Signal line: astrocyte	Minocycline could reduce the expression of GFAP and Iba-1 in hydrocephalic rats. Although it cannot prevent the development of hydrocephalus, minocycline can delay its progression. The mechanism may inhibit astrogliosis and glial scar formation, thereby reducing damage to the periventricular white matter.
Jin et al. (2013)	Postoperative cognitive dysfunction	Minocycline - 45 mg/kg - Intraperitoneal - 1x/day, for 30 days	(+) Signal line: astrocyte	This study demonstrates that astroglial scarring related to partial hepatectomy occurs, and minocycline is effective in inhibiting astrocyte activation in the hippocampus, as indicated by changes in GFAP as a marker of astrocyte activation
Lam et al. (2013)	TBI	Minocycline - 25 mg/kg - Intraperitoneal - 1x/day, for 7, 12, or 16 days.	(+) Signal line: microglia	Minocycline suppressed TBI-induced microglial activation in the hippocampus at defined time points after TBI and reduced astrogliosis with only 7 days of treatment. Minocycline also reduced the number of GFAP immunoreactive cells in the perilesional cortex.
Song et al. (2016)	Bone cancer pain	Minocycline - 80 mg/kg - Intraperitoneal - 2x/day, for 3 days	(+) Signal line: astrocytes through NF-κB p65	GFAP level was significantly decreased in rats with bone cancer pain treated with a high dose of minocycline.

(continued on the next page)

Hayn et al. (2017)	Chronic cannula implantation in the rat brain	Minocycline - 20 µg/µL	(+) Signal line: NA	Minocycline improves motor performance and causes temporary inhibition of astrogliosis.
Ogawa et al. (2017)	Sandhoff disease	Minocycline single or combination with FTY720, FK506 - 30 mg/kg - Intraperitoneal - 1x/day, for 7 days	(+) Signal line: microglia	Astrogliosis could be reduced by minocycline or FK506 treatment during the asymptomatic phase.
Shinozaki et al. (2017)	TBI	Minocycline - 50 mg/kg - Intraperitoneal	(-)	The enhancement of astrocyte process extension by microglia is suppressed by minocycline. Without microglia, minocycline does not affect the extension speed of astrocyte processes. Inhibition of microglial activity by minocycline significantly impaired peripheral astrocyte attachment of trauma nuclei *in vivo*.
Pourkhodadad et al. (2018)	SCI	Minocycline single or combination with OEC graft - 90 mg/kg - Intraperitoneal - 1x/day	(+) Signal line: astrocyte	The combination of grafted OECs and minocycline reduced astrogliosis in spinal tissues. The number of GFAP+ astrocytes was significantly attenuated in the minocycline and minocycline+OECs groups.
Squair et al. (2018)	SCI	Minocycline - 45 and 90 mg/kg - Intraperitoneal - 1 hour post injury (90 mg/kg) and 2x/day (45 mg/kg), for 14 days	(-)	GFAP (-) or GFAP (+) areas with disrupted or abnormal cytoarchitecture (demarcation by activated astrocytes) were significantly reduced in minocycline-treated animals compared to the control group.
Shah et al. (2019)	Prion disease	Minocycline + FK506 - 25 mg/kg (minocycline) - Intraperitoneal	(+) Signal line: microglia	FK506 + minocycline treatment efficiently reduced astrogliosis in prion-infected hamsters.
Ji et al. (2020)	Neuro-degenerative diseases	Minocycline - 40 mg/kg - Intraperitoneal - 1x/day	(-)	GFAP intensities significantly increased in the medial prefrontal cortex in the lipopolysaccharide group compared with the control group, which was suppressed by minocycline treatment.
Sano et al. (2021)	Epilepsy	Minocycline - 25 mg/kg - Intraperitoneal	(+) Signal line: microglia	Microglia inhibition with minocycline and depletion with CSF1R antagonist (PLX5622) reduced astrogliosis.

GFAP = Glial fibrillary acidic protein; NA = Not Available; NF-κB = nuclear factor kappa B; Signal line = signalling pathways inhibiting astrogliosis/glial scar by minocycline; TBI = Traumatic brain injury; OEC = Olfactory ensheathing cells; CSF1R = Colony stimulating factor 1 receptor; (+) = glial scar or astrogliosis is formed; (-) = not explained on glial scar or astrogliosis formation.

4.0 DISCUSSION

Animal models in TBI research are invaluable to understanding the pathophysiology of TBI. Most of the secondary injury events that occur in clinical TBI also occur in animal models. Thus, it validates the use of animal models to find drug targets to treat TBI. Almost all therapeutic time window studies have used rodent models of TBI. Therapeutic time window studies in rodents do not only assume that the pathophysiology of TBI is similar in animals and humans, but these pathophysiological events also occur with similar kinetics (Mohamadpour et al., 2019). Therefore, in this scoping review, we included rodents as one of the criteria for article selection to investigate minocycline's role in inhibiting glial scar.

Astrocytes respond to various injuries through a complex process known as reactive astrogliosis. Reactive astrogliosis is not a simple phenomenon of presence or absence but is a series of finely graded changes that occur context-dependently governed by specific signalling events. These changes range from reversible alterations in gene expression and cell hypertrophy with preservation of the cell environment and tissue structure, to forming lasting scars with the rearrangement of tissue structure. Although the changes in increasing severity of reactive astrogliosis occur seamlessly and become one entity, it is convenient for description and classification to recognize three broad categories as initially proposed by Sofroniew and Vinters (2010), namely mild to moderate reactive astrogliosis, severe diffuse reactive astrogliosis, and severe reactive astrogliosis with glial scar formation. The limitations of the research revealed by this review demonstrate that glial scar is not uniformly defined; some studies mentioned astrogliosis but did not explain the grading, and some studies only explained the increased GFAP synthesis without determining whether glial scar was formed. However, all these topics generally refer to glial scar formation.

The evidence presented in this review paper demonstrates that minocycline plays a function in the inhibition of glial scar or astrogliosis in a variety of disorders affecting the CNS, including TBI, SCI, obesity, hydrocephalus, postoperative cognitive dysfunction, bone cancer pain, chronic cannula implantation in the rat brain, Sandhoff disease, Prion disease, neurodegenerative diseases, and epilepsy. Several other reports support the association of minocycline with neurological diseases, such as hemorrhagic and ischemic stroke, multiple sclerosis, SCI, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), which lead to various clinical trials. Clinical trials of minocycline administration in ALS and Huntington's disease have been completed with positive results and are in progress for TBI cases. It is due to the relatively small size of minocycline (457 Da) and its highly lipophilic nature that can easily cross the blood-brain barrier and has been shown to penetrate human Colony Stimulating Factor (CSF) better than doxycycline and other tetracyclines (Pechacek, 2020).

According to the findings of this research, minocycline can inhibit the production of glial scar tissue in various disorders that affect the CNS. However, the number of studies on each disease/condition is still small (one to two studies on each disease), indicating no variety of research and in-depth analysis of the mechanism. In addition, not all studies explain the mechanism of minocycline in glial scar inhibition. In previous studies, indirect glial scar inhibition through microglia cells has been observed to be more dominant. However, very few studies have observed the inhibition of glial scar directly through astrocyte cells. One of the studies (Song et al., 2016) reported the inhibition of astrogliosis through the NF-κB p65 signalling pathway in astrocyte cells.

The discussion of minocycline inhibiting glial scar formation in TBI is still very limited. Two studies (Lam et al., 2013; Shinozaki et al., 2017) supported the above statement. Still, the inhibition of glial scar, specifically through astrocyte cells, and the signalling pathways involved have not been discussed in detail. This scoping review has several limitations, including the fact that we only reviewed full-text articles, while other articles contain proprietary information and are not publicly available. This scoping review is also limited to searches between 2012 and 2022, so there is potential to develop further scoping reviews with broader topics and updated publication years.

5.0 CONCLUSIONS

The results of this review support the initial research on the role of minocycline in inhibiting astrogliosis or glial scar in TBI, and similar studies in several other CNS diseases support this. However, the data are still very limited, and the discussion is still not in detail, so further research is needed that looks at the signalling pathways that become the factors, especially in astrocyte cells as the primary formers of the glial scar. This paper, hopefully, can support the proof of the effectiveness of minocycline as one of the potential neuroprotectants through the glial scar inhibition pathway.

Author contributions:
DWW conceptualized the idea, performed the literature search, selection, and quality analysis, wrote and edited the manuscript; HK, TAN and NN conceptualized the idea, guided the selection and quality analysis, and reviewed the manuscript. All authors have read and approved the final version of manuscript.

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Conflicts of interest:
The authors declare no conflict of interest.

References

Ahmed, S., Venigalla, H., Mekala, H. M., Dar, S., Hassan, M., & Ayub, S. (2017). Traumatic brain injury and neuropsychiatric complications. *Indian Journal of Psychological Medicine, 39*(2), 114–121. https://doi.org/10.4103/0253-7176.203129

Cai, Z. Y., Yan, Y., & Chen, R. (2010). Minocycline reduces astrocytic reactivation and neuroinflammation in the hippocampus of a vascular cognitive impairment rat model. *Neuroscience Bulletin*, *26*(1), 28–36. https://doi.org/10.1007/s12264-010-0818-2

Erning, K., & Segura, T. (2020). Materials to promote recovery after stroke. *Current Opinion in Biomedical Engineering, 14,* 9–17. https://doi.org/10.1016/j.cobme.2020.04.002

Galgano, M., Toshkezi, G., Qiu Xuecheng, Russel, T., Chin, L., & Zhao, L.-R. (2017). Traumatic Brain Injury: Current treatment strategies and future endeavors. *Cell Transplantation*, *26*(7), 1118–1130. https://doi.org/10.1177/0963689717714102

Hayn, L., Deppermann, L., & Koch, M. (2017). Reduction of the foreign body response and neuroprotection by apyrase and minocycline in chronic cannula implantation in the rat brain. *Clinical and Experimental Pharmacology and Physiology*, *44*(2), 313–323. https://doi.org/10.1111/1440-1681.12703

Hsuchou, H., Kastin, A. J., & Pan, W. (2012). Blood-borne metabolic factors in obesity exacerbate injury-induced gliosis. *Journal of Molecular Neuroscience*, *47*(2), 267–277. https://doi.org/10.1007/s12031-012-9734-4

James, S. L., Bannick, M. S., Montjoy-Venning, W. C., Lucchesi, L. R., Dandona, L., Dandona, R., Hawley, C., Hay, S. I., Jakovljevic, M., Khalil, I., Krohn, K. J., Mokdad, A. H., Naghavi, M., Nichols, E., Reiner, R. C., Smith, M., Feigin, V. L., Vos, T., Murray, C. J. L., … Zaman, S. B. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(1), 56–87. https://doi.org/10.1016/S1474-4422(18)30415-0

Ji, M. H., Lei., L., Gao, D. P., Tong, J. H., Wang, Y., & Yang, J. J. (2020). Neural network disturbance in the medial prefrontal cortex might contribute to cognitive impairments induced by neuroinflammation. *Brain, Behavior, and Immunity*, *89*, 133–144. https://doi.org/10.1016/j.bbi.2020.06.001

Ji, X., Peng, D., Zhang, Y., Zhang, J., Wang, Y., Gao, Y., Lu, N., & Tang, P. (2017). Astaxanthin improves cognitive performance in mice following mild traumatic brain injury. *Brain Research*, *1659*, 88–95. https://doi.org/10.1016/j.brainres.2016.12.031

Jin, W. J., Feng, S. W., Feng, Z., Lu, S. M., Qi, T., & Qian, Y. N. (2013). Minocycline improves postoperative cognitive impairment in aged mice by inhibiting astrocytic activation. *NeuroReport*, 25(1), 1–6. https://doi.org/10.1097/WNR.0000000000000082

Lam, T. I., Bingham, D., Chang, T. J., Lee, C. C., Shi, J., Wang, D., Massa, S., Swanson, R. A., & Liu, J. (2013). Beneficial effects of minocycline and botulinum toxin-induced constraint physical therapy following experimental traumatic brain injury. *Neurorehabilitation and Neural Repair*, *27*(9), 889–899. https://doi.org/10.1177/1545968313491003

Leibinger, M., Andreadaki, A., Diekmann, H., & Fischer, D. (2013). Neuronal STAT3 activation is essential for CNTF- and inflammatory stimulation-induced CNS axon regeneration. *Cell Death and Disease*, *4*(9). https://doi.org/10.1038/cddis.2013.310

Meythaler, J., Fath, J., Fuerst, D., Zokary, H., Freese, K., Martin, H. B., Reineke, J., Peduzzi-Nelson, J., & Roskos, P. T. (2019). Safety and feasibility of minocycline in treatment of acute traumatic brain injury. *Brain Injury*, *33*(5), 679–689. https://doi.org/10.1080/02699052.2019.1566968

Mohamadpour, M., Whitney, K., & Bergold, P. J. (2019). The importance of therapeutic time window in the treatment of traumatic brain injury. *Frontiers in Neuroscience*, *13,* 7. https://doi.org/10.3389/fnins.2019.00007

Ng, S. Y., & Lee, A. Y. W. (2019). Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. *Frontiers in Cellular Neuroscience, 13,* 528. https://doi.org/10.3389/fncel.2019.00528

Ogawa, Y., Sano, T., Irisa, M., Kodama, T., Saito, T., Furusawa, E., Kaizu, K., Yanagi, Y., Tsukimura, T., Togawa, T., Yamanaka, S., Itoh, K., Sakuraba, H., & Oishi, K. (2017). FcRγ-dependent immune activation initiates astrogliosis during the asymptomatic phase of Sandhoff disease model mice. *Scientific Reports*, *7*. https://doi.org/10.1038/srep40518

Pechacek, K. M. (2020). *Minocycline as a treatment for traumatic brain injury-induced impulsive and attentional deficits impulsive and attentional deficits*. [Master's Thesis, Eberly College of Arts and Sciences]

Pourkhodadad, S., Oryan, S., Kaka, G., & Sadraie, S. H. (2018). Neuroprotective effects of combined treatment with minocycline and olfactory ensheathing cells transplantation against inflammation and oxidative stress after spinal cord injury. *Cell Journal*, *21*(2), 220–228. https://doi.org/10.22074/cellj.2019.6126

Sadick, J. S., & Liddelow, S. A. (2019). Don't forget astrocytes when targeting Alzheimer's disease. *British Pharmacological Society*, *176*, 3585–3598. https://doi.org/10.1111/bph.14568

Sano, F., Shigetomi, E., Shinozaki, Y., Tsuzukiyama, H., Saito, K., Mikoshiba, K., Horiuchi, H., Cheung, D. L., Nabekura, J., Sugita, K., Aihara, M., & Koizumi, S. (2021). Reactive astrocyte-driven epileptogenesis is induced by microglia initially activated following status epilepticus. *JCI Insight, 6*(9), e135391. https://doi.org/10.1172/jci.insight.135391

Shah, S. Z. A., Zhao, D., Taglialatela, G., Hussain, T., Dong, H., Sabir, N., Mangi, M. H., Wu, W., Lai, M., Zhang, X., Duan, Y., Wang, L., Zhou, X., & Yang, L. (2019). Combinatory FK506 and minocycline treatment alleviates prion-induced neurodegenerative events via caspase-mediated MAPK-NRF2 pathway. *International Journal of Molecular Sciences*, *20*(5). https://doi.org/10.3390/ijms20051144

Shinozaki, Y., Shibata, K., Yoshida, K., Shigetomi, E., Gachet, C., Ikenaka, K., Tanaka, K. F., & Koizumi, S. (2017). Transformation of Astrocytes to a Neuroprotective Phenotype by Microglia via P2Y1 Receptor Downregulation. *Cell Reports*, *19*(6), 1151–1164. https://doi.org/10.1016/j.celrep.2017.04.047

Sofroniew, M. V., & Vinters, H. V. (2010). Astrocytes: Biology and pathology. *Acta Neuropathologica, 119*(1), 7–35. https://doi.org/10.1007/s00401-009-0619-8

Song, Z. P., Xiong, B. R., Guan, X. H., Cao, F., Manyande, A., Zhou, Y. Q., Zheng, H., & Tian, Y. K. (2016). Minocycline attenuates bone cancer pain in rats by inhibiting NF-κB in spinal astrocytes. *Acta Pharmacologica Sinica*, *37*(6), 753–762. https://doi.org/10.1038/aps.2016.1

Squair, J. W., Ruiz, I., Phillips, A. A., Zheng, M. M. Z., Sarafis, Z. K., Sachdeva, R., Gopaul, R., Liu, J., Tetzlaff, W., West, C. R., & Krassioukov, A. V. (2018). Minocycline Reduces the Severity of Autonomic Dysreflexia after Experimental Spinal Cord Injury. *Journal of Neurotrauma*, *35*(24), 2861–2871. https://doi.org/10.1089/neu.2018.5703

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Wardhana, D. W., Yudhanto, H. S., Riawan, W., Khotimah, H., Permatasari, H. K., Nazwar, T. A., & Nurdiana, N. (2023). Modification of the height of a weight drop traumatic brain injury model that causes the formation of glial scar and cognitive impairment in rats. *BMC Neurology*, *23*(1), 439. https://doi.org/10.1186/s12883-023-03494-y

Xu, H., Tan, G., Zhang, S., Zhu, H., Liu, F., Huang, C., Zhang, F., & Wang, Z. (2012). Minocycline reduces reactive gliosis in the rat model of hydrocephalus. *BMC Neuroscience*, *13*(1). https://doi.org/10.1186/1471-2202-13-148

Zhou, Y., Shao, A., Yao, Y., Tu, S., Deng, Y., & Zhang, J. (2020). Dual roles of astrocytes in plasticity and reconstruction after traumatic brain injury. *Cell Communication and Signaling*, 18(1), 62. https://doi.org/10.1186/s12964-020-00549-2