• Bibliometric Research •

Research on neurotrophic factor for glaucoma: a worldwide bibliometric analysis

Sahilah Ermawati[1], *Winastari Yarhanim Triniputri*[2], *Muhana Fawwazy Ilyas*[2,3,4], *Syahnaz Adilla*[2], *Shafira Nur Hanifa*[2], *Azka Auliarahman*[5]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Muhammadiyah Surakarta, Surakarta 57162, Central Java, Indonesia
[2]Medical Profession Program, Faculty of Medicine, Universitas Sebelas Maret, Surakarta 57126, Central Java, Indonesia
[3]Department of Anatomy, Faculty of Medicine, Universitas Sebelas Maret, Surakarta 57126, Central Java, Indonesia
[4]Department of Neurology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta 57126, Central Java, Indonesia
[5]Surakarta Central General Hospital, Surakarta 57144, Central Java, Indonesia

Correspondence to: Sahilah Ermawati. Department of Ophthalmology, Faculty of Medicine, Universitas Muhammadiyah Surakarta, A. Yani Street, Mendungan, Pabelan, Kartasura, Sukoharjo 57162, Central Java, Indonesia. se119@ums.ac.id

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Abstract

• **AIM:** To comprehensively investigate the current state of research on the application of neurotrophic factors in glaucoma therapy and identify potential research hotspots.

• **METHODS:** On September 30, 2023, a literature search was conducted on Scopus using specific keywords related to neurotrophic factors and glaucoma. Of the 918 articles retrieved, 780 met the inclusion criteria. These articles were subsequently analyzed and visualized using Google Sheets, Biblioshiny 3.1, and VosViewer 1.6.18.

• **RESULTS:** A total of 780 studies published between 1989 and 2023 were included, and the global publication count showed an upward trend through 2023 (projected to continue rising by 2030). The United States, China, Japan, Italy, and Australia were the most significant contributors to the publication output. Research in this field had been published in 313 journals, spanning categories such as pharmacology and drug development, ophthalmology, genetics and gene therapy, and neuroscience. A total of 2622 authors had contributed to these studies, with the most prolific author publishing 14 articles. The focus of research in this field had evolved sequentially from "glutamate" to "CNTF" and "GDNF", and finally to "optic nerve injury". Co-occurrence analysis identified five clusters: glaucoma and ocular health, neuroinflammation in ophthalmology, neuroprotection in ophthalmology, ocular drug delivery, and stem cell therapy. Several areas in this field require further exploration, including the neurophysiological mechanisms underlying glaucoma, ocular drug delivery systems, and the clinical value of specific neurotrophic factors.

• **CONCLUSION:** This study systematically reviews global research trends on neurotrophic factors in glaucoma therapy, clarifying the current research status and future directions.

• **KEYWORDS:** bibliometric; glaucoma; neurotrophic factor; optic nerve injury; retinal ganglion cell

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INTRODUCTION

Glaucoma is an optic neuropathy clinically manifested in visual field defects[1]. The optic nerve damage is mainly associated with intolerance to injury due to rising intraocular pressure (IOP), although several patients may have normal (<21 mm Hg) IOP[2-3]. Some vital pathological features of glaucoma include apoptosis of retinal ganglion cells (RGCs), retinal edge and nerve fiber layer thinning, as well as optic disc atrophy and depression, which eventually lead to irreversible peripheral-to-central visual field defects[4]. Glaucoma is still a global burden as it is the leading cause of irreversible blindness worldwide[5]. In 2020, 7.73 million people aged older than 50y suffered from glaucoma, while 3.6 million of those had already experienced blindness. This number kept rising during the last 20y. Glaucoma then accounted for 11% of worldwide blindness among people aged 50y and older in 2020[6].

Numerous IOP-lowering therapeutic strategies have been well-developed, adapting to the type of glaucoma[7]. Typically, glaucoma is classified into open or closure-angle, as well as primary or secondary based on underlying ocular or systemic diseases[8]. For open angle glaucoma, topical drugs, laser trabeculoplasty, and surgical intervention have been widely performed in an ordering manner. IOP-lowering drugs include carbonic anhydrase inhibitors, prostaglandin analogs, β-blockers, α-agonists, and muscarinic receptor agonists[9]. Surgical interventions include trabeculectomy, tube shunt, minimally invasive glaucoma surgery, and cyclodiode laser[7]. As for closure-angle glaucoma, it is treated emergently with laser peripheral iridotomy to open the drainage angle. Sometimes, it is also necessary to perform a lens extraction if the patients have cataracts[10]. However, there are still some patients who display increased IOP despite those combinations; this may be due to the effects of those treatments being transitory since IOP is volatile[11-12]. There is also this terminology called "normotension glaucoma", indicating that there is glaucomatous optic neuropathy despite having a normal IOP[7]. On top of that, the treatments mentioned above have adverse effects predictive of further retinal deterioration, making glaucoma therapy a remaining challenge[13].

Based on those challenges, the interest in glaucoma therapy has shifted from IOP-lowering to an optic-neuroprotection approach[14]. This is due to existing studies stating that elevated IOP does not always correlate with RGC degeneration[15]. Neuroprotection strategies improve RGC survival and/or prevent RGC death from an insult[7]. It targets glutamate and nitric oxide (NO) production, nerve cell trophic (nutritional) factor deprivation, and intracellular self-repair and destructive processes[16]. One of the identified substances that have neuroprotective features is neurotrophic factors[17]. Neurotrophic factors are biomolecules that support the growth, survival, and differentiation of neurons[18]. It consists of several subfamilies, but the most applicable ones to glaucoma are the neurotrophin (NT) family, the 130 kDa glycoprotein (GP130) cytokine family, and glial cell line-derived neurotrophic factor (GDNF) family[13]. This can be explained by RGC, which expresses receptors capable of binding to those families only[8]. NT family consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, NT-4, and NT-5. All these substances are produced locally by RGCs and retinal astrocytes. They are also synthesized in the brain, then transported retrogradely *via* RGC axon terminals, and bound to its receptor in the retina. This family is essential in the signalling pathway responsible for pro-survival and/or pro-growth cellular response[19]. The GP130 family is compromised of ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and interleukin (IL)-6, which regulate gene expression[20]. GDNF may function in the secretion of other growth factors[21]. Several studies have introduced various methods of neurotrophic factors administration, including direct application, slow-release devices, gene therapy, and cell transplantation[12,22].

The development of an approach in glaucoma treatment leads to more research. It is advantageous to have a tool that aids researchers in comprehending this topic's past, present, and future such as bibliometric analysis. Thus, unmet study hotspots can be evaluated and improved. Bibliometrics examines the quantity and quality of publications, eventually explaining the academic productivity and evolution of a particular area[23-24]. It analyzes and visualizes literature data using quantitative methods, assisted by software such as VOSviewer, CiteSpace, Microsoft Excel, and Scimago Graphica[25]. VOSviewer and CiteSpace helped us evaluate countries, regions, authors, organizations, journals, tendencies, hotspots, and knowledge networks[26-27]. The statistical findings can subsequently help to investigate research trends, healthcare guidelines, and clinical decision-making[23,28]. To our knowledge, no bibliometric analysis has been conducted previously addressing this issue. Thus, our study presents a comprehensive analysis regarding the current status of research on neurotrophic factors usage in glaucoma therapy and its potential research hotspots.

MATERIAIS AND METHODS

Data Sources and Search Strategy Data was acquired from a literature search using the Scopus database. The following keywords were used: ("Nerve Growth Factors" OR NGF OR "Growth-Associated Proteins, Neuronal" OR "Neurite Outgrowth Factor" OR "Neurite Outgrowth Factors" OR "Neuronal Growth-Associated Protein" OR "Neuronal Growth-Associated Proteins" OR "Neuronotrophic Factor" OR "Neuronotrophic Factors" OR "Neurotrophic Factor" OR "Neurotrophic Factors" OR "Neurotrophic Protein" OR "Neurotrophic Proteins" OR "Neurotrophin" OR "Neurotrophins" OR "Proteins, Neuronal Growth-Associated" OR "Brain-Derived Neurotrophic Factor" OR BDNF OR CNTF OR "Ciliary Neuronotrophic Factor" OR GMF OR "Glial Maturation Factor" OR "Glia Maturation Factor" OR "Glial Cell Line-Derived Neurotrophic Factors" OR "GDNF Family Ligands" OR "GDNF Protein Family" OR Netrin OR "Netrin Family" OR "NRG Proteins Neuregulin" OR "Neuronal Differentiation Factor, Cholinergic" OR "Neurotrophin 3" OR "Pituitary Adenylate Cyclase-Activating Polypeptide" OR PACAP OR "Pituitary Adenylate Cyclase Activating Polypeptide") AND (Glaucoma). The search processes were performed on September 30th, 2023, to avoid bias due to daily update of databases.

Selection Process Two independent and blinded reviewers (Triniputri WY and Ilyas MF) conducted the search and selection processes to avoid bias. The initial search revealed 918 studies. The search results were then confined to several inclusion criteria: 1) in the form of an article, review, or conference paper; 2) had reached the final stage of publication; 3) written in English; 4) sourced from a journal. Seven hundred and eighty obtained studies met those criteria. Afterwards, we collected all the metadata, including abstract and keywords, bibliographical information, citation information, and funding details. The metadata was downloaded in CSV format to ensure compatibility with the following software. The entire selection process is visualized in Figure 1.

Data Analysis and Visualization This study examined five research constituents: 1) annual scientific production; 2) most prolific countries; 3) most relevant journals; 4) most influential authors; 5) trend topics. This study also performed a co-occurrence analysis to evaluate the association between keywords and generated a suitable cluster analysis afterwards. A thematic map is analyzed to uncover critical topics for future research development.

Several software applications were used to analyze and visualize the data. Google Sheets (Google LLC, California, USA) generated "Annual scientific production". Biblioshiny 3.1 (University of Naples Federico II, Naples, Italy) was utilized to both analyze and visualize "Most prolific countries", "Most relevant journals", "Most influential authors", "Trend topics",[29], and the thematic map[30-33]. Last, VOSviewer 1.6.18 (Leiden University, Leiden, Netherlands) was utilized to display the overlay visualization[34-36], co-occurrence and the suitable cluster analysis[37-39].

RESULTS

General Description of Studies Involved The dataset includes 780 studies that were all conducted between 1989 and 2023. In general, 2622 authors contributed to those studies, with 51 working as a single author. Moreover, an average of 4.83 co-authors contributed to each document, with international partnerships accounting for 20% of collaborations. The documents above comprised 411 articles, 19 conference papers, and 350 reviews, with 47.55 average citations per document. In addition, all studies were derived from 313 journals and encompassed 1539 author's keywords.

Annual Scientific Production An upward cumulative publication trend line shown in Figure 2 suggests a constant rise of global research in neurotrophic factors usage in glaucoma therapy, particularly since 1989. Subsequently, it is predicted to keep rising until 2030. The number of publications underwent a minor decline several times but reached the highest point in 2021 with 81 published studies. Last, the

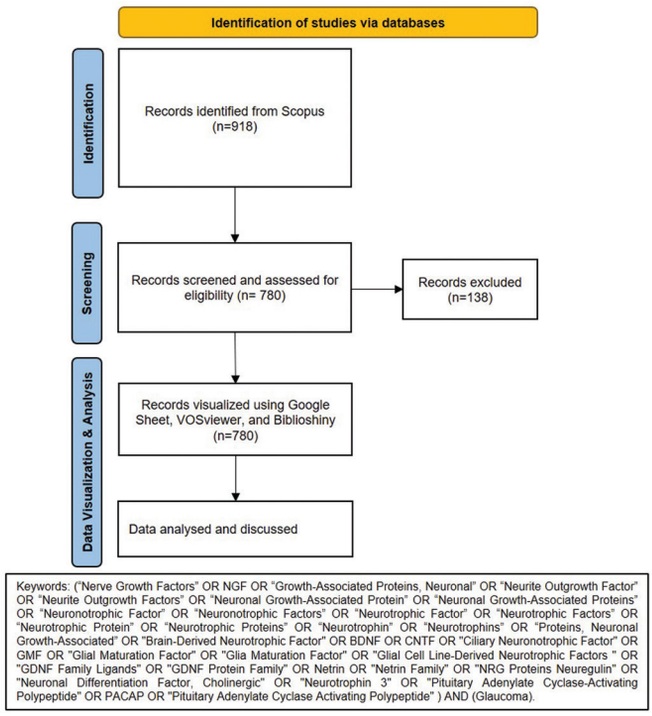

Figure 1 PRISMA-modified diagram visualizing search and selection processes.

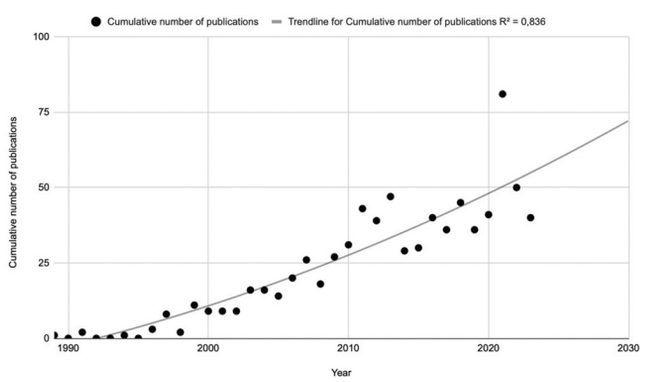

Figure 2 Cumulative number of global publications over years.

R-squared value of 0.836 represents this robust upward trend. This may indicate an increasing interest in the studies on neurotrophic factors for glaucoma.

Forty-eight countries have contributed to the global-published studies in this field. Figure 3 denotes that The United States initiated the study with two articles in 1989. Their productivity began to increase in 1997, and by the time of the search process, 941 studies had been published. However, China began its first contribution in 2001 by publishing 1 article. Their productivity significantly rose in 2007, resulting in 475 published studies. As for Japan, it started its initial participation in 1996, publishing seven articles. Their productivity experienced a significant increase in 2010, resulting in 312 published studies. Meanwhile, Italy made its initial contribution in 2003 with 1 article. In 2008, their productivity surged, resulting in 292 published studies. In the meantime, Australia initiated its contribution in 2006, publishing eight

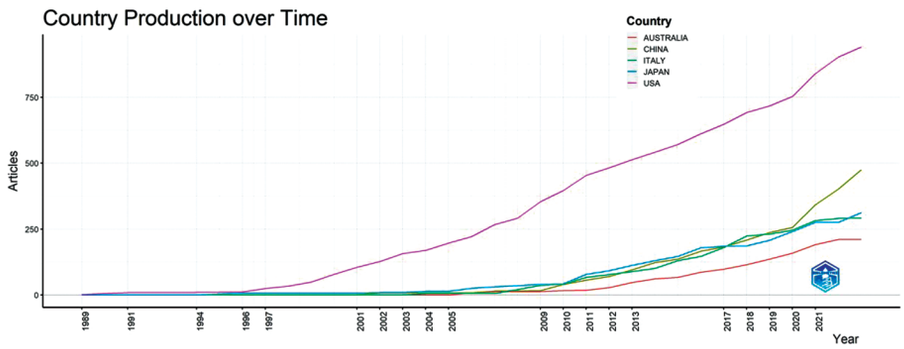

Figure 3 Five countries with highest number of studies production over years.

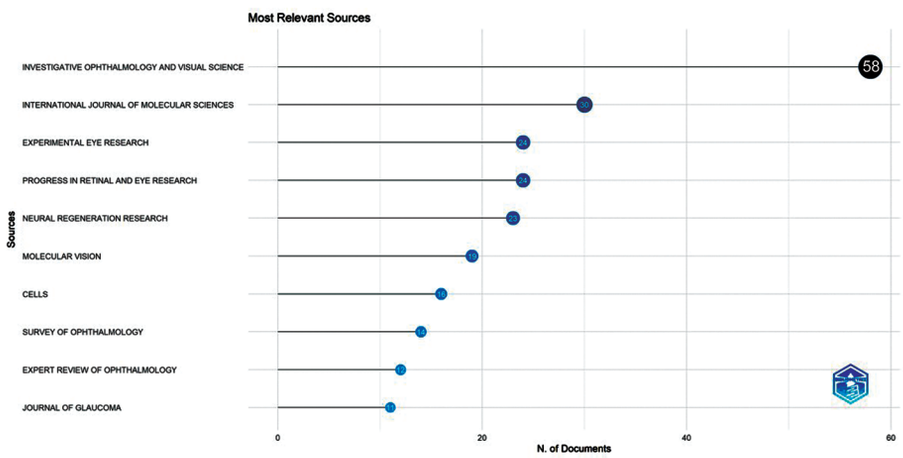

Figure 4 Numbers of studies published by the top 10 highest-publishing journals.

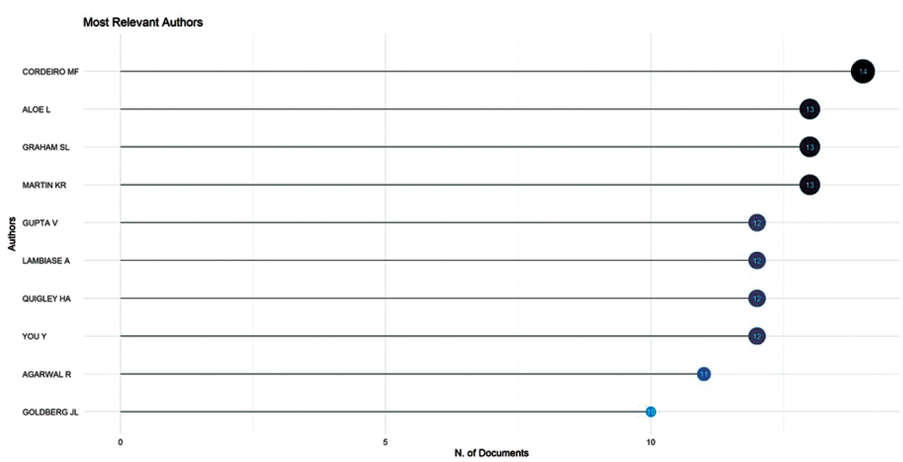

Figure 5 Cumulative numbers of studies produced by the top 10 highest-producing authors.

articles. In 2014, its productivity significantly rose, resulting in 211 published studies.

Most Relevant Journals A compilation of studies encompassing this field has been published in 313 reputable journals, whose categories varied from pharmacology and drug development, ophthalmology, genetics, and gene therapy to neuroscience journals. Each of those journals published a range of 1 to 58 studies. As illustrated in Figure 4, among all journals, "*Investigative Ophthalmology and Visual Science*" has successfully published the largest amount of studies, indicating its commitment and substantial impact on this field.

Two thousand six hundred and twenty-two authors have contributed to this field, constructing various studies ranging from 1 to 14. As seen in Figure 5, Cordeiro MF has appeared as the most prolific author, producing 14 studies, which account for 1.79% of all included studies. As a matter of initiation, Figure 6 shows that Quigley HA played an essential role in pioneering the study by producing two articles in 1997. Quigley HA also produced the second-most impactful article in 2011, as it received a total citation of 926 times and an average of 71.1 times being cited per year. It has been stated as the highest number from 1989 to 2023. Meanwhile, Gupta V took the spotlight in the latest contribution by producing two articles, receiving a total citation of 202 times in 2014.

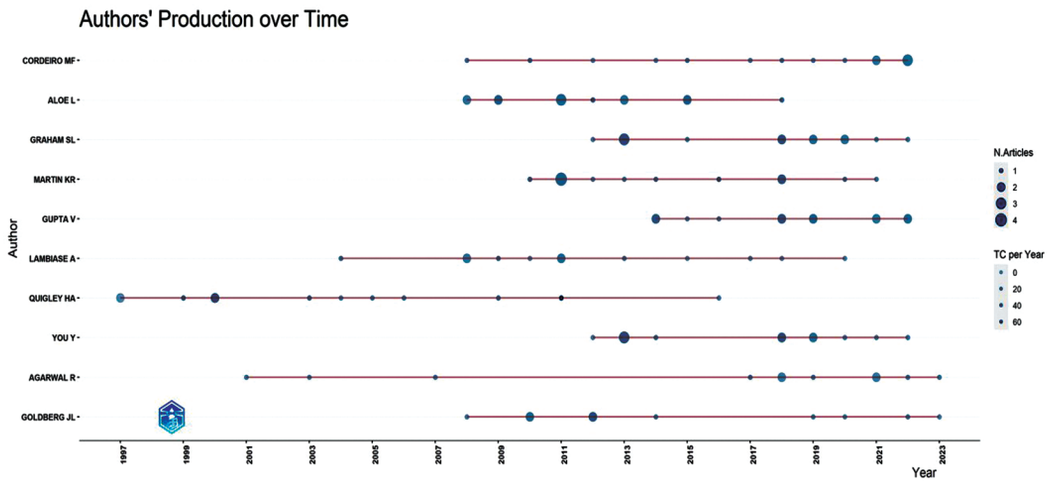

Figure 6 The top 10 highest-producing authors' production over time.

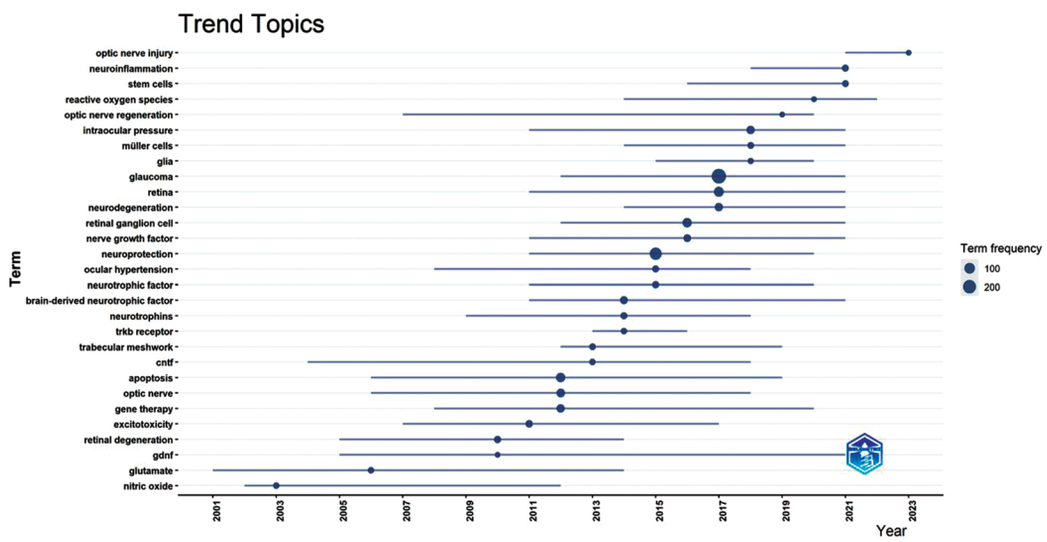

Figure 7 Trend topics diagram for time-based patterns of keyword usage.

Trend Topics This study demonstrates a noteworthy pattern shift in the interest of research topics. Figure 7 suggests that over the last 21y, research regarding neurotrophic factors and glaucoma revolved around words describing the cells involved, general and molecular underlying pathophysiology, subtypes of the neurotrophic factors, and therapeutic strategies. In the meantime, Figure 8 shows the visualization of the time-based trends of keywords. The terms "glaucoma", "retina", and "intraocular pressure" remain essential for comprehending and managing this issue. Subsequently, "Apoptosis", "oxidative stress", and "neuro-inflammation" underscore the continuous focus on molecular mechanisms in the development of glaucoma. As for emerging areas of research, the predominance of innovative therapeutic techniques is represented by "drug delivery", "nanoparticles", and "stem cells". Last, the recent incorporation of keywords such as "neuroregeneration" and "axon regeneration" indicates future research on restoring and reversing glaucoma.

Co-occurrence analysis has been employed to identify clusters of similar studies, which subsequently depict patterns and relationships between studies encompassing neurotrophic factors usage in glaucoma. This investigation uncovered five clusters distinguished by different colors, as illustrated in Figure 9. Cluster 1 (glaucoma and ocular health) specifically addresses factors associated with the pathogenesis and diagnosis of glaucoma including IOP, genetics, biomarkers, vascular endothelial growth factor, and aqueous humour. Cluster 2 (neuro-inflammation in ophthalmology) encompasses the processes of retinal aging, inflammation, oxidative stress, cellular and molecular processes of microglia, mitochondria, and diabetic retinopathy. Cluster 3 (neuroprotection in ophthalmology) discusses gene therapy, excitotoxicity, neurotrophic factors, axon regeneration, apoptosis, and optic nerve injury. Cluster 4 (ocular drug delivery) concentrates on technology for delivering medication into the eyes including the use of exosomes, nanoparticles, and sustained release mechanisms. Cluster 5 (stem cell therapy) revolves around clinical trials, cell treatment, stem cells, photoreceptors, retinal

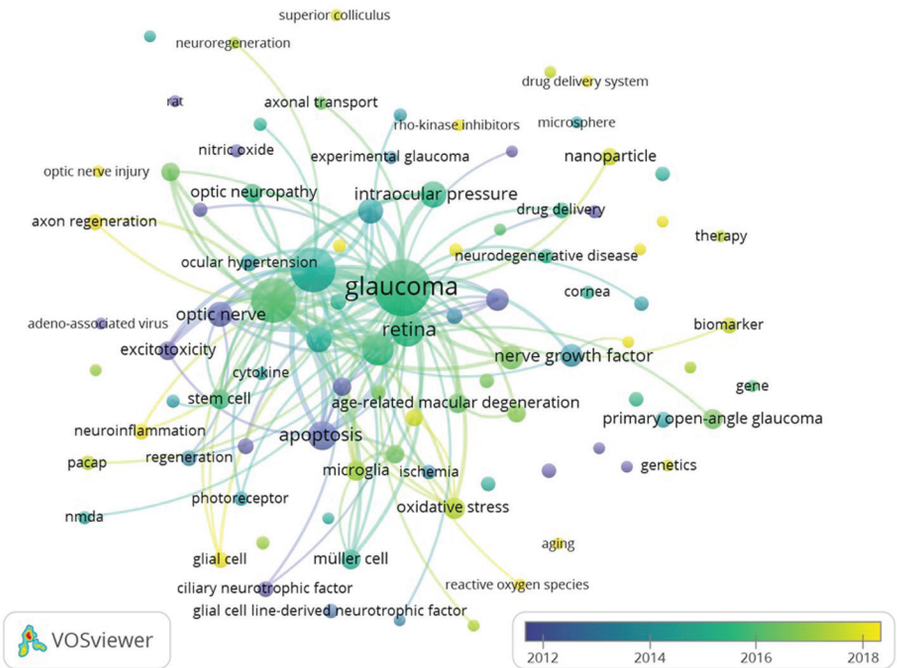

Figure 8 Overlay visualization of association between keywords on time basis.

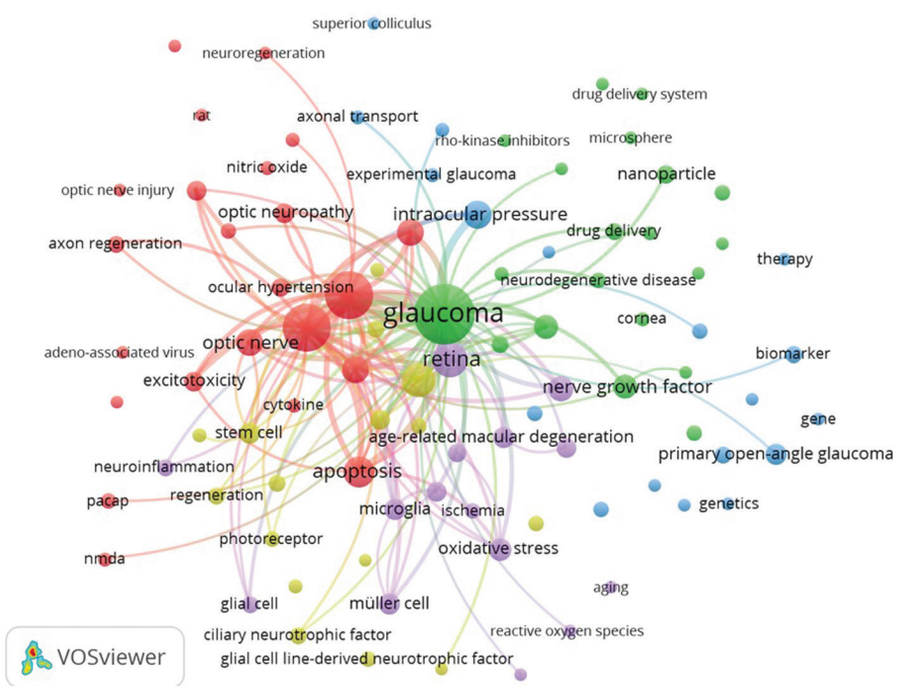

Figure 9 Network visualization of co-occurrence analysis regarding association between keywords.

degeneration, and transplantation suggesting the potential of this regenerative approach.

Thematic map In the studies of neurotropic factor usage in glaucoma, we identified motor, niche, declining or emerging, and basic themes based on the scientific map. As seen in Figure 10, motor themes such as microglia, axonal transport, neuro-inflammation, and oxidative stress indicate well-developed subjects with substantial effects in this field. Future research could investigate the role of neurotrophic factors on oxidative stress and neuro-inflammation associated with glaucoma. Subjects, either new or diminishing, such as neurotrophic keratitis and Alzheimer's disease may require additional research and revitalization. The comparable pathogenic mechanisms and therapeutic potential of both neurodegenerative illnesses and glaucoma may be further investigated. Last, the basic themes highlight the necessity of fundamental topics exploration, including glaucoma, neuroprotection, RGC, apoptosis, excitotoxicity, and genetics to refine and enhance the neuroprotective approach utilizing neurotrophic factors.

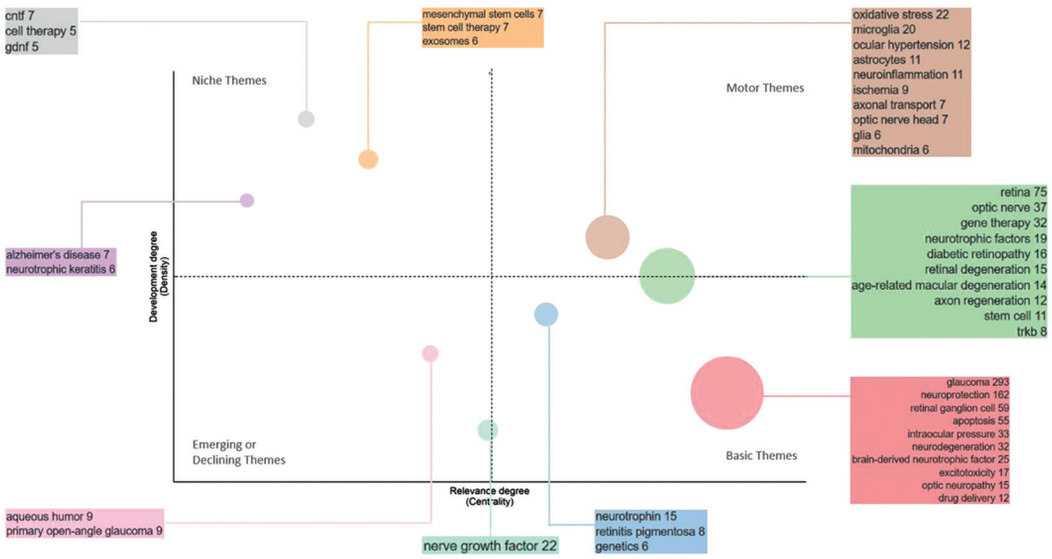

Figure 10 Thematic map of keywords regarding neurotrophic factors usage in glaucoma therapy.

DISCUSSION

General Description of Included Studies Since 1989, the interest in glaucoma therapy studies has shifted from IOP-lowering to an optic-neuroprotection approach. The first article was "Neural crest origin of human trabecular meshwork and its implications for the pathogenesis of glaucoma". It addressed the capability of NGF to restore the expression of neuronal-specific enolase (NSE) in the trabecular meshwork, while NSE itself is an isoenzyme that marks neuronal maturation[40-42]. This statement is possibly thought to trigger the idea of neurotrophic factor's involvement in the pathogenesis and possible treatment of glaucoma. Subsequently, worldwide authors started to collaborate to unravel the complexities of this disease, potentially leading to more effective clinical interventions and treatments.

Most Impactful Study on the Given Field A study entitled "Müller cells in the healthy and diseased retina", written by Bringmann *et al*[43] in 2006, exhibits the most significant impact on this field. It was cited 1342 times, while the average citations of each document were 47.55 times. The study discussed the basic properties of Müller cells, their role in retinal physiology, and the basic concept of Müller cells-targeted therapy in retinal neurodegeneration. Müller cells itself are the most common glial cells in the retina. It protects retinal neurons from cell death by releasing neurotrophic factors such as BDNF and NGF, which promote RGC survival and regeneration[44]. Meanwhile, in retinal injury or disease such as glaucoma, Müller cells undergo reactivation (gliosis)[45].

Shifting Pattern of Sub-topic Usage The use of neurotrophic factors in glaucoma therapy began with the idea of neuronal involvement in the pathophysiology of glaucoma. The previous interest in the topic emphasizes "glutamate" in the early years. Glutamate is an excitatory neurotransmitter in the retina released into the extracellular space due to injury, especially ischemia. A few cells known to release glutamate include photoreceptor, bipolar, retinal ganglion, horizontal, and amacrine cells, as well as retinal glial cells, including Muller cells and astrocytes[46]. However, excess glutamate due to increased synthesis or decreased clearance results in neurotoxicity and apoptosis of RGC[47]. Inhibitors of several ionotropic receptors that support glutamate excitotoxicity, including N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and Kainate, are an effective targeted therapy for attenuating RGC death[48]. Following the exploration of Glutamate, "GDNF" and "CNTF" took over the landmark by holding the most extended duration of interest. Due to the glutamate, Müller glia upregulates their secretion of several neurotrophic factors, including GDNF and CNTF, to prevent glutamate toxicity[21]. The binding of GDNF to its suitable receptor called GDNF receptor-alpha (GFRα1 and GFRα2) triggers a signalling cascade that prevents injury to photoreceptors in animal models of retinal degeneration[49]. As for CNTF, extracellular CNTF binds to a receptor complex in Müller cells, activating signalling pathways for gene expression that stimulate the regeneration of rod photoreceptor and cone cells in the degenerating retina, as well as protection in RGCs axon[50]. At last, in recent years, "optic nerve injury" has become a highlighted topic. They indicate that a more profound concept of optic nerve injury as the basic pathophysiology of glaucoma might alter future neuroprotective strategies.

Cluster 1: Glaucoma and Ocular Health It is critical to note that increased IOP is not the primary etiology of glaucoma but an essential cause for inducing its symptoms[51]. Several IOP-independent risk factors for glaucoma have been identified, including ocular biomechanics, a family history, age, gender

(male), ethnicity (mainly African), and lower systolic blood pressure or any other events causing vascular insufficiency to optic nerve head[52]. Mechanisms independent of elevated IOP[15], such as degeneration or even death of RGC, axonal loss, and disruption of the lamina cribrosa, are the main events of glaucoma pathogenesis[53]. From a molecular perspective, RGC damage can occur due to various mechanisms triggered by baric trauma (increased IOP)[54], ischemia (low ocular perfusion pressure)[55], or metabolic toxins such as glutamate, which then stimulate the inflammatory process and extensive apoptosis in the optic nerve head[51]. However, elevated IOP is the only modifiable factor for glaucoma[53].

Nowadays, the detection of visual field defects is commonly done by perimetry after 40%-50% RGC loss has occurred, making this method less sensitive for early glaucoma identification. Meanwhile, treatment interventions at the early stage are most likely to improve clinical results[56]. Several modalities to detect early RGC loss have been identified, including: optical coherence tomography (OCT), which detects retinal nerve fiber layer (RNFL) thinning, making it predictive of visual field defect in pre-perimetric glaucoma[57]; pattern electroretinogram (PERG), which measures the electrical activity of RGCs even in early defect[58]; detection of apoptosis retinal cells (DARC), which uses a confocal scanning laser ophthalmoscope (cSLO) to detect a fluorescent-conjugated apoptosis marker[59]. By now, a range of neuroprotective therapies have been suggested to reduce the rate of RGC loss. However, most studies only originated from preclinical disease models, and none have successfully made it to clinical practice.

Cluster 2: Neuro-inflammation in Ophthalmology Glial cell activation marks ongoing neuro-inflammatory processes in glaucoma[60]. Retinal glial cells are classified as macroglia, including Müller cells, astrocytes, and microglia[53]. In early-stage of this disease, glial cells provide growth factors to the damaged RGCs to initially isolate and resolve the neural distress; however, when chronically stimulated, glial cells lose their supportive function and the ability to buffer extracellular glutamate, thus exacerbating damage and apoptosis of RGCs by producing pro-inflammatory cytokines, and complement[53]. Under glaucomatous conditions, parasympathetic activity is reduced, causing autoreactive compensatory vasodilatation mediated by NO, specifically the neurotoxic inducible nitric oxide synthase (iNOS). Both hypoxic and ischemic conditions can also activate the retinal glia, which then increases its secretion of the pro-inflammatory cytokine, typically tumour necrosis factor-α (TNF-α), IL-1β, and IL-6. In glaucoma, there is also a reduced glutamate aspartate transporter (GLAST) expression, lowering the glutamate uptake by Muller cells, which may result in glutamate excitotoxicity. The increase in pro-inflammatory cytokine secretion and excitotoxicity mentioned above leads to the apoptosis of RGC. On the other hand, increased IOP or disruption of lamina cribosa can compress the RGC axon. This contributes to impaired retrograde transport of BDNF and NGF from the superior colliculus to the body of RGC, worsening the apoptosis of RGC. Lastly, an overexpressed transforming growth factor beta (TGF-β2) in glaucomatous injury can lead to fibrosis, increased production, and deposition of extracellular matrix proteins in trabecular meshwork cells, subsequently inhibiting aqueous humour drainage[51].

Cluster 3: Neuroprotection in Ophthalmology Based on its therapeutical targets, the neuroprotection approach can be categorized into substances that counter excitotoxicity, oxidative stress, mitochondrial dysfunction, inflammation-abnormal immune response, glial cell modulation, and stem cell therapy[7]. Excitotoxicity refers to cell death due to toxic actions of excessive Glutamate. Memantine, Brimonidine, and cannabinoids act in interfering with this process[61]. In addition, dysfunctional mitochondria lead to an imbalance between the generation and detoxification of reactive oxygen species (ROS); this condition is known as oxidative stress, which subsequently stimulates RGC death. Vitamin E (α-tocopherol), vitamin C, coenzyme Q10, and citicoline are antioxidants targeting this damage[62-63]. Several natural compounds such as Gingko Biloba and Curcumin are also a well-known antioxidant and anti-inflammatories due to their activity in scavenging ROS and inhibiting nitric oxide synthase (NOS), as well as anti-apoptotic through the inhibition of TGF-β, caspase-3, BAX, Fas and its ligand (FasL)[64]. Furthermore, RGC degeneration resulting from pathological insult is mediated through inflammation due to activation of glial cells releasing pro-inflammatory cytokines, such as TNF-α and IL-1β. Thus, TNF-α has been proposed as a possible targeted therapy[7]. As mentioned in the previous section, activation of glial cells during the early phase of injury results in the release of neurotrophic factors[65]. However, in chronic injuries such as glaucoma, neurotrophic factor levels decreased in aqueous humour and lacrimal fluid[66]. Thus, the administration of neurotrophic factor may act as a promising target of therapy[7].

Up to this day, the neurotrophic factor is the most studied neuroprotective agent. Neurotrophic factors have been proven to support neural differentiation, growth, and survival. It can be classified into the NT, CNTF, GDNF, insulin-like growth factor, and basic fibroblast growth factor family[18]. The NT family consists of NGF, BDNF, NT-3, NT-4, NT-5, NT-6, and NT-7[67]. The most widely used neurotrophic factors in the glaucoma set are NGF, BDNF, CNTF, and GDNF. Those four factors are generally secreted by various retinal parts (including RGC and glial cells) and superior colliculus, passing through both anterograde and retrograde transport to

reach RGC soma[14]. Subsequently, NGF binds to tropomyosin receptor kinase (TrkA); BDNF, NT-4, and NT-5 bind to TrkB; NT-3 binds to TrkC, whereas all bind to the p75 NT receptor (p75NTR)[67]. Neurons, Schwann cells, oligodendrocytes, T cells, mast cells, and macrophages also secrete NGF. It binds to 2 types of retinal receptors: the TrkA expressed by RGC and glial cells[68]. Binding to TrkA induces activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/Akt pathways, which promote growth, differentiation, survival, and anti-apoptotic RGC. Conversely, signaling *via* p75NTR promotes apoptosis[18]. As for BDNF, it is produced by RGCs, retinal Muller cells, astrocytes, amacrine cells, and photoreceptors. Its binding to TrkB stimulates a protective effect due via the reduction in activity of caspase-9 and caspase-3 in the PI3K-dependent mechanism; it also alters the MAPK pathway[69]. Meanwhile, CNTF was expressed in every retina layer and in the optic nerve head[14]. It binds to a GP130 receptor to activate the janus kinase/signal transducers and activators of transcription (JAK/STAT) and MAPK pathways, stimulating neuron regeneration[50]. Both BDNF and CNTF expression can be modulated by inhibiting the purinergic receptor P2X7 (P2X7R) expressed by the cornea, lens cells, retinal astrocytes, microglia, and central nervous system neurons. P2X7R itself can secrete pro-inflammatory molecules that promote neuro-inflammation and neurodegeneration[70]. At last, GDNF can upregulate GLAST in Müller glia, which reduces glutamate excitotoxicity, indirectly promotes RGC and axonal survival, increased density of the RGCs, as well as lowered pro-inflammatory glial cell activation[71].

Cluster 4: Ocular Drug Delivery The advancement in ocular drug delivery is closely linked to the most pertinent study, "Topical treatment for retinal degenerative pathologies: a systematic review"[72]. Ocular drugs can be administered via juxta scleral, intravitreal, intraocular, subconjunctival, intracameral, or retrobulbar routes. However, self-administered topical therapy is the most convenient[73]. When treating optic neuropathy such as glaucoma, the eye barrier, including the blinking system, corneal epithelium, aqueous outflow, lens, vitreous body, blood-retinal barrier, and retinal pigment epithelium can hinder most drugs to the posterior segment[74]. Besides the physiological wall, the effectiveness of topical drug administration depends on the active pharmaceutical ingredients (API) lipid solubility, as the more lipophilic, the better it penetrates the cornea[75]. However, recent trends aim to develop topical drugs that ensure effective therapeutic concentration even when reaching the retinal level. Concentrations of APIs are 10–100 times lower in the vitreous than those in the aqueous humour and cornea after topical treatment. However, this study demonstrates that specific APIs can still be absorbed in the retina up to an adequate level through corneal or non-corneal pathways[72].

Neuroprotective drugs such as citicoline, recombinant human NGF, and coenzyme Q10 were all investigated in the review. Citicoline, assisted with hyaluronic acid and benzalkonium chloride as penetration enhancers, can reach the vitreous in an animal experimental model[76]. Therefore, this substance may directly act on ganglion cells and their fibres, which are affected both morphologically and functionally in glaucoma. Topical coenzyme Q10 administration to Alzheimer's patients also increased RNFL on OCT, indicating its favorable activity on retinal ganglion cells[77]. In contrast, Beykin *et al*[78] discovered that topical recombinant human NGF did not affect glaucoma patients. However, the authors claim that their study could be underpowered. On the other hand, the kinetics of those APIs in the eye are not yet known for long-term administration; thus, testing the toxicity of the preparations in the eye is also required.

Cluster 5: Stem Cell Therapy The main attraction of stem cell therapy is that grafted cells can produce and secrete neurotrophic factors locally continuously without the need for repeated applications or genetically altered endogenous cells[13]. Despite that excellence, it has become a controversy as there are no licensed stem cell therapies for glaucoma or other visual neuropathies yet. However, there is a clinical trial that show promising outcomes[14]. Basically, stem cells can be divided into embryonic, adult, and induced pluripotent stem cells based on their origin. Adult stem cells for ocular use include mesenchymal, neural progenitor, ocular progenitor, and olfactory ensheathing[79]. Stem cells can also be extracted from bone marrow aspirates for autologous transplantation, avoiding the ethical, logistical, and rejection difficulties associated with other stem cell sources[80]. Mesenchymal stem cells (MSC) have been numerously reported to have neuroprotective properties in glaucoma[81]. MSCs express a range of neurotropic factors and anti-inflammatory cytokines such as CNTF, GDNF platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Thus, its intraocular administration leads to a sustained supply of neuroprotective and neurorestorative agents[82]. Meanwhile, embryo, adult-derived neural progenitor, and Müller glia stem cell transplantation have similarly shown to be neuroprotective and neurorestorative[83]. Other than neuroprotective and neurorestorative properties, some stem cells can also differentiate into phagocytes for trabecular meshwork cells, improving aqueous humour filtration and decreasing IOP[84]. Regarding its delivery, intravitreal and sub-tenon have been widely used[85]. However, one significant reason stem cells became a controversy is their complications, including severe and irreversible vision loss due to ocular hypertension, lens dislocation, vitreous hemorrhage, vitreous

clumping, endophthalmitis hemorrhagic retinopathy, combined rhegmatogenous and traction retinal detachment, retinal folding, and epiretinal membrane formation[86]. Another challenge in stem cell therapy is the difficulty in addressing the stem cells to differentiate into a particular target tissue. There is also a possible constant risk of undesired tissue generation at MSC transplantation sites, associated with its likelihood of developing into bone and cartilage cells[87].

In conclusion, this study thoroughly examines the worldwide research trends on neurotrophic factors in glaucoma. The outcomes reveal various noteworthy patterns and insights. First, research in this sector has experienced a significant rise since 1989, indicating the increased recognition of the importance of neurotrophic factors in glaucoma. The United States, China, Japan, Italy, and Australia, among other productive countries, have substantially contributed to this sector. The multinational participation highlights the significance of addressing glaucoma and investigating neurotrophic factors on a global scale. The analysis identifies Cordeiro MF, Aloe L, Graham SL, and Martin KR as the leading authors who have significantly contributed to the advancement of this field, showcasing their long-standing passion and commitment. In addition, the co-occurrence analysis and thematic map identify clusters of research that emphasize on glaucoma and ocular health, neuro-inflammation in ophthalmology, neuroprotection, ocular drug delivery, and stem cell therapy. These clusters aid in organizing either progressing or emerging areas, thus offering valuable suggestions for future research avenues.

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