• Bibliometric Research •

Mapping key trends, relationships, and molecular pathways for neuroprotection in glaucoma: a bibliometric approach

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Received: 2024-08-26 Accepted: 2025-02-08

Abstract

● Glaucoma, a degenerative optic neuropathy, causes retinal ganglion cell (RGC) apoptosis and irreversible vision loss. Current therapies often fail to stop disease progression despite lowering intraocular pressure, the main risk factor. Thus, neuroprotective strategies have gained interest. We performed a bibliometric analysis to determine global publishing trends and relationships among prolific authors, publications, institutions, funding agencies, and journals. We also analyzed author keywords to identify research hotspots in glaucoma neuroprotection. Further, based on keyword analysis, we reviewed most recent literature to understand mechanistic pathways underlying glaucoma-related pathophysiological responses leading to RGC loss. Bibliographic data were sourced from Scopus. Basic bibliographic features were characterized using Scopus's functions. VOSviewer was used for mapping and visualizing bibliometric networks. The analysis included trends in publications since 2000, the most prolific countries, institutions, authors, and the strength of their linkages. A significant increase in publication output over the past two decades was noted. The United States leads in funding support, research output, and citation links, followed by China and the UK. Among the top 10 most cited authors, three are from Japanese institutions. Keyword analysis shows a focus on molecular targets related to ischemia, excitotoxicity, inflammation, and oxidative stress, with fewer emerging drug candidates and limited clinical trials. Based on the most recent literature, emerging molecular targets underlying these key pathophysiological mechanisms are summarized. In conclusion, while pathophysiology and molecular mechanisms are the current focus, there is not much progress in developing new drug candidates and conducting clinical trials.

● **KEYWORDS:** glaucoma; neuroprotection; bibliometric analysis; publishing trends; molecular pathways; molecular targets

DOI:10.18240/ijo.2025.06.21

Citation: Agarwal P, Agarwal R, Iezhitsa I. Mapping key trends, relationships, and molecular pathways for neuroprotection in glaucoma: a bibliometric approach. *Int J Ophthalmol* 2025;18(6):1131-1145

INTRODUCTION

Glaucoma, a leading cause of irreversible blindness, is characterized by apoptotic loss of retinal ganglion cells (RGCs) and degeneration of optic nerve fibers. Various risk factors are known to be associated with glaucoma and among these, elevated intraocular pressure (IOP) is the most significant one[1]. Other risk factors include advanced age, race, myopia, genetic predisposition, family history, smoking, cardiovascular abnormalities and others[2]. The global prevalence of glaucoma among people aged 40-80y is estimated to be 3.54%. In 2013, the number of people in this age group that were affected by glaucoma worldwide was estimated to be 64.3 million and this number is expected to increase to 111.8 million in 2040[3]. Various sub-types of glaucoma include primary open angle glaucoma (POAG), primary angle-closure glaucoma, primary congenital glaucoma, and secondary glaucoma. Although elevated IOP is known to be associated with all types of glaucoma, a subset of POAG patients develop glaucomatous changes despite normal IOP, the normal tension glaucoma (NTG). Importantly, the proportion of NTG among POAG cases has been reported to be as high as 46.9% and 92.3% among Iranian[4] and Japanese people[5], respectively.

The pathological hallmark of glaucoma irrespective of presence or absence of elevated IOP remains the loss of RGCs and optic nerve fibers and this manifests clinically as changes in visual fields. Currently, the treatment of glaucoma is primarily based on managing the risk factors. Since

elevated IOP is the only modifiable risk factor, the mainstay of treatment remains IOP reduction either by using medications or surgery. It has, however, been observed that IOP lowering alone is often insufficient to halt neuronal loss and provide adequate control of disease progression[6]. In this context, a search into neuroprotective options that can prevent RGC and optic nerve axon loss independent of IOP lowering has attracted great attention particularly over the past few decades. As a result, several mechanisms have been outlined to play a significant role in glaucomatous RGC apoptosis in the presence as well as absence of elevated IOP and these include retinal ischemia, excitotoxicity, neuroinflammation, growth factor deprivation, oxidative and nitrosative stress, mitochondrial dysfunction, endoplasmic reticulum stress and activation of apoptotic signaling[7-8].

Considering the vast amount of research in the field of glaucoma related neuroprotection, it is of utmost importance that current literature is examined to get an insight into the trends and networks of ongoing research and recognize future direction. This is of particular significance as a guide for researchers to recognize the areas of interest and opportunities to establish linkages for meaningful research output. Various reviews have analyzed findings from animal and clinical studies to understand the approach for neuroprotection in glaucoma[9-10]. However, to the best of our knowledge, the global trends and research hotspots in this field have not been analyzed and presented. From this viewpoint, bibliometric analysis is an efficient tool to analyze and summarize literature to understand the current and future research trends and hotspots. It incorporates quantitative techniques to analyze and visualize data. The analysis has several dimensions and helps researchers to visualize the trends and evolution of published literature. In this paper we performed a bibliometric analysis to determine the global publishing trends, most prolific authors, publications, institutions, funding agencies and journals in the field of neuroprotection for glaucoma. We also determined the cooperative relationship between authors, institutions, and countries/regions in this field of research. Importantly, we also attempted to highlight the frontier topics that are attracting the attention of researchers over time and are currently the research hotspots in the field of neuroprotection in glaucoma.

MATERIALS AND METHODS

Data Source, Search Strategy and Data Collection The search for bibliographic data was made using Scopus database that has a wide collection of papers published in biomedical sciences. The VOSviewer software (2020)[11] used in the analysis in this study allows data extraction from a single database. Keeping this in mind Scopus was chosen over the Web of Science database due to its more inclusive and wider coverage of biomedical research articles[12]. In fact, it has been reported that for citation analysis, Scopus gives a 20% greater coverage than Web of Science[13]. The initial search was done using key words “glaucoma” AND “neuroprotection”. The duration of publications was then limited from the year 2000 till March 2024. In the next step the search was limited to publication type “article” and “review”. Further the inclusion was limited to articles published in “English” only. The search was completed on 10.03.2024. Our initial search discovered 2258 documents. With application of further inclusion criteria, the total number of articles retrieved was 1773 (Figure 1).

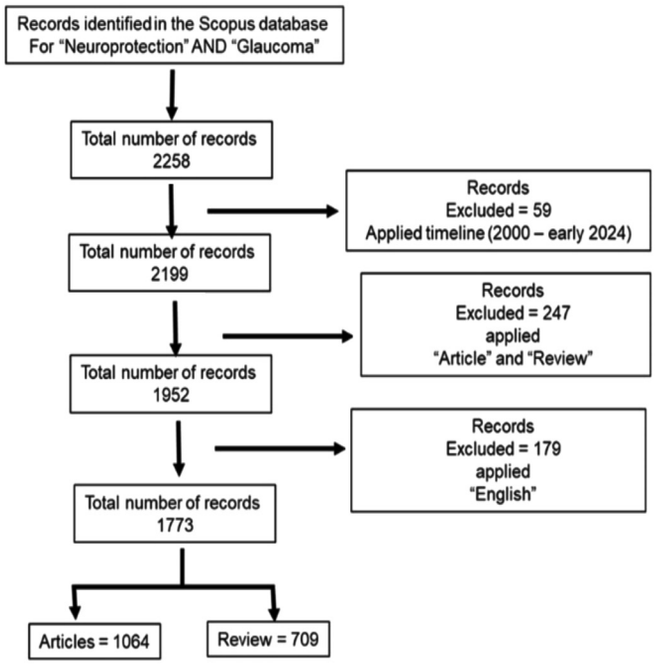

Figure 1 Search strategy and the number of documents retrieved.

Data Cleaning and Analysis Bibliographic Meta-data was obtained from Scopus and the intrinsic function of Scopus was used to characterize the basic bibliographic features of included publications which included journal source, publication year, authors name, country, and funding source. The Meta-data was exported in a comma-separated values (CVS) file format. VOSviewer version 1.6.20 was utilized for mapping and visualizing bibliometric networks. Before analysis, the data were “cleaned” through a process of “data disambiguation” by detecting similarities[14] using OpenRefine version 3.8-beta1[15]. Bibliometric analysis uses Meta-data (such as author names, document titles, affiliations, keywords, citations) rather than research findings in individual data items. Hence it is important that all “ambiguities” in the dataset are identified and eliminated[16]. For example, the same author’s names and affiliations stated differently in different documents are identified as different items. Hence, we recognized these similarities and merged the same items for accurate analysis. The keyword analysis was carried out in three sequential steps. First, author keywords occurring most frequently were identified to get an insight into the “topics” that have

attracted the greatest attention from researchers in the field of neuroprotection in glaucoma. Next, we performed keyword co-occurrence analysis in VOSviewer[11] in order to visualize the relationships of keywords to one another. Keyword co-occurrence analysis is a text-mining technique that analyzes the "co-occurrence" of pairs of keywords in the documents[14]. The findings of analysis were presented as a network map that helps to visualize the frequency of occurrence of keyword and patterns of its co-occurrence. The network map helps to identify thematic clusters within a specific research area. Lastly, we performed a "temporal co-word analysis" to highlight the changing patterns of research foci in the literature on neuroprotection in glaucoma. To perform keyword analysis a thesaurus file was created in which the occurrence of similar keywords was merged. For example, "glaucoma" and "Glaucoma"; "Clinical trials" and "Clinical trial"; "neuroprotection" and "Neuroprotection"; "Retinal ganglion cells/retinal ganglion cells" and "rgcs"; "Intraocular pressure/intraocular pressure/IOP" and "iop" *etc*.

Overall, analysis included trends in the number of publications since 2000 in the area of neuroprotection and glaucoma, most prominent countries, institutions, funding agencies and authors involved in this area of research and how they are connected. Citation linkages among authors, countries and documents and author-coauthor linkages highlight hotspots of collaborative linkages that have been most productive in the research field of neuroprotection in glaucoma. Keyword analysis gave an insight into the topics that have been attracting attention of researchers over past two decades.

RESULTS

Global Trends in the Total Publication Output on Glaucoma and Neuroprotection A steady increase in the number of publications in the field of glaucoma and neuroprotection is evident over the past 23y. Publication output increased by more than 500% with an increase in the total number of publications from 23 publications in 2000 to 145 publications in 2023 (Figure 2).

Prominent Affiliating Countries, Institutions, Funding Sources and Publishing Journals A total of 66 countries were affiliated in the retrieved documents. Affiliation to The United States was discovered in 692 documents (29.35%) followed by China (266 documents; 11.28%); The United Kingdom (150 documents; 6.36%); Japan (147 documents; 6.23%) and Italy (128 documents; 5.43%; Figure 3A). The top 10 funding agencies that supported research in the field of glaucoma and neuroprotection are shown in Figure 3B. Of these 5 are from the United States, two from Japan and one each from China, Germany and Canada. Among the top 10 affiliations, 4 institutions were from the United States, 3 from China and 1 each from Australia, Italy and the UK. The maximum number

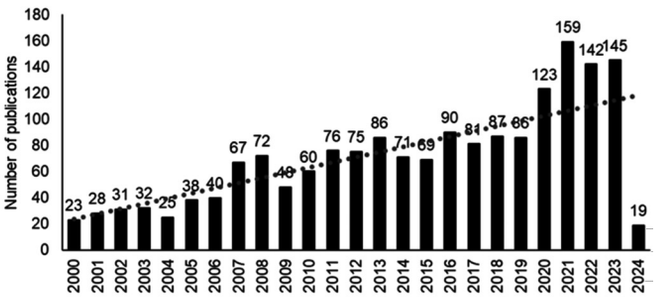

Figure 2 Trend in the total annual publications in the field of neuroprotection in glaucoma from Jan 2000 till early 2024.

of research papers in the field of neuroprotection in glaucoma were published by *Investigative Ophthalmology and Visual Sciences* followed by *Experimental Eye Research* and *Neural Regeneration Research*. The top 10 journals publishing this area of research are presented in Figure 3D. Five of these journals are not Ophthalmology specialist journals.

Prominent Author Profiles and Top Cited Publications We examined the retrieved data for authors with maximum citations. The top 10 authors that have produced the maximum number of documents are listed in Table 1 along with their H-index and affiliations. The affiliating countries among these authors were Japan (3), UK (2), China (1), the USA (1), Spain (1), Germany (1), and Canada (1). If the authors had more than one affiliation, the 1st among the list was chosen. Table 2 presents the top cited articles in the field of glaucoma and neuroprotection[17-26]. Among these, 8 are review papers while two were original research of which one involves human subjects, and the other is the *in vitro* study using retinal ganglion and glial cells.

Citation Linkages Among Authors, Countries and Documents The linkages among various items were represented as networks consisting of items (*e.g.*, author, country *etc.*) and links between items. Based on linkages, items are grouped into clusters. One item belonged to only one cluster, hence there was no overlap. Some items, however, fell outside any cluster. The circular nodes represented each item, and the size of the node indicates the weight of the item. The weight of an item indicates the importance of the item. An item with a higher weight is regarded as more important (and hence represented with a larger node) compared to an item with a lower weight. The weight of an item reflects the number of its links with other items and total strength of these links. All items in one cluster are represented in one colour. The lines between items are a representation of links. The distance between nodes indicates the relatedness of two items.

Author citation links To determine the author-citation links, the minimum number of documents of an author was set at 5; a total of 216 authors met the threshold. Network visualization showed 10 clusters. Of these top 3 clusters consisted of 57, 29,

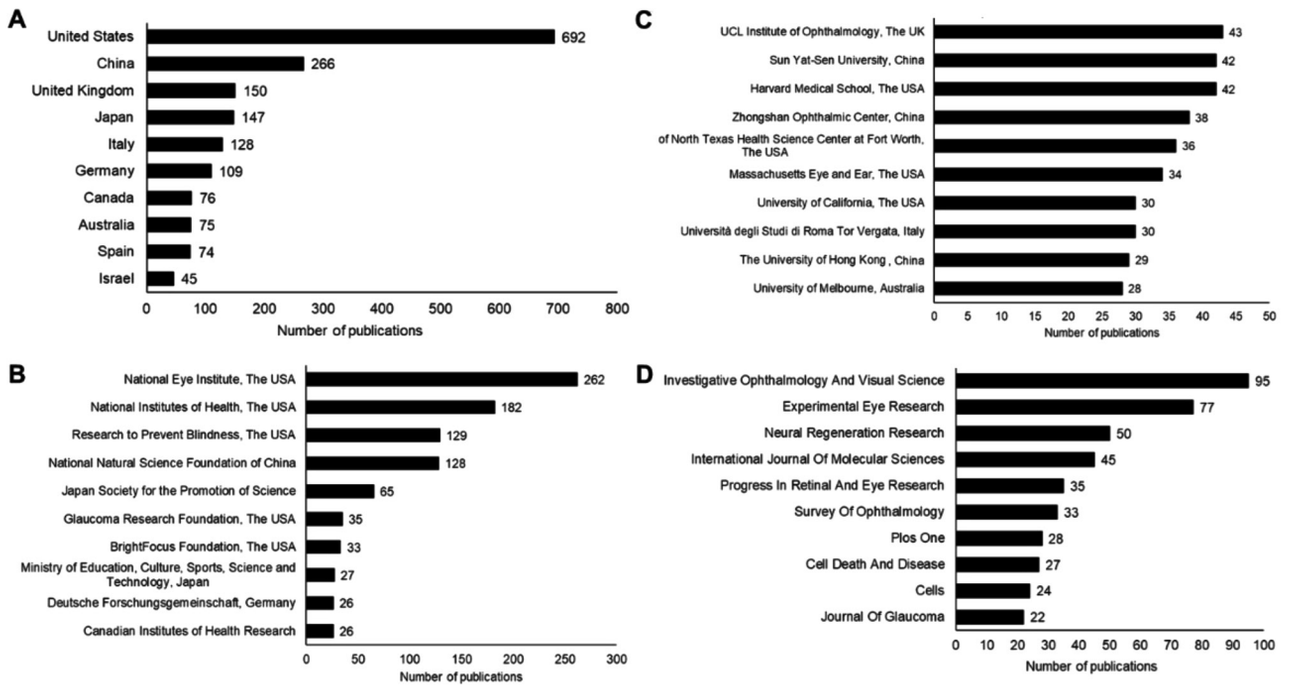

Figure 3 Data retrieved from Scopus database A: Top 10 countries from where maximum number of papers were published in the field of glaucoma and neuroprotection from Jan 2000 till early 2024; B: Top 10 funding agencies for research in the field of glaucoma and neuroprotection from Jan 2000 till early 2024; C: Top 10 affiliations of authors that published in the field of glaucoma and neuroprotection from Jan 2000 till early 2024; D: Top 10 journals that have published in the field of glaucoma and neuroprotection from Jan 2000 till early 2024.

Table 1 Top 10 authors that have published maximum number of papers in the field of glaucoma and neuroprotection and their H-index

Authors	Total number of documents	H-index	Authors' affiliation[a]
So KF	25	72	Key Laboratory of Central CNS Regeneration (Ministry of Education), Guangdong-Hong Kong-Macau Institute of CNS Regeneration, Jinan University, Guangzhou, 510632, China
Cordeiro MF	24	46	Glaucoma and Retinal Neurodegeneration Group, Department of Visual Neuroscience, UCL Institute of Ophthalmology, London EC1V 9EL, UK
Osborne NN	24	60	Fundación de Investigación Oftalmológica, Avda. Doctores Fernández-Vega 34, E-33012 Oviedo, Asturias, Spain
Harada T	23	44	Visual Research Project, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, Japan
Williams PA	23	24	The Jackson Laboratory, Bar Harbor, ME 04609, USA
Martin KR	22	46	John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
Namekata K	22	32	Visual Research Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
Pfeiffer N	22	63	Department of Ophthalmology, University Medical Center Mainz, Germany
Levin LA	21	46	Maisonneuve-Rosemont Hospital Research Center and Department of Ophthalmology, University of Montreal, Canada
Nakazawa T	21	51	Department of Ophthalmology, Tohoku University, 2-1 Seiryo-machi, Aoba-ku, Sendai, 980-8575, Japan

[a]Only 1st affiliation is included.

27 authors, respectively (Figure 4). Table 3 shows the top 10 authors, the number of documents published by each, citations and strength of citation links with other authors.

Country citation links The citation links among countries were visualized using a network for which minimum number of documents of a country were set at 5. A total of 37 countries and regions met the criteria. A network of these 37 countries and regions was created to visualize the total strength of citation links (Figure 5). The network analysis showed a total of 7 clusters. The first 3 clusters consisted of 7, 7 and 6 countries, respectively. The USA with a total of 34524 citations showed the strongest citation links with other countries followed by China and the UK. Among all, the top 10 countries with the strength of their citation links with other countries are listed in Table 4.

Document citation links To develop document citation link network, the minimum number of citations of a document was set at 10. A total of 1211 documents met the threshold. The strength of citation links of these documents is visualized in the network presented in Figure 6. A total of 39 clusters were identified. The first 3 clusters consisted of 46, 41 and 39 documents, respectively. Among all, top 10 document authors, their citations and the strength of their citation links with other documents are listed in Table 5[19,25,27-34].

Table 2 Top leading titles published in the field of glaucoma and neuroprotection

Titles	Authors	Type of paper	Citations	Keywords
Adult-onset primary open-angle glaucoma caused by mutations in optineurin	Rezaie *et al*, 2002[17]	Original research	953	Not found
Paradigm shift in neuroprotection by NMDA receptor blockade: Memantine and beyond	Lipton, 2006[18]	Review	777	Not found
The molecular basis of retinal ganglion cell death in glaucoma	Almasieh *et al*, 2012[19]	Review	709	Apoptosis; dendritic remodeling; excitotoxicity; glaucoma; neuroprotection; neurotrophic factor; optic nerve; oxidative stress; reactive gliosis; retinal ganglion cell; synaptic loss
Mitochondrial dysfunction as a cause of optic neuropathies	Carelli, *et al*, 2004[20]	Review	669	Complex I; DOA; Leber's; LHON; mitochondria; OPA1; optic neuropathy; retinal ganglion cell
Glia-neuron interactions in the mammalian retina	Vecino, *et al*, 2016[21]	Review	527	Astrocytes; extracellular matrix; glaucoma; glial cells; integrins; macrophages; microglia; Müller glia; neurons; neuroprotection; neurotrophins; photoreceptors; plasticity; retina; retinal ganglion cells; retinitis pigmentosa
Mitochondrial optic neuropathies-disease mechanisms and therapeutic strategies	Yu-Wai-Man *et al*, 2011[22]	Review	486	Dominant optic atrophy; glaucoma; hereditary spastic paraplegia; Leber hereditary optic neuropathy; mitochondrial DNA; Mitofusin; multiple sclerosis; neuroprotection; optic neuritis; optic neuropathy; retinal ganglion cell
A review of botanical characteristics, phytochemistry, clinical relevance in efficacy and safety of *Lycium barbarum* fruit (Goji)	Amagase and Farnsworth, 2011[23]	Review	437	Anti-aging; anti-oxidant; energy; general well-being; Goji; immune; Lycium barbarum; polysaccharides
The chemical biology of clinically tolerated NMDA receptor antagonists	Chen and Lipton, 2006[24]	Review	408	Fast off-rate; open-channel block; uncompetitive antagonism
Increased production of tumor necrosis factor-α by glial cells exposed to simulated ischemia or elevated hydrostatic pressure induces apoptosis in cocultured retinal ganglion cells	Tezel and Wax, 2000[25]	Original research	368	Apoptosis; glaucoma; glia; nitric oxide; retinal ganglion cell; tumor necrosis factor-α
Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures - A short review	Svíženská *et al*, 2008[26]	Review	364	Cannabinoid; CB receptors; endocannabinoid system; nervous system; therapeutic potential

Table 3 The top 10 authors with strongest citation links with other authors

Authors	Documents	Citations	Strength of citation links
Harada T	19	696	475
Kimura A	17	651	471
Namekata K	18	690	468
Harada C	16	645	464
Guo X	15	597	435
Di Polo A	10	1193	341
Cordeiro MF	15	1007	334
Nucci C	18	750	323
Noro T	8	338	261
So KF	20	1353	251

Table 4 The top 10 countries with strongest citation links with other countries

Country	Documents	Citations	Strength of citation links
USA	691	34524	3044
China	267	5865	1236
UK	149	7368	1148
Italy	128	5643	1056
Canada	76	4093	864
Japan	147	4966	771
Australia	75	3257	622
Germany	109	3901	487
Spain	74	2949	373
Israel	45	2302	349

Table 5 The top 10 document authors with strongest citation links with other documents

Authors	Citations	Strength of citation links
Almasieh 2012[19]	709	110
Pease 2009[27]	191	62
Baltmr 2010[28]	134	57
Woldmussie 2001[29]	286	55
Tezel 2000[25]	368	54
Ji 2004[30]	187	50
Ko 2001[31]	141	43
Childlow 2007[32]	78	41
Guo 2007[33]	290	41
Schori 2001[34]	266	39

Author co-authorship links To visualize the author co-author linkages, a minimum number of citations of a document was set at 5. A total of 216 authors met the threshold. The strength of author co-author links of these documents is visualized in the network presented in Figure 7. A total of 15 clusters were identified. The first 3 clusters consisted of 20, 15 and 15 co-authors, respectively.

Keywords Analysis: Co-occurrence of Author Keywords The co-occurrence author keyword was analyzed with a setting of a minimum number of occurrences at 10. A total of 80 keywords met the threshold. The strength of co-occurrence of a key word with other key words is visualized in the network presented in Figure 8. Each circular node represents a keyword, with its size corresponding to the number of co-occurrences. The larger the node, the more important is the key word. All keywords in one cluster are represented in one

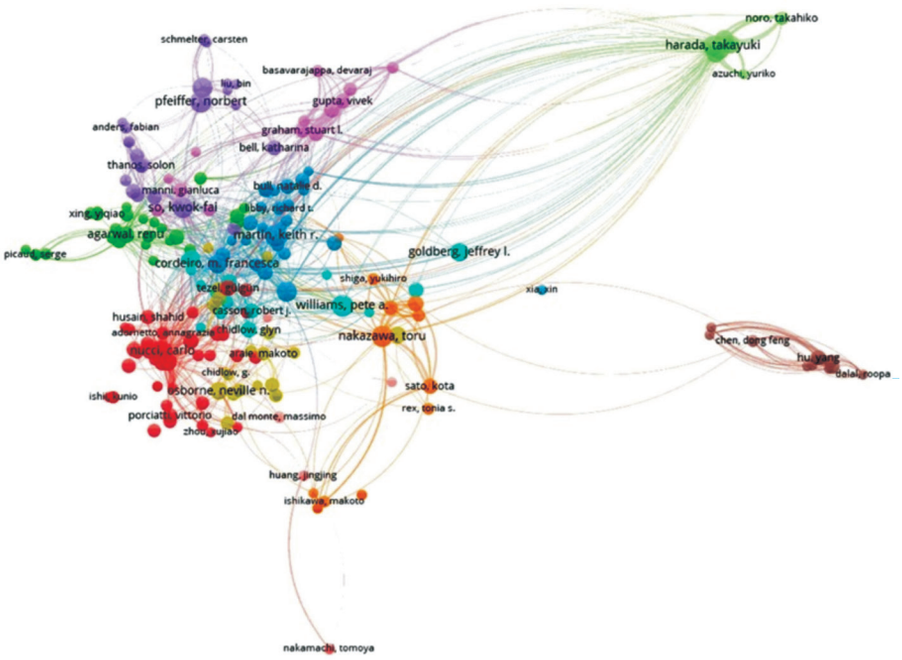

Figure 4 A Network visualization of authors depicting strength of citation links with other authors The size of circular nodes represents the number of an author's links with other authors and total strength of these links. All authors in one cluster are represented in one colour. Lines between nodes are a representation of links. The distance between nodes indicates the relatedness of two authors.

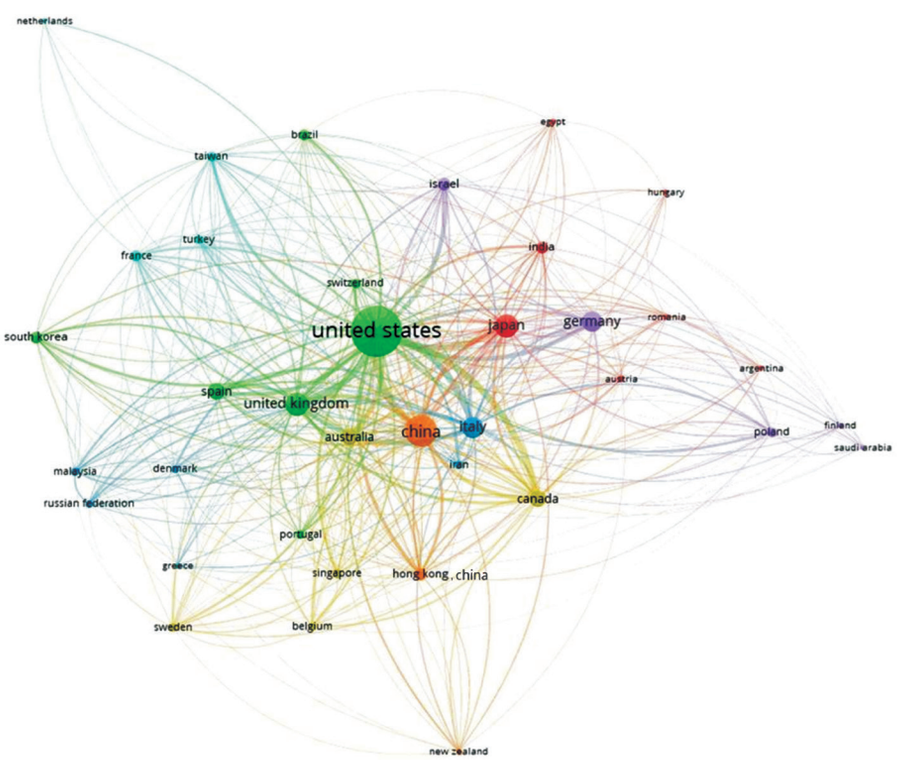

Figure 5 Network visualization of countries and regions depicting strength of citation links with other countries and regions The size of circular nodes represents the number of a country's links with other countries and regions and total strength of these links. All countries and regions in one cluster are represented in one colour. Lines between nodes are a representation of links. The distance between nodes indicates the relatedness of two.

colour. The lines between them are a representation of links. The distance between nodes indicates the relatedness of the keywords. A total of 8 clusters were identified. The first 3 clusters consisted of 15, 15 and 14 items, respectively. Besides "glaucoma", "neuroprotection" and "retinal ganglion cells", the largest clusters included "retina", "neurodegeneration", "IOP" and "apoptosis (Figure 8A). Figure 8B represents a time-based change in the importance of keywords from 2012 to 2018

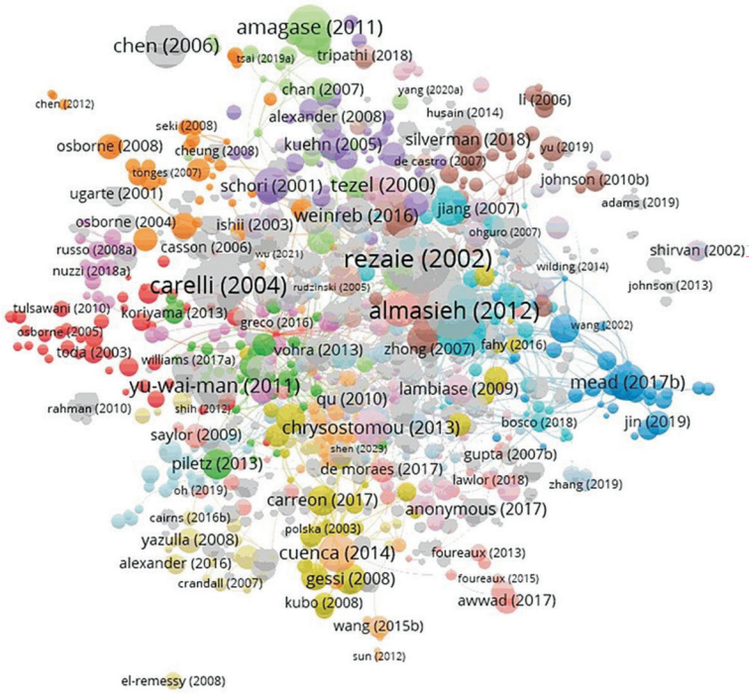

Figure 6 Network visualization of documents depicting strength of citation links with other documents The size of circular nodes represents the number of a document's links with other documents and total strength of these links. All documents in one cluster are represented in one colour. Lines between nodes are a representation of links. The distance between nodes indicates the relatedness of two documents.

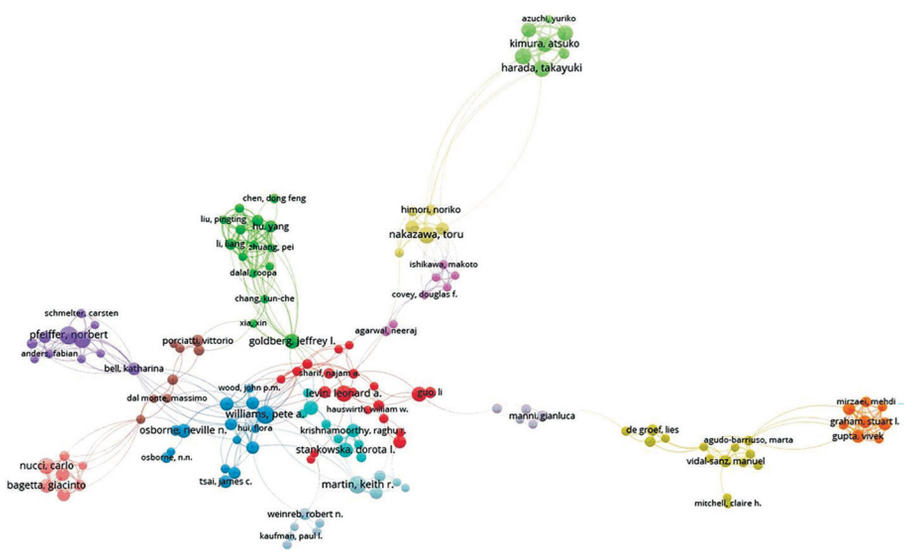

Figure 7 Network visualization of authors depicting strength of links with co-authors The size of circular nodes represents the number of an author's links with co-authors and total strength of these links. All authors in one cluster are represented in one colour. Lines between nodes are a representation of links. The distance between nodes indicates the relatedness of two authors.

onwards. Most recent trends (2018 onwards) are highlighted in yellow with prominence of "microglia", "astrocytes", "mitochondria" and "drug delivery". Among all, the top 10 key words with strongest co-occurrence link with other key words included glaucoma, neuroprotection, retinal ganglion cells, retina, neurodegeneration, IOP, apoptosis, oxidative stress, optic nerve and excitotoxicity.

Summary of Trends and Relationships Investigations into neuroprotective therapies for the treatment of glaucoma have attracted considerable attention over the past few decades and this is evident by huge surge in the number of publication output over the past two decades, globally (Figure 2). This is of particular importance as the outcomes of treatment with currently available therapeutic options that primarily target intraocular pressure are variable across patient populations and remain suboptimal[35]. The overall objective of investigating neuroprotective therapies remains the protection of RGCs irrespective of the status of IOP[36].

Bibliometric analysis provides quantitative and visual interpretations of literature to understand the current trends and

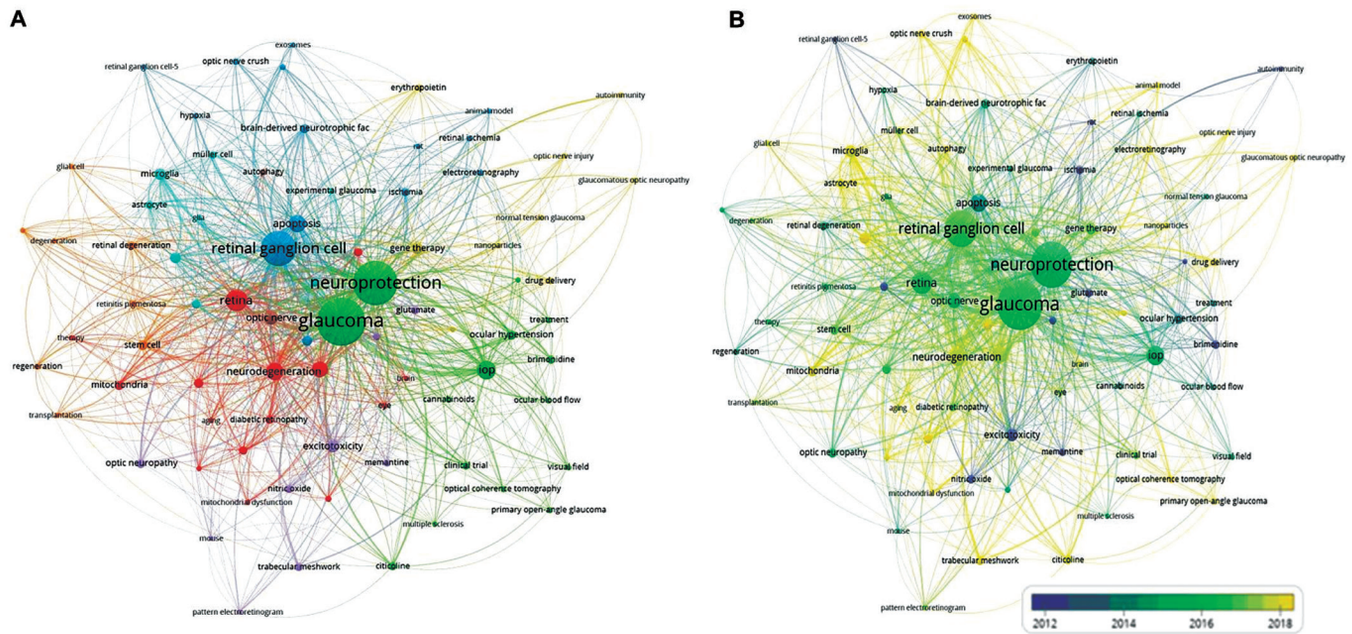

Figure 8 Visualization of keyword co-occurrence networks and temporal evolution of research themes A: Network visualization of key words depicting strength of links with other key words; B: Time-based change in the importance of keywords from 2012 to 2018 onwards. The circular nodes represent each keyword, and the size of the node relates to number of co-occurrences. All keywords in one cluster are represented in one color. The lines between them are a representation of links. The distance between nodes indicates the relatedness of the keywords.

networking in a specific area of research. The technique has been widely used in various areas of research interest[37-38]. In the current study, it was observed that the maximum funding support for studies in the area of neuroprotection in glaucoma is coming from the United States and globally the research output is maximum from American institutions. The United States also stands at the top position in terms of strength of citation links with other countries followed by China and the UK. However, among the top 10 authors publishing most papers in this area of research (Table 1), Williams PA was noted as the only author affiliated to an American institution with 23 publications. Although, So KF from China emerged as the most prolific author with maximum number of publications, three out of 10 most prolific authors were from Japanese institutions. Moreover, So KF did not make it to the list of top 10 authors with strongest co-author links and the authors of top 10 papers with strongest citation links (Table 5). This author was, however, noted at 10th position among authors with strongest citation links with other authors (Table 3). On the other hand, the top 5 authors with strongest citation links with other authors (Table 3) were also the top 5 authors with strongest co-authorship links. The data indicates greater scope for establishing linkages among authors and institutions across countries for more meaningful research output.

Interestingly, among the top 10 cited articles, 8 were review papers and two were original research papers (Table 2). One of the original research papers was a clinical study involving human subjects while the other was experimental. A closer look at the title and key words of these 8 review papers shows that out of eight of these papers, the focus of six was on molecular mechanistic targets involved in the pathophysiology of RGC loss in glaucoma. We observed that in relation to molecular targets, four themes that emerge by closely examining the key word of top 10 cited articles are role of excitotoxicity, neurotrophins, oxidative stress and inflammatory responses in the pathogenesis of glaucoma. It is also evident that besides RGCs, glial cells functions are also of considerable interest in this context.

To further understand the areas of emphasis in this field of research we examined the complete list of 80 author key words that met the threshold of at least 10 occurrences. The authors are expected to select key words to closely represent the study objectives and body of the work detailed in the manuscript. Hence, a closer look at the author key words is likely to indicate the research areas attracting greater attention. In this study, the author key words indicating the study objectives to explore the pathophysiological mechanisms such as apoptosis, oxidative stress, excitotoxicity, microglia, neuroinflammation, inflammation, mitochondria, ischemia, ocular hypertension were noted among the top 20 key words with strongest link strength with other key words. Visualization of the network (Figure 8A) indicates larger and centrally placed nodes or “retinal ganglion cell(s)”, “retina”, “apoptosis”, and “neurodegeneration”. Another prominent node appearing in the vicinity is “IOP”, indicating a prominent research focus towards RGC apoptosis and neurodegeneration in the context

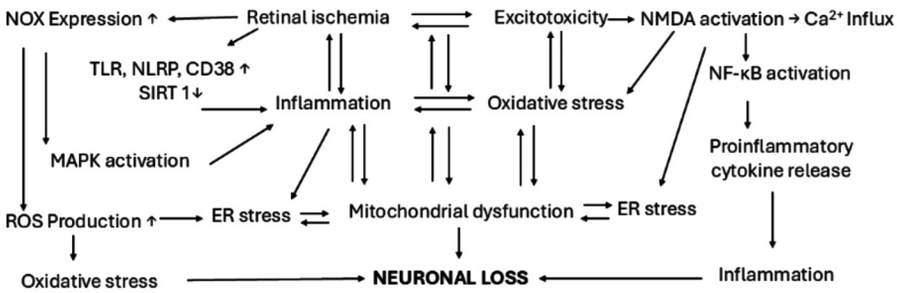

Figure 9 A diagrammatic representation of the complex relationship among several pathophysiological mechanism such as ischemia, excitotoxicity, inflammation, mitochondrial dysfunction and oxidative stress leading to neuronal loss in glaucoma.

of elevated IOP. Notably, among the 80 author key words, we observed only 7 key words indicating the evaluation of possible drug candidates in relation to neuroprotection in glaucoma and these included “brimonidine”, “citicoline”, “memantine”, “erythropoietin”, “melatonin”, “timolol”, and “cannabinoids”. When the keyword selection was made with a setting of at least 5 occurrences, 191 keywords met the threshold. Among these, additional keyword indicating use of potential drug candidates included “latanoprost”, “betaxolol”, “resveratrol”, “rho kinase inhibitors”, “taurine”, “coenzyme Q10”, “nicotinamide”, “prostaglandin analogues”, and “curcumin”. It is also of interest to note that among the list of 80 key words the occurrence of keyword “clinical trial” was noted 21 times. Hence, it could be interpreted that larger research in the field of neuroprotection in glaucoma seems to focus on pathophysiological and molecular targets in experimental set up and relatively lesser number of drug candidates have emerged so far. Furthermore, very limited clinical trials have been undertaken so far in this area of therapeutics.

The occurrence of author keywords over time presented as network in Figure 8 indicates that involvement of excitotoxicity and ischemia continue to be research focus areas from time before the year 2012. Subsequently greater focus seems to emerge in relation to RGC and optic nerve degeneration and even use of stem cells in this context. Keywords represented by yellow nodes and linkages indicate the emerging keywords from 2018 onwards and these include “microglia”, “astrocytes”, “mitochondria”, and “neurodegeneration”. These emerging keywords highlight the current hotspots in the area of neuroprotection in glaucoma.

Review of Recent Literature Based on Keyword Analysis The author keywords including apoptosis, oxidative stress, excitotoxicity, microglia, neuroinflammation, inflammation, mitochondria, ischemia, microglia and astrocytes were prominently highlighted in this bibliometric analysis. The mechanistic themes that emerge from these keywords are retinal ischemia, inflammation, excitotoxicity, mitochondrial dysfunction, and oxidative stress. These responses to glaucoma-relevant stresses have been discussed in literature extensively. However, to understand the molecular pathways underlying these responses that are currently in focus, we carried out a review of the most recent literature. Using Scopus database, we selected only the original studies published 2020 onwards and synthesized evidence to understand the mechanistic pathways underlying retinal ischemia, neuroinflammation, excitotoxicity and oxidative stress either to understand glaucoma pathophysiology better or to investigate new substances for antiglaucoma activity. These molecular pathways considerably overlap and interconnect, hence we discuss them showing the logical connections ultimately leading to cell death. Retinal ischemia and excitotoxicity perpetuate each other and promote inflammatory responses and oxidative stress, which in turn are associated with mitochondrial dysfunction and cell loss. These events are so intertwined and mutually reinforcing that it is difficult to discern which one initiates the insult and which one follows. This complex relationship among some of these events leading to neuronal loss is depicted in Figure 9. Keeping in view these intricate and complex relationships, in the section below we describe how 1) retinal ischemia predisposes to inflammation and oxidative stress leading to cell apoptosis 2) retinal excitotoxic injury promotes inflammation and oxidative stress leading to cell apoptosis 3) oxidative stress and inflammation associated with mitochondrial dysfunction and apoptotic cell loss. The keywords used were Glaucoma AND neuroprotection AND ischemia OR neuroinflammation OR excitotoxicity or oxidative stress OR mitochondrial dysfunction.

Ischemia, inflammation and oxidative stress Changes in ocular blood flow either due to fluctuation of IOP or faulty autoregulation predispose to RGC loss and this concept is utilized in experimental studies in which retinal ischemia/reperfusion (I/R) is achieved by inducing acute high IOP *in vivo* and oxygenation-glucose deprivation/reoxygenation *in vitro*. I/R induces inflammation and oxidative stress leading to retinal cell apoptosis[39]. In a recent study, that used *in vivo* and *ex vivo* models, it was observed that exposure to high pressure causes generation of NADPH oxidase (NOX)2-

dependent reactive oxygen species (ROS) that trigger proinflammatory signaling. NOX2/ROS induce endothelin-1 (ET-1) overexpression, which in turn activates the ERK1/2 signaling and triggers neuroinflammatory response by shifting microglial activation to a pro-inflammatory M1 phenotype[40]. NOX1 and NOX4 expression also increases in retina after exposure to I/R and contributes to ROS generation. Exposure to ROS leads to cellular senescence making neurons vulnerable to injury and apoptosis and hence, senescence-associated β-galactosidase (SA-β-gal) and p16-INK4a expression increases in retinas exposed to I/R injury. Furthermore, ROS-associated redox signaling pathways, including hypoxia-inducible factors (Hif)-1α, nuclear factor erythroid 2-related factor (NRF) 2, and forkhead box O (FOXO) 1 are activated that participate in apoptosis and cellular senescence. Setanaxib, a highly selective NOX1 and NOX4 inhibitor, prevents these responses to I/R[41].

In the retina subjected to I/R injury, toll-like receptor (TLR) 4 signaling and endoplasmic reticulum (ER) stress leading to inflammatory response and neuronal apoptosis are also initiated. Inhibition of TLR4 signaling and ER stress by a calcium binding protein S100A4 was shown to provide neuroprotection in an *in vivo* model of retinal I/R injury[42-43]. Increased neuronal expression of p58IPK, an ER chaperone, which regulates ER stress response, was shown to exert neuroprotective effect in retinas exposed in I/R injury[44]. Astrocyte damage induced by I/R injury also causes increased expression of NOD-like receptor protein 3 (NLRP3) and CD38 while reduces sirtuin 1 (SIRT1) protein expression. Both NLRP3 and CD38 promote inflammation whereas SIRT1 inhibits NLRP3 and suppresses inflammation[45]. LRP3 also activates caspases that trigger cell death not only by apoptosis but also pyroptosis in retinas subjected to I/R injury and particularly involves Müller glial cells. Activated NLRP3 inflammosomes cause activation of gasdermin D (GSDMD) protein that forms water channels in the cytoplasmic membrane promoting cellular swelling, lysis, release of inflammatory cytokines such as interleukin (IL)-1β and IL-18 and caspase-1 activation leading to cell death by pyroptosis[46]. Ferroptosis, which refers to non-apoptotic cell death resulting from accumulation of lipid peroxides and iron may also contribute to RGC loss in glaucoma. In an in vitro model of I/R injury, ferroptosis was associated with aberrantly upregulated retinal SOX9 that mediated its effect through inactivation of protective ERK/p38 signaling[47]. In activated microglial subsequent to I/R insult, ERK1/2 expression decreases and this is associated with increased NF-κB expression and release of pro-inflammatory cytokines such as IL-1β and TNF-α. Reduced ERK1/2 expression may be a consequence of downregulation of Nr4a1, a transcription factor upstream of ERK1/2. Moreover, peroxisome proliferator-activated receptor-γ (PPARγ) activation may suppress microglial activation and inflammatory response[48-49]. Besides NF-κB, signal transducer and activator of transcription 3 (STAT3) is also involved in reactive gliosis and retinal degeneration after I/R injury[50]. STAT3 upregulation enhances expression of the antiapoptotic, Bcl-2 proteins and antioxidants such superoxide dismutase hence conferring neuroprotection[51]. RGC apoptosis associated with microglia-induced neuroinflammation also involves release of cytosolic double-stranded DNA (dsDNA) that initiates inflammatory responses by activating cyclic GMP-AMP (cGAMP) synthase (cGAS)–stimulator of interferon genes (STING) pathway[52]. Moreover, cAMP signaling may also have a significant role to play in I/R induced RGC loss. It was observed that exchange protein activated by cAMP (Epac) upon binding with cAMP activates Ras GTPases, which cause Ca^{2+} mobilization and activation of calmodulin-dependent protein kinase II (CaMKII) culminating into RGC apoptosis[53]. Under ischemic conditions, increased Ca^{2+} level in the mitochondrial matrix causes the opening of mitochondrial permeability transition pore (mPTP) leading to depolarization of mitochondrial membrane. Further, there is increased ROS production, reduced ATP production and increased mitochondrial membrane permeability, leading to mitochondrial swelling and release of cytochrome C. Cytochrome C forms apoptosome with caspase 9, which in turn activates caspase cascade leading to apoptosis[54].

Excitotoxicity, inflammation and oxidative stress

Excitotoxicity refers to cell injury arising from excessive stimulation of glutamate receptors. This may result from excessive synaptic levels of glutamate. One of the studies has shown that increased synaptic clearance of glutamate by increased expression of excitatory amino acid transporter (EAAT) 1 and EAAT2, which transport glutamate from synapses into glial cells, reduces excitotoxic injury[55]. Postsynaptically, glutamate may mediate cell injury via metabotropic receptors, however, inotropic receptors, particularly the NMDA subtype, are primarily implicated. Phosphorylation of NMDA receptor 2B (NR2B) subunit and its interaction with postsynaptic density protein-95 (PSD95) complex was shown to enhance excitotoxic injury and neuronal death[56]. I/R insult may also trigger excitotoxic injury that involves excessive inflow of Ca^{2+} and activation of Ca^{2+}-dependent calpain. In fact, calpain-specific, 150/145 kDa alfa-spectrin breakdown products (SBDPs) were detected in retinas exposed to I/R injury[57]. Apelin receptors, that are of G protein-coupled type for an endogenous peptide ligand, upon activation exert neuroprotective effect by reducing Ca^{2+} influx and increasing Akt phosphorylation[58]. Moreover, intracellular signaling *via* PI3K/AKT pathway may have a role to play as it

is inhibited by NMDA resulting in oxidative stress, autophagy, and apoptosis[59].

Excitotoxicity induced massive Ca^{2+} influx also initiates inflammatory response. It causes microglial activation, activation of NF-κB and increased expression of inflammatory cytokines such as TNFα, IL-1β, IL-6 and MCP-1. This pro-inflammatory response is associated with ER stress[60]. Increased expression of parkin has been shown to be neuroprotective against glutamate induced neuronal injury as NLRP3 inflammosomes are parkin substrates[61]. It is noteworthy that intracellular stress causes ATP depletion resulting in activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK). Activated AMPK has a protective role by stimulating metabolic processes such as fatty acid oxidation and ketone synthesis that generate ATP and at the same inhibiting events that are not required for short-term cell survival but consume ATP. Ketones are transported by monocarboxylate transporters (MCTs), and by regulating mitochondrial functions, exerting neuroprotective effects. Hence, compounds that activate AMPK exert a neuroprotective effect[62].

The role of dysregulated lipid metabolism in enhancing excitotoxic injury has attracted attention recently. In a vitro study, disturbances of sphingolipid species were also shown to contribute to excitotoxic injury. Accordingly, increased ceramide and reduced sphingosine-1-phosphate (S1P) levels were shown to promote excitotoxic injury[63]. Modulation of S1P receptor 1 signaling has been shown to play a vital role in the survival of RGCs and the neurons of dorsolateral geniculate against NMDA-induced injury[64]. Furthermore, apolipoprotein E by promoting phosphorylation of STAT3 reduces expression of α2-macroglobulin in Müller glial cells and this in turn was shown to provide neuroprotective effect against NMDA-induced excitotoxic injury[65].

Oxidative stress, mitochondrial dysfunction and apoptosis Experimental induction of high IOP in mice is associated not only with retinal ischemia and neuroinflammation but also oxidative stress[39]. Increased production of nitrogen free radicals also contributes to oxidative stress[41]. Elevated IOP was shown to decrease expression of apolipoprotein A-I binding protein (AIBP) in RGCs and increase expression of TLR4 and IL-1β expression in Müller glial cells. These changes were associated with impaired mitochondrial function and oxidative stress in RGCs[66]. Excessive glutamate mediated neurotransmission such as that resulting from reduced EAAT1 expression was also shown to cause retinal oxidative stress and RGC apoptosis indicating that Ca^{2+} overload due to excitotoxic injury promotes oxidative stress in RGCs and may involve mitochondrial dysfunction. Correction of mitochondrial function restores mitochondrial membrane potential (MMP), ATP contents, ROS generation and antioxidant defenses[67]. Nrf2 is one of the targets that enhances cellular antioxidant capacity by enhancing transcription of antioxidant target genes such as heme oxygenase 1 (HO-1). In response to oxidative stress, Nrf2 is released from its binding with Keap1 in the cytoplasm, migrates to nucleus and modulates transcription. Hence, substances inducing activation of Nrf2/HO-1 pathway exert neuroprotective effect by mitigating oxidative stress[68]. Nrf2/HO-1 pathway was also shown to be activated in RGCs by exposure to transforming growth factor β (TGF-β), in particular TGF-β1, under oxidative stress conditions. TGF-β1 upregulation also promoted the aldehyde dehydrogenase 3A1 protein expression which exerts antioxidant activity[69]. Mitochondrial dysfunction and oxidative stress associated with glaucoma-relevant stresses also involves wide range of metabolic disruptions including changes in α-ketoglutaric acid, homocysteine, glycerophosphocholine and creatine/creatinine. Correction of this metabolic stress and consequently oxidative stress provides neuroprotection[70]. Some of the other pathways implicated in H_2O_2-induced apoptosis of RGCs include RhoA/ROCK pathway[71]. Additionally, cleavage of tau, a constituent of neurofibrillary tangles (NFT) known for its role in Alzheimer's disease, may also play a role in enhancing retinal oxidative stress and RGC loss. Optic nerve head astrocytes were also shown to express activated caspases, cleaved Tau, and NFT formation under the conditions of oxidative stress[72]. Maintenance of cellular antioxidant defenses has an important role in providing neuroprotection. In this regard, in the rat model of optic nerve crush expression of glutathione peroxidase 4 (GPx4) and system xc(−) cystine/glutamate antiporter (xCT) was found to be downregulated particularly in the mitochondrial compartment leading to mitochondrial dysfunction, production of ROS and lipid peroxides. Both glutathione peroxidase 4 (GPx4) and system xc(−) contribute to maintenance of anti-oxidant defenses[73].

Current option for neuroprotection in glaucoma Although several agents have shown promising outcomes in preclinical studies for efficacy as neuroprotective agents in glaucoma treatment, many have not reached the stage of clinical application. As noted above, the possible drug candidates in relation to neuroprotection in glaucoma that appeared in this bibliometric analysis included "brimonidine", "citicoline", "memantine", "erythropoietin", "melatonin", "timolol", "cannabinoids", "latanoprost", "betaxolol", "resveratrol", "rho kinase inhibitors", "taurine", "coenzyme Q10", "nicotinamide", and "curcumin". The role of many of these agents such as timolol, rho kinase inhibitors, latanoprost and cannabinoids is largely towards reduction in IOP which in turn is expected to provide neuroprotective effect. Melatonin has also shown largely the IOP lowering effects in clinical studies[74]. Memantine although showed promising results as a

neuroprotective agent in preclinical studies but failed clinical trials. Agents like resveratrol have shown efficacy in preclinical studies while others have been tested in clinical trials and may have potential for clinical application. For example, brimonidine and betaxolol provided greater visual function protection compared to timolol despite similar reduction in IOP indicating its added neuroprotective effects in glaucoma patients[75-76]. The neuroprotective effect of brimonidine may be attributed to activation of the Trk signaling and anti-amyloidogenic effect[77-78]. Citicoline is a naturally occurring endogenous compound, which may exert neuroprotective effect by increasing the synthesis of phospholipids in the neuronal tissue. The neurotrophic effects of citicoline have been reported in glaucoma patients[79]. Coenzyme Q10 affects mitochondrial machinery for potent antioxidant effects and exerts anti-inflammatory effects. In patients with open angle glaucoma, administration of coenzyme Q10 along with vitamin E improved the retinal electrophysiological responses[80]. The neuroprotective effect of nicotinamide may be attributed to its ability to preserve energy homeostasis. Accordingly, oral nicotinamide was shown to protect RGC functions in glaucoma patients irrespective of IOP[81-82]. Most of the drugs noted in this bibliometric analysis, however, need further investigations in clinical studies to clearly identify their potential use in clinical setting.

In conclusion, the importance of the outcomes of the bibliometric analysis presented in this paper is evident as it shows the current trends, directions, linkages and focus areas in the field of neuroprotection in glaucoma, which can be utilized as a guide for future research. Some of the limitations, however, are to be considered. Firstly, the included data was in English language only and secondly the analysis was based on records captured in the Scopus database and hence the records existing outside the database were not taken into analysis. The keyword analysis leading to review of recently explored molecular pathways underlying glaucomatous RGC loss shows the direction of future research.

In can be concluded that the landscape of neuroprotection research in glaucoma has seen significant growth in the past two decades, reflecting a critical need for effective treatments of this leading cause of irreversible blindness. While current strategies mainly focus on reducing IOP, there's a rising awareness of its limitations, leading to increased exploration of alternative neuroprotective approaches. Key areas of focus include understanding molecular mechanisms like ischemia, inflammation, excitotoxicity and oxidative stress, highlighting efforts to explore the causes of RGC cell loss in glaucoma. Despite robust preclinical studies, there's a notable gap in clinical trials, signaling a need for more translation of research findings into therapeutic interventions.

ACKNOWLEDGEMENTS

Declaration of Generative AI and AI-assisted technologies in the writing process: Statement: During the preparation of this work the author(s) did not use any AI tool. Authors take full responsibility for the content of the publication.

Foundations: Supported by the Ministry of Higher Education (Malaysia) (No.FRGS/1/2023/SKK15/IMU/01/1); International Medical University [No.PHMS I-2023 (01)].

Conflicts of Interest: Agarwal P, None; **Agarwal R,** None; **Iezhitsa I,** None.

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