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Mapping the current trends of autophagy in retinal diseases: A bibliometric analysis

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ABSTRACT

Background: Several scholarly publications have thoroughly examined the significant role of autophagy in the pathogenesis, progression, and treatment of retinal diseases. This research utilized bibliometric analysis to identify the primary areas of focus and emerging trends within the discipline and offer a comprehensive summary.

Methods: The research articles and reviews regarding autophagy and retinal diseases from 2009-01-01 to 2022-12-31 were from the Web of Science Core Collection (WOSCC). The software VOSviewer and CiteSpace were applied to analyze and visualize maps of countries, organizations, authors, journals, keyword networks, and citations in the field of autophagy in retinal diseases. *Results*: 854 qualified records (721 articles and 133 reviews) were retrieved in this research. The annual publication output of literature shows a growing trend. China is the most productive country, and the author with the most publications is Kai Kaarniranta. Journal *Autophagy* published the most articles in this field. Keywords analysis can effectively reflect the research hot spots and indicate that diabetic retinopathy and glaucoma have drawn more attention recently. Researchers have shifted the research emphasis on "AMPK", "angiogenesis", "mutation", and "inflammation".

countries, regions, authors, institutions, keywords, and citations, which further helps researchers understand the hot spots and trends in the field of autophagy in retinal diseases and explore the

1. Introduction

Retinal diseases represent a prevalent cause of blindness, affecting millions of individuals. Among the spectrum of retinal diseases are diabetic retinopathy, glaucoma, age-related macular degeneration, retinitis pigmentosa, and numerous other conditions [1,2]. The retina is responsible for light perception and is part of the central nervous system. The diversity of retinal structural features and functions increases its susceptibility to internal and external stimuli and results in a series of pathological changes, including

issues in the rapidly developing area.

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congenital abnormalities, dystrophies, degenerations, vascular alterations, toxicities, neoplasms, and detachment [3,4]. Retinal diseases mainly manifest as visual impairment, color vision impairment, and visual distortion. The limited efficacy of its treatment, coupled with the high treatment expenses, significantly impairs the quality of life for patients [5,6].

Autophagy is an intricate and evolutionarily conserved biological process in which eukaryotic cells employ lysosomes to dismantle damaged organelles and misfolded proteins. It is regulated by autophagy-related genes (ATGs) [7]. Autophagy mediates several retinal diseases and is ambiguous in retinal cell survival and death mechanisms [8]. Optimal autophagic activity at normal levels serves as a protective mechanism for retinal cells against environmental insults. However, an excess of autophagy may contribute to the deterioration of the retina [9,10].

Autophagy has gained considerable attention in the context of retinal diseases [11,12], yet our comprehension of its role in these conditions remains unclear. The intricate regulation and multifaceted nature of autophagy suggest that it could either exert a detrimental or beneficial influence on the progression of retinal diseases. Hence, investigating the precise mechanisms underlying autophagy in retinal diseases is undoubtedly promising and meaningful. However, the explosive growth of publications may hinder researchers from fully understanding autophagy in the field of retinal diseases. Therefore, a systematic analysis of this area's hot topics and trends is necessary. Bibliometric analysis applies mathematical and statistical techniques to analyze academic literature quantitatively. It has been employed to evaluate the hot spots and research trends related to retinal diseases and autophagy [13,14]. However, there is a gap in comprehensive bibliometric analysis regarding autophagy within the field of retinal diseases.

Therefore, in this study, a bibliometric approach was employed to investigate the related literature in the field of autophagy and retinal disease. The aim was to evaluate current research hot spots, explore novel research trends, provide directions for future research, and ultimately give our readers a comprehensive understanding of the past, present, and future in this field.

2. Methods

2.1. Data sources and search strategy

In this research, the Science Citation Index Expanded (SCI-Expanded) of the Web of Science Core Collection (WOSCC) was employed as a data source, because it is the largest comprehensive academic information resource covering multiple disciplines [15]. On October 9, 2023, all documents published between January 1, 2009, and December 31, 2022 were retrieved. The scope of topic searching (TS) includes the following fields: title, abstracts, author name, and keywords plus. The detailed retrieval strategies are as follows: (TS=("autophagy" OR "macroautophagy" OR "microautophagy" OR "chaperone-mediated autophagy" OR "autophagocy-tosis" OR "reticulophagy" OR "nucleophagy" OR "ribophagy" OR "lipophagy" OR "mitophagy") AND TS=("retinopathy" OR "retinal" OR "epiretinal" OR "macular" OR "retinitis") [16,17]. Only "research articles" and "review articles" published in English were considered, and the language was restricted to English only. Then, we identified the documents relative to autophagy



Fig. 1. Workflow of the data collection and bibliometric analysis for research on autophagy of retinal disease. "N" is an abbreviation for "number".

in retinal diseases. The exact progress of the search and analysis is shown in Fig. 1. In the end, 721 articles and 133 reviews satisfied the requirements and were incorporated into the subsequent study, fulfilling the minimum sample size requirement of no fewer than 200 documents [15]. We gathered basic information about each article, including the title, abstract, author, journal, institution, keywords, year of publication, and citations.

2.2. Data analysis and visualization

The bibliometric analysis was conducted using VOSviewer, CiteSpace, GraphPad Prism, and R software. VOSviewer is a Java-based free computer program Van Eck and Waltman developed to visually construct and generate bibliometric maps. It provides various easily interpretable visual maps, including network, overlay, and density visualization [18]. CiteSpace was developed by Chen, and the two software have their advantages, which can complement each other [19,20]. GraphPad Prism (version 9.5.0) was employed to draw the bar chart about the annual output of publications related to autophagy and retinal diseases. R software (4.3.0) was also used for data analysis. The processed data was subjected to bibliometric analysis with the help of R package bibliometrix to determine further the variations of the annual literature quantity [21].



Fig. 2. The number of publications (A), articles (B), and reviews (C) about autophagy in the field of retinal diseases from 2009 to 2022.

3. Results

3.1. General data of the publications on autophagy in retinal diseases and annual trend of publication quantity

In this study, 854 publications were screened and applied from 2009 to 2022, and the screening process workflow is shown in Fig. 1. 4464 authors wrote them from 1032 organizations in 51 countries and regions, published in 282 journals, and cited 35509 references from 3306 journals.

We counted the annual quantity of publications to figure out the academic dynamics and cutting-edge trends in this field (Fig. 2A). Except for 2013 and 2010, the yearly publication output exhibits a consistent upward trend. Furthermore, annual publication output grew substantially, especially after 2017, indicating that this research field has gained increasing attention from researchers in recent years. We also tallied the annual publication status of articles and reviews. Both types show a consistent upward trend over the years (Fig. 2B and C).

3.2. Analysis of the distributions of countries/regions of the publications

A total of 51 countries and regions have published articles related to autophagy in the field of retinal diseases, and the top 10 productive countries and regions are listed in Table 1. China is the most productive country (318), followed by the United States (258) and Poland (61). However, Chinese literature has relatively fewer citations. The average number of research citations in Poland is the highest, followed by Germany and Finland, reflecting high quality of research.

The cooperation network between countries is displayed in Fig. 3, and lines delineating countries or regions signify their collaborative efforts. The network was divided into four clusters by VOSviewer. The largest cluster (green dots) contained China, the USA, Japan, Canada, South Korea, and Singapore. The second cluster (red dots) contained Italy, Switzerland, France, Sweden, Russia, and Spain. The third cluster (blue dots) included England, Ireland, North Ireland, Belgium, and Argentina. The fourth cluster (yellow dots) included Poland, Finland, Norway, and Germany. Cooperation was concentrated mainly in China and the USA.

3.3. Analysis of the distributions of authors of the publications

VOS viewer was used to create the co-authorship analysis network. Up till December 2022, there were 4464 authors in this discipline. The top 10 authors with published research on autophagy in retinal diseases are displayed in Table 2. Among those authors, Kai Kaarniranta is the most productive author who published 55 papers, followed by Anu Kauppinen, Janusz Blasiak, Juha M T Hyttinen, Antero Aslminen, Ali Koskela, Debasish Sinha, Patricia Boya, Rong Li, David N Zacks. They are from Finland (3 authors), Poland (3 authors), the USA (3 authors), and China (1 author).

Fig. 4A displays the co-authorship analysis network. The lines between the dots indicate that authors from the same country have a strong connection, which represents a close co-authorship. Further research in the literature database shows that these core authors frequently publish articles as co-authors. Fig. 4 B displays the co-citation relationship network of authors with at least 70 citations. The network has three main clusters, which reflect the authors with significant influence in the field of autophagy in retinal diseases.

3.4. Analysis of the distributions of institutions of the publications

Aggregately, 1032 organizations were active in this field. The top 10 productive institutions are listed in Table 3, and they are from Poland, Finland, the USA, and China. They published 276 papers, accounting for 32.3 % of all literature. The University of Eastern Finland and Kuopio University Hospital in Poland are the two institutions that have published the most literature in this field.

Furthermore, VOSviewer was applied to conduct institutional cooperation analysis and institutional co-citation relationship analysis to reveal the cooperation and co-citation relationship between institutions (Fig. 5A and B).

 Table 1

 Top 10 countries/regions with the most published research on autophagy in retinal diseases.

Rank	Country/Region	publications	Citations	Average citations
1	China	318	5932	18.65
2	USA	258	11168	43.29
3	Finland	61	2786	45.67
4	Italy	59	1667	28.25
5	Japan	45	1292	28.71
6	Germany	40	1831	45.78
7	Spain	40	1557	38.93
8	South Korea	38	989	26.03
9	Poland	36	2261	62.81
10	England	33	983	29.79



Fig. 3. Visualization of the cooperation among countries/regions where publications related to autophagy in retinal diseases were visualized by VOSviewer. The lines connecting countries/regions signify collaborative engagements. The largest cluster (green dots) included countries such as China and the United States, and cooperation was mainly concentrated in the two of them.

 Table 2

 Top 10 authors with published research on autophagy in retinal diseases.

Rank	Author	publications	citations	Country/region
1	Kai Kaarniranta	55	2563	Finland
2	Anu Kauppinen	21	874	Finland
3	Janusz Blasiak	22	1313	Poland
4	Juha M T Hyttinen	14	548	Finland
5	Antero Aslminen	12	1071	Finland
6	Ali Koskela	15	490	Poland
7	Debasish Sinha	13	908	USA
8	Patricia Boya	11	615	Spain
9	Rong Li	16	152	China
10	David N Zacks	13	477	USA



Fig. 4. Visualization of authors in the field of autophagy in retinal diseases. (A) The co-authorship analysis by VOSviewer. (B) The co-citation relationship analysis. The size of each circle corresponds to the number of articles published by the authors, while the connecting lines symbolize co-authorship and co-citation relationships among the authors, respectively.

3.5. Analysis of journals

Overall, 282 journals recorded research related to this field. Table 4 presents the top 10 journals with the highest number of publications in the field. They included 283 papers in the field of autophagy in retinal diseases, accounting for 33.1 % of the total publications. Based on the 2022 edition of Journal Citation Reports (JCR), six journals were in the Q1 JCR division, and three journals were in the Q2 JCR. *Autophagy* is the most productive journal, with the most citations and impact factor among the top 10 journals in this field. A visualization of the network of journal co-citation relationships in this field is shown in Fig. 6. The co-citation network revealed that the journals *Investigative Ophthalmology & Visual Science, Autophagy*, and *PLoS One* are the top three journals at the center

Table 3Top 10 prolific institutions in the field of autophagy in retinal diseases.

Rank	Affiliation	Publications	Citations	Average citations	Country/Region
1	University of Eastern Finland	59	2581	43.75	Finland
2	Kuopio University Hospital	54	2489	46.09	Finland
3	Shanghai Jiao Tong University	30	508	16.93	China
4	University of Lodz	25	1408	56.32	Poland
5	University of Michigan	19	646	34.00	USA
6	Fudan University	18	264	14.67	China
7	National Eye Institute	18	754	41.89	USA
8	Sun Yat-sen University	18	643	35.72	China
9	Xi'an Medical University	18	177	9.83	China
10	Johns Hopkins University	17	1114	65.53	USA



Fig. 5. Visualization of institutions in the field of autophagy in retinal diseases generated by VOSviewer. (A) The institutional cooperation analysis. (B) The institutional co-citation relationship analysis.

Table 4

Top 10 journals in the field of autophagy in retinal diseases.

Rank	Journal	Publications	Citations	JCR	IF (2021)
1	Autophagy	43	2236	Q1	13.3
2	International journal of molecular sciences	39	714	Q1	5.6
3	Experimental eye research	37	793	Q2	3.4
4	Investigative ophthalmology & visual science	35	1287	Q1	4.4
5	PLoS One	32	1550	Q2	3.7
6	Cell death & disease	22	1537	Q1	9.0
7	Scientific reports	19	481	Q2	4.6
8	Antioxidants	17	275	Q1	7.0
9	Cells	16	261	Q2	6.0
10	Biochemical and Biophysical Research Communications	16	352	Q2	3.1

of network, representing their significant positions in this field. Based on the data presented, it can be inferred that *Autophagy* is the most widely published and influential journal in this field. *Investigative Ophthalmology & Visual Science* and *PLoS One* rank fourth and fifth in publication volume, yet they hold a central position in the network, suggesting their significance in this field.

3.6. Analysis of keywords

Keywords play a crucial role in providing a clear and intuitive representation of the research's theme, allowing readers to promptly understand the paper's primary focus before delving into the abstract or the main text, which aids them in deciding whether to invest time in reading the full text. Therefore, in this research, we conducted a frequency analysis of the keyword occurrences in the field of autophagy in retinal diseases using the VOSviewer (Table 5). The most frequent keywords include "Autophagy", "Oxidative stress", "Apoptosis", "Macular degeneration", and "Activation".

The co-occurrence network map and density map of the most common keywords of autophagy in retinal disease literature were built using VOSviewer (Fig. 7A and B). Node size and shadow size represent the frequency of keywords, respectively. It can be inferred that "autophagy", "oxidative stress", and "apoptosis" are the most frequent and vital keywords. The keywords overlay map is generated based on the average year of appearance of keywords in the articles (Fig. 7C). Yellow nodes represent the latest keywords and the most



Fig. 6. Visualization of journal co-citation relationship in the field of autophagy in retinal diseases by VOSviewer. Circles denote journals, and lines denote their co-citations.

Rank	Keyword	Occurrences
1	Autophagy	528
2	Oxidative stress	269
3	Retinal pigment epithelium	228
4	Apoptosis	195
5	Macular degeneration	141
6	Activation	124
7	Expression	118
8	Cells	97
9	Mechanisms	95
10	Death	91
11	Degeneration	85
12	Disease	84
13	Retina	84
14	Age-related macular degeneration	81
15	Inflammation	75
16	Mitophagy	75
17	Mouse model	73
18	Diabetic retinopathy	72
19	Glaucoma	69
20	Cell death	66

Table 5
Top 20 keywords in the research of autophagy in retinal diseases

recent hot topics. Keywords with intense citation bursts from 2009 to 2022 were extracted through keyword burst analysis using CiteSpace (Fig. 7D). The blue line signifies the period, while the red line indicates the timeframe during which keyword bursts were detected.

3.7. Analysis of citations

We tabulated the citation count of literature published in different years, as shown in Fig. 8. In 2016, we observed the highest citation count, with a notable proportion attributed to reviews. Table 6 lists the top 10 publications with the highest citations in autophagy research in retinal diseases. The most cited publication, titled "The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults" is authored by Nita, Malgorzata et al. and was published in the journal *Oxidative Medicine and Cellular Longevity*.



Fig. 7. The co-occurrence analysis visualization of keywords in the field of autophagy in retinal diseases via VOSviewer and CiteSpace. (A) Network map of the keywords. (B) Density map of the keywords. The brightness of the color indicates the frequency of occurrence. (C) Network map of the keywords according to the appearance for the average time. (D) Keywords with intense citation bursts in the field of autophagy in retinal diseases. The blue lines delineate the foundational timeline, whereas the red segments denote the duration of the keyword burst. The two endpoints of the red segments correspond to the commencement and conclusion times of the burst.



Fig. 8. Stacked bar chart of the annual citations for studies on autophagy in the field of retinal diseases from 2009 to 2022.

4. Discussion

Retinal diseases are common reasons for vision impairment and blindness and negatively impact the life quality of numerous adults and children [22]. Multiple etiological factors contribute to the pathogenesis and progression of retinal diseases, including genetic factors [23,24], oxidative stress [25], metabolism dysregulation [1], m6A methylation [26], excitotoxicity [27], and pyroptosis [28, 29]. A growing number of literature has illustrated the relationship between autophagy and retinal diseases, including age-related macular edema [30], diabetic retinopathy [31], glaucoma [32], and retinitis pigmentosa [9]. Autophagy plays a "double-edged sword" role in multiple disorders. In the initial stage, autophagy functions as a self-repair mechanism, which cleans despaired and aged organelles, proteins, and cellular components to maintain intracellular homeostasis. With the development of the disease, autophagy is over-induced by excessive oxidative stress, inflammation, and other stimulations causing damage to the intracellular structure [33,34]. This perspective has been confirmed in various retinal diseases [10,35,36]. Over the last few years, autophagy has received extensive attention as a pathological mechanism or therapeutic method in retinal diseases.

Scientific publications are essential tools for developing novel treatment methods and acquiring up-to-date knowledge in the health domain. Bibliometric analysis helps researchers fully understand their research field [37]. We performed a comprehensive bibliometric

Table 6

The top 10 publications with the highest citations in the research of autophagy in retinal diseases.

Rank	Title	First author	Journal	Document Type	Publication Year	Citations
1	The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults	Nita, Malgorzata	Oxidative Medicine and Cellular Longevity	Review	2016	727
2	Stimulation of the insulin/mTOR pathway delays cone death in a mouse model of retinitis pigmentosa	Punzo, Claudio	Nature Neuroscience	Article	2009	395
3	Dysregulated autophagy in the RPE is associated with increased susceptibility to oxidative stress and AMD	Mitter, Sayak K.	Autophagy	Article	2014	328
4	Autophagy and Exosomes in the Aged Retinal Pigment Epithelium: Possible Relevance to Drusen Formation and Age-Related Macular Degeneration	Wang, Ai Ling	PLoS One	Article	2009	276
5	Glutathione depletion induces ferroptosis, autophagy, and premature cell senescence in retinal pigment epithelial cells	Sun, Yun	Cell Death & Disease	Article	2018	260
6	Autophagy and heterophagy dysregulation leads to retinal pigment epithelium dysfunction and development of age-related macular degeneration	Kaarniranta, Kai	Autophagy	Review	2013	257
7	Noncanonical Autophagy Promotes the Visual Cycle	Kim, Ji-Young	Cell	Article	2013	254
8	Age-Related Retinopathy in NRF2-Deficient Mice	Zhao, Zhenyang	PLoS One	Article	2011	243
9	Mechanisms of acute axonal degeneration in the optic nerve in vivo	Knoeferle, Johanna	Proceedings of the National Academy of Sciences	Article	2010	243
10	Interplay of oxidative, nitrosative/nitrative stress, inflammation, cell death and autophagy in diabetic cardiomyopathy	Varga, Zoltan V.	Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease	Review	2015	240

analysis of literature related to autophagy-related retinal diseases from the WOSCC using VOSviewer, CiteSpace, and R package. This research is the first bibliometric analysis of autophagy and retinal diseases. From 2009 to 2022, the number of annually published papers increased from 13 to 142, with an average annual growth rate of 49.95 %, indicating a significant increase in research interest in this field. It is worth mentioning that annual growth is exceptionally rapid after 2017, possibly associated with the Nobel Prize in Physiology or Medicine, awarded for the research progress in autophagy by Yoshinori Ohsumi in 2016 [38,39]. Additionally, the rapid expansion of annual citations reflects the increasing influence of related publications.

Through further study, 4464 researchers from 1032 organizations in 51 countries/regions have contributed to this field. China is the country with the most publications, which account for 37.2 % of the total publications. Furthermore, four of the top 10 institutions in terms of publication volume are from China. However, only one Chinese author was included among the top 10 authors, and the average number of citations is relatively low, indicating that many scholars in China investigate this field. Still, the depth of their



Fig. 9. Diagram of the classification of the top 20 keywords of autophagy in retinal diseases.

research and cooperation is relatively limited. These situations become obstacles and decelerate the progress of scientific research in China. Regarding collaboration, there are networks of cooperation among different countries/regions, it can be inferred from the network that cooperation in this field exhibits a certain degree of regional specificity. Geographically close countries tend to collaborate more. The most productive author in this field is Kai Kaarniranta from the University of Eastern Finland, and his research focuses on age-related macular degeneration. A total of 282 journals recorded papers about autophagy in retinal diseases. Autophagy is the most productive journal with a contribution of 5 % in this field. It is also the most influential journal with the highest citations and impact factor.

Frequently occurring keywords in the literature often indicate research hot spots. Here we classified the top 20 keywords in the research of autophagy in retinal diseases (Fig. 9). In terms of keywords about biological processes, apoptosis, and oxidative stress are the most frequent keywords apart from autophagy. Apoptosis and autophagy are two primary cell death modes, and their signaling pathways are interconnected [40]. The crosstalk between autophagy and apoptosis remains a novel field. Autophagy is a catabolic process induced by various stimuli, including hypoxia, nutrition deprivation, exogenous substances, and oxidative stress, which functions as the converging point of these stimuli [41]. Reactive oxygen species (ROS) is the upstream regulator and acts at multiple levels in the process of autophagy, which has been gradually unveiled in recent years [42,43]. Inflammation is a contributing cause to the development of multiple retinal diseases, autophagy may function as an anti-inflammation mechanism, protecting the retinal tissues against damage caused by excessive and unnecessary inflammation [8,44]. With its high-energy demands, the retina is susceptible to mitochondrial imbalance, which is observed in various retinal diseases [45]. Mitophagy is a process of selectively clearing damaged or dysfunctional mitochondria through the autophagy mechanism, which is crucial in maintaining mitochondrial homeostasis [46]. Consequently, targeting mitophagy emerges as a novel therapeutic avenue for the treatment of retinal diseases. The extensively researched type in the realm of retinal cells is the retinal pigment epithelial cells (RPEs). RPEs play a role in the pathogenesis of age-related macular degeneration and diabetic retinopathy, which receive extensive research in retinal diseases [47,48].

Keyword overlay analysis can effectively reflect the research hot spots and indicates that diabetic retinopathy and glaucoma have drawn more attention recently. But in the past, researchers paid more attention to the connection between autophagy and macular degeneration. Recently, researchers have shifted the research emphasis to "AMPK", "angiogenesis", "mutation", and "inflammation".

There are some limitations to this research. Firstly, the text data were only collected from the WOSCC due to software restrictions. However, unitizing the WOSCC alone is sufficient to meet the requirements as it is an authoritative academic citation database widely used for academic research and literature retrieval [49]. Secondly, the study only included English-language documents, and documents that were not articles or reviews were excluded. Thirdly, like all bibliometric studies, there is a potential length-time-effect bias, which disadvantages newer articles regarding citations.

5. Conclusion

In this research, we conduct a bibliometric analysis on autophagy in retinal diseases, identifying the number of publications, countries/regions, authors, institutions, and keywords from 2009 to 2022. In recent years, an increasing amount of research has concentrated on the role of autophagy in the pathogenesis, progression, and treatment of retinal diseases. The accumulating quantity of related publications supports evidence for this viewpoint. Oxidative stress closely interacts with autophagy. Besides age-related macular degeneration, diabetic retinopathy and glaucoma are the retinal diseases that are most studied, according to the occurrence of keywords.

Ethical approval

Not applicable.

Data availability statement

All data generated or analyzed during this study are included.

CRediT authorship contribution statement

Chengzhi Liu: Writing – original draft, Data curation. Xiaonan Li: Writing – review & editing, Resources. Laraib Imdad: Writing – review & editing, Data curation. Shengnan Xu: Writing – review & editing. Jun Li: Supervision, Project administration. Xiang Ren: Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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