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TraceEyeDisease: a web-based database for investigating trace elements and their imbalances in eye diseases

Jyoti Kant Choudhari[1*], Hritik Yadav[2] and Usha Chouhan[1]

Abstract
Eye diseases remain a significant global health concern, with trace elements crucial in maintaining ocular health and preventing ocular disorders. In ocular health, trace elements have been recognized as critical factors influencing the development and progression of multiple eye diseases. In this study, we conducted a thorough literature search through PubMed to acquire data concerning different eye diseases associated with trace elements. These diseases are essential in trace element imbalances or deficiencies in their progression. Our approach included a meticulous compilation of information from various databases, systematically integrated into a carefully curated database. In total, we identified 178 distinct genes that encode proteins linked to fourteen trace elements in this comprehensive list. A web-based database designed to formulate evidence-based hypotheses regarding the impact of trace element deficiency and imbalance on eye diseases was presented using Shiny R. This study underscores the vital role of trace elements in preserving ocular health. The Shiny R application facilitates subsequent investigations, fostering enhanced insights into public health, clinical practices, and eye disease research. The URL of TraceEyeDiseas is https://tredis.shinyapps.io/TraceEyeDisease/.

Keywords Eye diseases, Database, Trace elements, Shiny R

Introduction

Trace elements, essential nutrients, are minerals found in small amounts within living tissues. These minerals, such as iron, copper, zinc, selenium, iodine, and chromium, are essential for the human body, often less than 0.1% of the total body weight. While some are considered nutritionally crucial, evidence supporting their essential nature is suggestive or incomplete [1, 2]. In the context of ocular health, Trace elements have been recognized as crucial components that impact the progression and development of many eye disorders. Multiple studies have highlighted the impact of trace elements on various eye tissues, including the cornea, lens, retina, and optic nerve. Ocular health is significantly influenced by trace elements, which play a crucial role in maintaining normal eye function and development. These trace elements include zinc, copper, iron, selenium, and manganese, essential for maintaining normal eye tissues like the cornea, lens, retina, and optic nerve. Deficiencies or imbalances in these trace elements can contribute to the development of various eye diseases. Zinc is essential for the retina, choroid, and other ocular tissues, while copper is crucial for antioxidant defenses and corneal opacities. Iron overload or deficiency can lead to retinal degeneration and optic nerve damage. Selenium protects the eye from oxidative stress, and its deficiency has been linked

*Correspondence:
Jyoti Kant Choudhari
jtchoudhary27@gmail.com
[1]Maulana Azad National Institute of Technology, Bhopal, India
[2]Govt. V.Y.T. Post Graduate Autonomous College, Durg Chhattisgarh, India

to cataract formation [3]. Exposure to heavy metals like lead, cadmium, and mercury may contribute to the development of glaucoma and other neurodegenerative eye diseases. Emerging evidence suggests trace element levels in tears may be associated with dry eye disease, underscoring the importance of ocular surface homeostasis [4, 5]. Considering their critical roles, imbalances or deficiencies in trace elements can lead to the development of various eye diseases such as cataracts, Age-related macular degeneration, night blindness, retinitis pigmentosa, Glaucoma, diabetic retinopathy, uveitis, Retinal detachment, Behçet's disease, and retinal vein occlusion. Cataracts are prevalent factors that lead to visual impairment. Although aging significantly contributes to the development of cataracts, it is possible to avoid or slow down their advancement by identifying and addressing modifiable risk factors. Multiple studies have indicated that the levels of micronutrients and trace elements found not only in the blood serum but also in the lens and aqueous humor can impact the likelihood and severity of cataracts. Trace elements have been recognized as essential factors that influence the progression and occurrence of various eye conditions. Multiple studies have highlighted the impact of trace elements on various eye tissues, including the cornea, lens, retina, and optic nerve [6]. Age-related macular degeneration (AMD) is an ocular condition that can result in the blurring of central vision. AMD is a condition that arises when aging causes harm to the macula, the region of the eye that is accountable for clear and direct vision. The macula is situated within the retina, the photosensitive tissue positioned at the posterior part of the eye [7]. Trace elements could potentially play a role in the complex multifactorial pathogenesis of AMD [8] Night blindness is a condition where individuals have difficulty seeing in low-light conditions. It can be caused by various factors, including pigmentosa, cataracts, and other conditions like vitamin A deficiency and certain medications [9, 10].The most common cause is retinitis pigmentosa, a genetic disorder affecting the retina's rod cells. Deficiencies in essential minerals have been observed in children with night blindness. Retinitis pigmentosa is a group of rare eye diseases that gradually lead to vision loss [11]. Metal cations, such as zinc, play a role in the development of retinitis pigmentosa. Recent findings provide insights into the pathogenesis of the condition [12]. Collectively, current research indicates that trace elements significantly impact the regulation and function of proteins associated with the pathogenesis of ophthalmology. Within this framework, we thoroughly examine the interactions between proteins related to ocular disease and trace elements and subsequently offer the findings in an online database.

Materials and methods

Data collection and curation

Relevant literature and research papers were extensively searched on PubMed [13] to gather information on various trace elements that lead to different eye diseases. After studying several articles, ten different types of eye diseases were identified, in which imbalance or deficiencies of trace elements play a crucial role in their development. Eye diseases include Cataracts, AMD, Night blindness, Retinitis pigmentosa, Glaucoma, Diabetic retinopathy, Uveitis, Retinal detachment, Behcet's disease, and Retinal Vein Occlusion. Data on protein-coding genes, protein names, UniprotIDs, biological processes/pathways, and associated eye diseases were taken from UniProt [14]. Gene locations and gene synonyms from NCBI [15]. Relevant information about their 3D structure from RCSB/PDB [16]. Structure information about specific genes was not accessible within the RCSB/PDB database. We sourced structural data from AlphaFold [17] to address this limitation, ensuring a comprehensive coverage of gene structures for our analysis. We linked the GeneCards [17] database to integrate more information about gene summaries, descriptions, protein information, and expression patterns. Further details regarding the interaction between proteins and trace elements were annotated with PubMed identifiers (PMID) from relevant publications. Gene ontologies were assigned to genes using ClueGO, linking them to specific biological processes and pathways. Additionally, a protein-protein interaction network was constructed using information integrated from the STRING database [18].

Data preparation and database creation

Data about trace elements, gene interactions, protein names, UniProtIds, Genecards biological processes/pathways, PubMedIds, locations, and structures were extracted and compiled into an Excel spreadsheet. The Excel spreadsheet containing curated data was imported into the R environment. The data was processed and cleaned to remove any duplicates, missing values, or inconsistencies [19].

Shiny R web application development

The Shiny [20] R framework was utilized to develop a web-interactive database for trace elements-related eye diseases. The R [21] offers numerous packages that help build the application easily. Using the 'tidyr' and 'dplyr' packages, the data was transformed into a well-structured data frame with columns. The 'shiny,' 'shinyWidgets,' and 'DT' packages were employed to build an interactive user interface (UI) with dynamic filtering options.

Data visualization and user interaction

All the information was integrated into the database and implemented using Shiny R app [19, 20].

Interactive tables were generated to display curated data in a user-friendly manner, enabling easy exploration and analysis. The UI allows users to select and filter trace elements, biological processes/pathways, genes, and eye diseases of interest. The web-interactive database was hosted on a web server, making it accessible to users worldwide.

Result

We developed a web-based interactive database that contains comprehensive information about interactions between trace elements and proteins in the context of various trace element-related eye diseases. Our approach involved systematically gathering and integrating data from multiple databases to create a highly curated resource.

The web-based tool is built using Shiny, a computational framework that allows the development of interactive web applications using scripts written in the R language. Within the web interface:

I. Gene-related information such as gene names, synonyms, and identifiers from databases like Ensembl and Genecards is provided, along with details about the significant trace elements associated with those diseases.
II. Protein information includes protein names, locations, and identifiers from relevant databases like UniProt.
III. 3D structure identifiers from databases such as RCSB/PDB and AlphaFold are available.
IV. Pathways and biological processes linked to the gene are described using Gene Ontology (GO) terms.
V. PubMed IDs for linked publications are provided, allowing users to access further information about the role of trace elements in disease development.
VI. Identifiers for protein-protein interaction networks are included, providing insights into protein interactions relevant to the disease.
VII. All identifiers are directly linked to their respective databases, enabling users to access detailed information directly from these sources.
VIII. PMID of linked publications are provided for additional reading and research into the involvement of trace elements in disease processes.

Users can browse the entire dataset, download specific information, or filter the data by selecting genes, trace elements, biological processes/pathways, or other interest criteria. The tool generates tables that aggregate and visualize multiple types of information, enhancing understanding and exploration of trace element-related eye diseases.

The online database features a single table that can be filtered by trace elements, proteins, pathways, and biological process (BP) terms. Figure 1A provides a snapshot of the UI visible to users. Our database encompasses fourteen trace elements, specifically Ca, Cr, Cu, Fe, Hg, K, Mg, Mn, Na, Ni, Pb, Se, and Zn. In total, 178 unique genes were identified in the analyzed datasets and associated with these fourteen trace elements. We also observed that certain genes exhibit repeated interactions with the same trace elements. This occurrence is due to their involvement in multiple diseases that interact with these shared genes. Specifically, 55 genes demonstrate overlaps with at least two trace elements, whether the same or different [Fig. 2 (b)]. The online database contains one table filtered by trace elements, proteins, pathways, and BP terms. Figure 1A captures the user-visible front end of the app. In total, 33 trace elements had three to four interactions with trace elements. Genes such as SOD2, CA2, PXDN, MMP2, CFH, RHO, CRP, PON1, PIK3C2A, CA4, COL18A1, MMP9, CFI, NOS3, MYOC, CRB1, ZNF408, BEST1, IDH3A, PDE6A, TKT, PDE6B, ADIPOQ, COL9A1, had three interactions. After further observations, 25 genes had interactions with the same trace element interacting with them (CFH, PIK3C2A, PXDN, BEST1, CA4, COL9A1, IDH3A, PDE6A, ZNF408, AGBL5, ARHGEF18, ARL2BP, COL18A1, LOXL1, LOXL3, MMP14, MMP2, NR2E3, P3H2, RHO, RP9, TNFAIP3, TOPORS, TRIM44, ZNF513), indicating that multiple disease can interact with the same gene. Among the trace elements analyzed, zinc (Zn) demonstrated the highest level of interaction with genes associated with trace element-related eye disease, with a remarkable 76 interactions across various eye diseases. magnesium (Mg) exhibited the second-highest count, with 41 interactions, followed by Calcium (Ca) with 41 interactions, and copper (Cu) with 15 interactions, as shown in Fig. 2 (B). AMD, Behçet's disease, cataracts, diabetic retinopathy, glaucoma, night blindness, retinal detachment, retinal vein occlusion, retinitis pigmentosa, and uveitis are all associated with specific genes. Age-related macular degeneration is linked to 21 genes in six trace elements, while Behçet's disease has five genes in two trace elements. Cataract has 50 genes in nine trace elements, while diabetic retinopathy has 20 genes in seven. Glaucoma has 27 genes in eight trace elements. Night blindness has 42 genes in seven trace elements, retinal detachment has 17 genes in six trace elements, retinal vein occlusion has seven genes in three trace elements, and retinitis pigmentosa has 21 genes in five trace elements, as shown in Table 1.

Enrichment analysis of highly interacting genes reveals significant associations. CA2 is associated with the

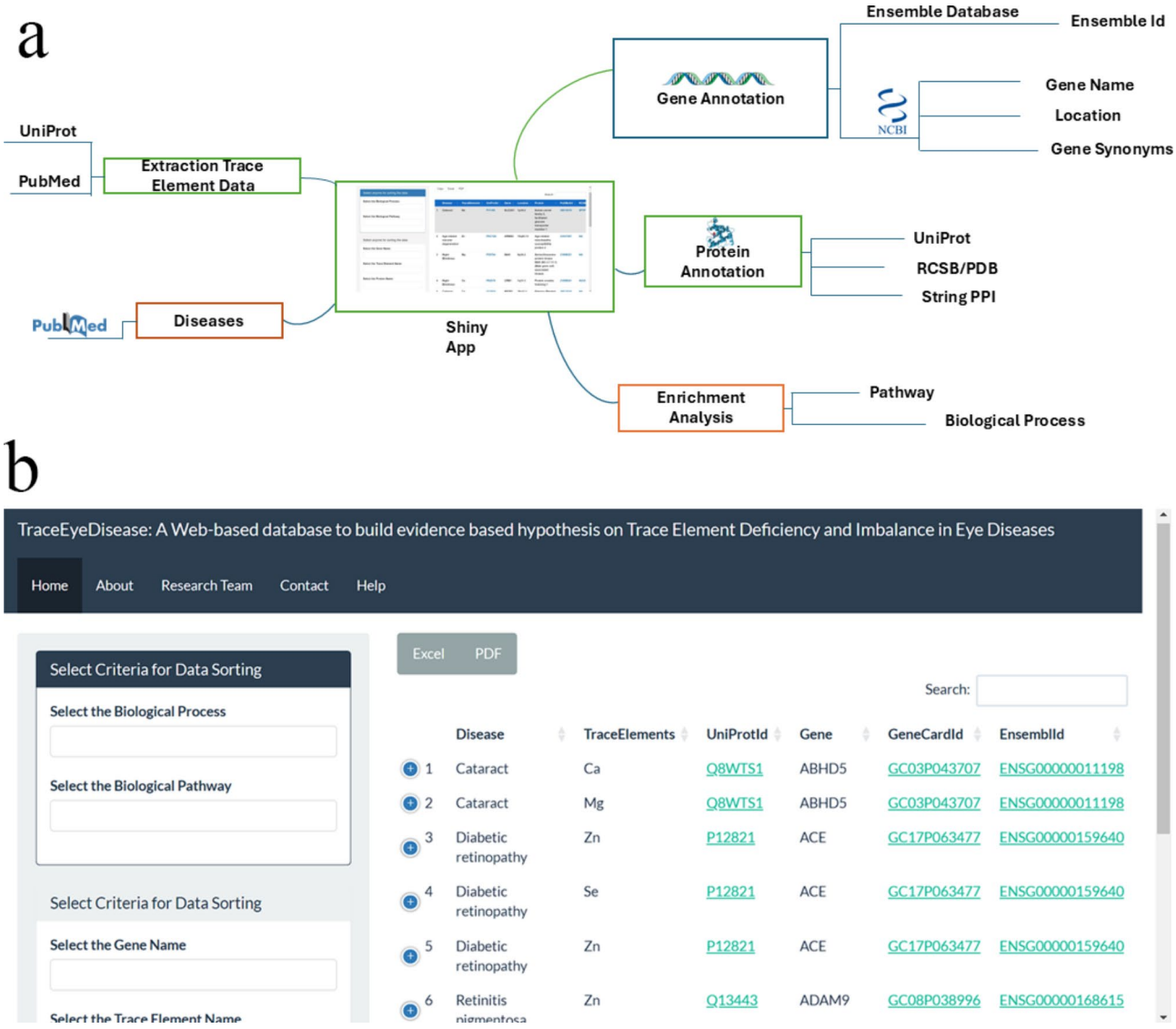

Fig. 1 (**A**) Illustration of the workflow used to develop TraceEyeDisease. (**B**) Screenshot of the Shiny R application interface. The left panel contains filters that allow users to select interactions based on different criteria: (**1**) a gene or protein list (with a default display of 10 data points when empty), (**2**) a specific trace element, and (**3**) gene attribute linked to selected pathways or biological processes. The data are presented in the table on the right-hand side of the interface

regulation of oligopeptide transport, which is intricately linked to nutrient uptake, trace element transport, cell signaling, and immune responses within ocular tissues. Dysregulation of this process could disrupt trace element homeostasis and impact cellular functions relevant to trace element-related eye diseases. CFH is associated with regulation of complement activation and complement activation, alternative pathway, in AMD, there is growing evidence that complement dysregulation, including activation of the alternative pathway, plays a role in disease pathogenesis. CFH plays a role in maintaining complement homeostasis. MIPEP shows peptide metabolic processes, peptides may play a role in transporting essential trace elements to the eye and regulating their availability for cellular functions. Imbalances or disruptions in peptide metabolism could impact trace element homeostasis and contribute to eye diseases. PIK3C2A is associated with the phosphatidylinositol biosynthetic process, and phosphatidylinositol and its derivatives are also involved in signaling pathways that affect vision, retinal function, and the maintenance of ocular tissues. PON1 plays part in response to fluoride, high levels of fluoride exposure have been associated with oxidative stress, which can impact trace element homeostasis and contribute to trace element-related eye diseases. PXDN is linked to eye development, proper eye development is essential for normal vision and ocular function. Abnormalities or disruptions in eye development's molecular

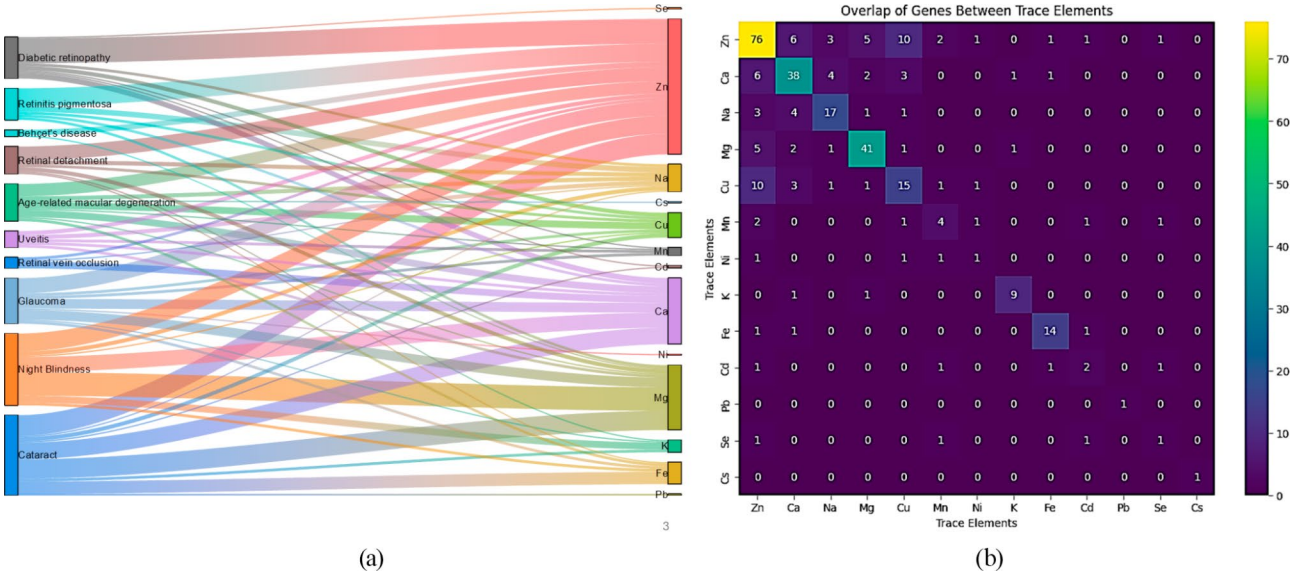

Fig. 2 (**A**) Sankey diagram visualizing complex relationships of multiple trace element-interacting genes. (**B**) Pairwise trace element intersections accounting for mutual shared interactions

Table 1 List of genes associated with diseases and their interaction with trace elements

Disease	Trace Elements	Genes
Age-related macular degeneration	Ca, Na, Zn, Cu, Mg, Fe, Mn, Cs	ADIPOQ, P2RX4, C3, C9, P2RX7, CFB, CFH, CFI, CRP, ENO1, HSF4, MMP9, NOS3, PON1, PPARA, RPE, SOD2, TIMP2, VEGFC, ARMS2
Behçet's disease	Zn, Mg	ERAP1, ICAM1, RELA, TNFAIP3, MEFV
Cataract	Zn, Mg, Ca, Fe, Cd, Pb, Cu, Na, K	ACE2, ARL2, ARL2BP, BEST1, CLPB, CNBP, COL18A1, COL9A1, CRYAA, CRYAB, CYP51A1, FTL, GALT, GJA1, ITPA, LOXL1, PXDN, MBNL1, MT-CYB, SLC33A1, ABHD5, PGRMC1, PHYH, CAPN15, RHO, SLC2A1, EYA1, TKT, TRIM69, XDH, INPP5K, KCNA4, KCNJ13, MIPEP, TKFC, TRIM44, COL11A1, COL2A1, DMPK, EBP, FYCO1, LOXL3, MVK, P3H2, PIK3C2A, RAB3GAP1, UNC119, ZNF526, BFSP1, CYP27A1
Diabetic retinopathy	Zn, Ca, Na, Cu, Mn, Cd, Se	ACE, ADIPOQ, AGER, ANGPT1, CRP, GH1, GSTM1, IL6, INS, MMP14, MMP2, MMP9, NOS3, PON1, SERPINE1, SIRT1, SOD1, SOD2, SORD, VDR
Glaucoma	Ca, Cu, Mn, Zn, Ni, Fe, Mg, K	BEST1, CA2, COL18A1, CREBBP, CYP1B1, FBN1, GNAQ, IFIH1, MYOC, OPTN, POMGNT1, RHOD, RIGI, RPGRIP1, SYNE2, TMCO1, WDR36, LOXL1, PXDN, ADAMTS10, EFEMP1, FOXC1, GLIS3, TRIM44, ADAMTS17, LTBP2, PIK3C2A
Night Blindness	Mg, Ca, Na, Zn, K, Cu, Fe	ARL2BP, ARL6, BEST1, CA4, CNGA1, CRB1, DHDDS, GRK1, HK1, IDH3A, IDH3B, MERTK, NEK2, PRPF31, RHO, SCAPER, TIMP3, ARHGEF18, CACNA1F, CACNA2D4, RPE65, ZNF408, CABP4, GNB3, GUCA1B, GUCY2D, KCNV2, MAK, PDE6A, PDE6B, SLC24A1, TOPORS, TRPM1, ZNF513, AGBL5, ARL3, CRB2, GNAT1, IMPDH1, NR2E3, CNGB1, CYP4V2
Retinal detachment	Zn, K, Cu, Na, Mg, Fe	APAF1, CCL2, CDKN1B, CFH, COL18A1, COL9A1, CRB1, CTNNB1, KIF11, PDGFB, PRKCQ, TNF, ZNF408, GZF1, LOXL3, MMP19, P3H2
Retinal vein occlusion	Na, Ca, Zn	CBS, CRP, FGA, FGB, FGG, MMP2, SERPINE1
Retinitis pigmentosa	Na, Zn, Cu, Ca, Mg	AIPL1, CA4, CALR, CRB1, MYOC, PRKCG, PRPF31, PRPF8, RHO, RPGR, SNRNP200, TIMP1, IDH3A, ZNF408, ADAM9, PDE6A, PDE6B, TOPORS, ZNF513, AGBL5, NR2E3
Uveitis	Zn, Ca, Mn, Na, Mg	COL9A1, CRP, HLA-A, HSPA1L, HSPA9, IL2, IL23R, IL6, MRAP, SOD2, TNFAIP3, TNFRSF1A

and cellular processes can lead to congenital eye disorders or other visual impairments. SOD2 and SORD are linked to the cellular response to oxidative stress; oxidative stress can lead to cellular damage and contribute to the pathogenesis of various conditions, such as AMD, cataracts, glaucoma, and diabetic retinopathy.

Discussion

Patients with trace element-related eye diseases are observed to have two or more trace elements interacting with genes that lead to the pathogenesis of the disease, except for diseases like retinal vein occlusion and uveitis, which only interact with one trace element. We now know that the imbalance of trace elements can lead to various eye diseases. In the case of AMD, elevated zinc (Zn) levels and decreased copper (Cu) levels were

found in the AMD patient [22]. The involvement of the ARMS2 gene in AMD and cognitive impairment (CI) varies depending on the circumstances. A study found that women with specific genetic factors experienced a decrease in CI when given low-dose zinc supplementation. However, in AMD, those same genetic factors led to a higher rate of disease progression with high-dose zinc. This suggests that the function of the ARMS2 gene and the effects of zinc supplementation can differ based on genetic variables [23]. In Behçet's disease, lower levels of Magnesium (Mg) and elevated zinc (Zn) levels were found in the patient [24, 25]. It is responsible for the inflammation condition that causes eye inflammation in about 70% of patients [26]. Moreover, the use of zinc supplementation has been investigated as a prospective therapeutic approach in the management of Behçet's disease. Studies suggest it could decrease disease activity and enhance clinical results [24]. In cataracts, elevated levels of sodium, potassium, calcium, iron, zinc, lead, and lower levels of magnesium were found [6]. In diabetic retinopathy, elevated levels of cadmium, chromium, and lower levels of manganese and zinc were found [27, 28]. However, research has shown that trace elements associated with antioxidant enzymes are altered in diabetes, and imbalances in specific elements may disrupt insulin metabolism. Most cohort studies focus on a single element or limited combination. Congruently, in glaucoma, elevated levels of manganese, mercury, zinc, lead, and lower levels of iron were found. In patients with night blindness, lower levels of iron, copper, zinc, magnesium, calcium, and potassium were found in the biological samples (blood, serum, scalp, and hair). Several trace elements, such as selenium, chromium, manganese, magnesium, iron, cobalt, copper, and zinc, have been associated with glaucoma. These trace elements can affect intraocular pressure, trabecular meshwork, optic nerve oxidative stress, and other factors involved in glaucoma development. These elements can impact intraocular pressure, trabecular meshwork, optic nerve oxidative stress, and other factors involved in the development of glaucoma [29]. Additionally, eye diseases in cases of retinal detachment and elevated iron levels cause the disease's pathogenesis. In retinal vein occlusion, lower iron levels lead to the pathogenesis of the disease [30]. Elevated levels of copper and lower levels of zinc were found in the patients with retinitis pigmentosa [31]. Studies have found that patients with primary retinitis pigmentosa have normal or almost average serum copper concentration, low plasma caeruloplasmin concentration, and high urine output of copper. This suggests that retinitis pigmentosa may be caused by an inborn error in copper metabolism, similar to hepatolenticular degeneration [32]. In another rare eye disease, uveitis, a decrease in zinc levels is the cause behind the pathogenesis of the disease [33]. This study examined selenium and zinc levels in the blood of individuals with uveitis. Participants with chronic uveitis had lower levels of selenium and zinc, especially zinc. Additionally, there was a decrease in trace elements with age. The study suggests that more research should be conducted to investigate the potential benefits of selenium and zinc supplementation for individuals with chronic uveitis [33].

Conclusion

This study has underscored the vital role that trace elements play in maintaining ocular health. Imbalances or deficiencies in these elements can lead to various eye diseases and vision loss. The web-based interactive database provides an accessible means of retrieving information related to these diseases and trace elements. Offering comprehensive data significantly enhances the quality of care for patients with a trace element-related eye. The TraceEyeDisease database should help further investigate and better understand public health, clinical practice, and research on eye disease. The creation of this web-based database represents a significant step towards advancing our knowledge of the intricate interplay between trace elements and eye health. Integrating biological data from various sources not only streamlines access to critical information but also facilitates the identification of patterns and connections that might otherwise remain obscured. The user-friendly interface of the Shiny R application empowers users to explore the database intuitively, fostering informed decision-making and driving further research in this vital domain.

Limitations.

The limitation of this study is that it is based on a thorough literature search and compilation of information from various studies rather than conducting original research. Therefore, the data are dependent on the existing literature and databases. The database could be expanded to include more eye diseases and trace elements. Additionally, further research could be conducted to investigate the specific mechanisms by which trace elements influence the development and progression of eye diseases. This could involve studying the interactions between trace elements and proteins in more detail and exploring the role of trace elements in ocular tissues and cellular processes. Furthermore, the database could be updated regularly to include new research findings and ensure that the information remains up-to-date and relevant.

Abbreviations

AMD	Age—related macular degeneration
BP	Biological Process
GO	Gene Ontology
NCBI	National Center for Biotechnology Information
PDB	Protein Data Bank
PMID	PubMed Identifier

RCSB	Research Collaboratory for Structural Bioinformatics
RNA	Ribonucleic Acid
R	Programming language for statistical computing and graphics
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
UniProt	Universal Protein Resource

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Author contributions
JKC: Conceptualization (idea development). Methodology design (literature search strategy). Data curation (compilation and integration of information). Formal analysis (contributing to data analysis) Writing - Original Draft (lead author). Writing - Review & Editing (overall responsibility). HY: Literature search (conducting searches). Data curation (contributing to information compilation). Writing - Original Draft (specific sections). Writing - Review & Editing. UC: Supervision (guidance and oversight). Writing - Review & Editing.

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Data availability
Project Name: TraceEyeDiseaseProject home page: https://tredis.shinyapps.io/TraceEyeDisease/. Operating Systems: Platform-independent. Programming language: R. Other requirements: internet connection, internet browser. License: CC-BY-4.0. Any restrictions to use by non-academics: No.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This manuscript does not contain any data from which individual persons can be identified.

Competing interests
The authors declare no competing interests.

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References

1. Health NRC, editor. C on D and. Trace Elements. Diet and Health: implications for reducing Chronic Disease Risk. National Academies Press (US); 1989.
2. Mehri A. Trace Elements in Human Nutrition (II) – an update. Int J Prev Med. 2020;11:2.
3. Bunce GE. Trace element and Mineral Nutrition in diseases of the Eye. In: Bogden JD, Klevay LM, editors. Clinical Nutrition of the essential Trace Elements and minerals: the Guide for Health professionals. Totowa, NJ: Humana; 2000. pp. 371–80.
4. Chen Y-J, Chen Y-Y, Lai C-H. Clinical association between trace elements of tear and dry eye metrics. Sci Rep. 2022;12:18052.
5. Karcioglu ZA. Zinc in the eye. Surv Ophthalmol. 1982;27:114–22.
6. Dolar-Szczasny J, Święch A, Flieger J, Tatarczak-Michalewska M, Niedzielski P, Proch J, et al. Levels of Trace Elements in the aqueous humor of cataract patients measured by the inductively coupled plasma Optical Emission Spectrometry. Mol Basel Switz. 2019;24:4127.
7. Arnold JJ, Heriot W. Age related macular degeneration. BMJ Clin Evid. 2007;2007:0701.
8. Jünemann AGM, Stopa P, Michalke B, Chaudhri A, Reulbach U, Huchzermeyer C, et al. Levels of aqueous humor trace elements in patients with non-exsudative age-related macular degeneration: a case-control study. PLoS ONE. 2013;8:e56734.
9. Mehra D, Le PH, Physiology. In: StatPearls, editor. Night Vision. Treasure Island (FL): StatPearls Publishing; 2024.
10. Combs F Jr, McClung JP. Chapter 5 - vitamin A. In: Combs F Jr, McClung JP, editors. The vitamins (Sixth Edition). Academic; 2022. pp. 77–132.
11. Afridi HI, Kazi TG, Kazi N, Kandhro GA, Baig JA, Shah AQ, et al. Evaluation of status of zinc, copper, and iron levels in biological samples of normal children and children with night blindness with age groups of 3–7 and 8–12 years. Biol Trace Elem Res. 2011;142:323–34.
12. Liu W, Liu S, Li P, Yao K. Retinitis Pigmentosa: Progress in Molecular Pathology and Biotherapeutical strategies. Int J Mol Sci. 2022;23:4883.
13. Fiorini N, Canese K, Bryzgunov R, Radetska I, Gindulyte A, Latterner M, et al. PubMed labs: an experimental system for improving biomedical literature search. Database J Biol Databases Curation. 2018;2018:bay094.
14. UniProt. The Universal protein knowledgebase in 2023. Nucleic Acids Res. 2022;51:D523–31.
15. Sayers EW, Bolton EE, Brister JR, Canese K, Chan J, Comeau DC, et al. Database resources of the National Center for Biotechnology Information in 2023. Nucleic Acids Res. 2022;51:D29–38.
16. Burley SK, Bhikadiya C, Bi C, Bittrich S, Chen L, Crichlow GV, et al. RCSB Protein Data Bank: celebrating 50 years of the PDB with new tools for understanding and visualizing biological macromolecules in 3D. Protein Sci Publ Protein Soc. 2022;31:187–208.
17. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards suite: from Gene Data Mining to Disease Genome sequence analyses. Curr Protoc Bioinforma. 2016;54:1301–13033.
18. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51:D638–46.
19. Choudhari JK, Eberhardt M, Chatterjee T, Hohberger B, Vera J. Glaucoma-TrEl: a web-based interactive database to build evidence-based hypotheses on the role of trace elements in glaucoma. BMC Res Notes. 2022;15:348.
20. Chang W, Cheng J, Allaire JJ, Sievert C, Schloerke B, Xie Y et al. shiny: Web Application Framework for R. 2023.
21. Hackenberger BK. R software: unfriendly but probably the best. Croat Med J. 2020;61:66–8.
22. Erie JC, Good JA, Butz JA, Pulido JS. Reduced zinc and copper in the retinal pigment epithelium and choroid in age-related macular degeneration. Am J Ophthalmol. 2009;147:276–e2821.
23. Cc RK, C A, R-F BZ. CFH and ARMS2 polymorphisms interact with zinc supplements in cognitive impairment in the women's Health Initiative Hormone Trial. PubMed.
24. Sharquie KE, Najim RA, Al-Dori WS, Al-Hayani RK. Oral zinc sulfate in the treatment of Behcet's disease: a double blind cross-over study. J Dermatol. 2006;33:541–6.
25. Faghfouri AH, Baradaran B, Khabbazi A, Abdoli Shadbad M, Papi S, Faghfuri E, et al. Regulation of NLRP3 inflammasome by zinc supplementation in Behçet's disease patients: a double-blind, randomized placebo-controlled clinical trial. Int Immunopharmacol. 2022;109:108825.
26. Zając H, Turno-Kręcicka A. Ocular manifestations of Behçet's Disease: an update on Diagnostic challenges and Disease Management. J Clin Med. 2021;10:5174.
27. Zhu X, Hua R. Serum essential trace elements and toxic metals in Chinese diabetic retinopathy patients. Med (Baltim). 2020;99:e23141.
28. Zhang Y, Liu X, Zhang X, Li L, Li Q, Geng H, et al. Association between serum heavy metal levels and diabetic retinopathy in NHANES 2011–2020. Sci Rep. 2024;14:1268.
29. Choudhari JK, Chaterjee T. Impact of trace elements and risk factor for glaucoma: MGM Journal of Medical Sciences.
30. Daruich A, Le Rouzic Q, Jonet L, Naud M-C, Kowalczuk L, Pournaras J-A, et al. Iron is neurotoxic in retinal detachment and transferrin confers neuroprotection. Sci Adv. 2019;5:eaau9940.
31. Za K, Hj RS. H. Serum zinc levels in retinitis pigmentosa. PubMed.
32. Gahlot DK, Khosla PK, Makashir PD, Vasuki K, Basu N. Copper metabolism in retinitis pigmentosa. 1976. https://doi.org/10.1136/bjo.60.11.770
33. Dawczynski J, Winnefeld K, Strobel J. Selenium and zinc in patients with acute and chronic uveitis. Biol Trace Elem Res. 2006;113:131–7.

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