BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092600
Article Type:	Protocol
Date Submitted by the Author:	19-Aug-2024
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Keywords:	Corneal and external diseases < OPHTHALMOLOGY, Diagnostic microbiology < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Molecular diagnostics < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES

Human ocular trematode infections- A scoping review protocol

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Abstract

Introduction: Human ocular trematode infections caused by parasitic flatworms, is a significant global public health concern due to the associated severe consequences if left untreated. This protocol outlines a scoping review methodology, aiming to explore the knowledge on clinical-epidemiological, aetiopathogenesis, molecular, and histopathological characteristics, and patient perspectives related to ocular trematode infections in humans.

Methods and analysis: The Joanna Briggs Institute (JBI) Reviewers' Manual and the framework developed by Arksey and O'Malley will be used as the guidelines for the proposed scoping review. The research question has been developed using the PCC (Population, Concept, Context) framework, as per the JBI manual for evidence Synthesis 2020. The JBI three-stage search strategy will be used in this review and databases such as MEDLINE/PubMed, Science Direct, CINAHL, and Google Scholar will be used in the collection and synthesis of evidence.

Ethics and dissemination: Since the secondary data will be used in the study, ethical approval will not be required. The findings of the scoping review will be published in a scientific journal and presented at relevant conferences, aiming to improve patient outcomes and to guide future research in ocular trematode infections.

Strengths and limitations of this study

- The standard protocol followed in this scoping review will ensure the transparency and clarity of the synthesized evidence on ocular trematode infections in human.
- Searching evidence in multiple electronic databases using an effective search strategy will guarantee thorough coverage of the available evidence to enhance the accuracy of the findings.
- Studies that are only published in English will be included in this review.
- There will not be an assessment of the quality of the included studies.

Introduction

Eye infections encompass a broad spectrum of diseases, ranging from mild conjunctivitis to severe conditions that can lead to vision loss or blindness. Common causes of eye infections include bacteria, viruses, fungi, and parasites [1]. Among parasitic eye infections, trematode eye infections represent a distinct and relatively rare subset. Trematodes, or flukes, are a diverse group of parasitic flatworms. Ocular trematode infections can lead to a spectrum of pathological consequences, ranging from mild irritation to severe vision impairment or even blindness if left untreated. These parasites can infiltrate various ocular tissues, causing inflammation, tissue damage, and structural alterations compromising the ocular functions of the affected individual.

Trematodes have complex life cycles involving intermediate hosts such as snails or fish. In the context of ocular trematode infections, humans may become accidental hosts when they ingest or come into contact with water containing cercariae, the free-swimming larval stage of the parasite [3]. In a prospective case series, waterborne ophthalmic granulomas of the anterior chamber were analyzed in Egyptian patients, revealing digenic trematode DNA in 6 out of 14 excised nodules [2]. Several South Indian studies highlighted the role of trematodes in ocular granulomas in children who bathed in lakes or rivers. DNA analysis linked trematode cercariae released by the snail *Melanoides tuberculata* to ocular parasitosis, emphasizing snail vectors as environmental risk factors. The DNA sequences of the trematode cercariae and the granuloma samples from Polymerase chain reaction (PCR) products revealed the highest degree of similarity to *Procerovum varium*. Further, this study identified snail vectors as environmental risk factors for ocular parasitosis, confirming the cause of the ocular infection [3]. Alternatively, individuals may acquire ocular trematode infections by consuming raw or undercooked freshwater fish or crustaceans that serve as intermediate hosts for certain trematode species (Eg; Procerovum spp). Ingestion of infected intermediate hosts introduces the infective larvae into the human digestive tract. These larvae can then penetrate the intestinal wall, enter the bloodstream, and migrate to various organs, including the eyes, where they can cause localized pathology [4].

The clinical symptoms and signs vary, depending on the type of the infected parasite, the stage of the infection, and the ocular tissue/part involved. Further, the host immune responses which include local defense mechanisms play a pivotal role in determining the severity of the infection

[5,6]. However, several typical features may aid in clinical suspicion and diagnosis such as eye redness, pain or discomfort, excessive tearing or watery eyes, itching or irritation, eye discharge, swollen eyelids, change in the appearance of the eye, photophobia, foreign body sensation and blurred or decreased vision. Granuloma formation or systemic symptoms due to the infection are some occasional clinical consequeces. In the absence of timely intervention, the disease can cause serious consequences like blindness. Thus, as delayed diagnosis can affect the quality of life of the patient, understanding their perception of disease is also important in understanding the disease burden.

The insidious nature of these infections underscores the importance of timely detection and intervention to mitigate the risk of irreversible ocular damage. A recent case report identified different trematode species causing ocular infections in Sri Lankan children and stressed the need for good collaboration between clinicians and parasitologists, for improved community awareness for effective diagnosis, control, and prevention of the disease [7]. Thus, understanding the epidemiology, clinical presentation, risk factors, and patient's perception of ocular trematode infections is crucial in identifying effective disease control and prevention strategies. Thus, summarizing the current body of evidence not only provides insights into the epidemiology, clinical characteristics, and treatment outcomes of ocular trematode infections but also helps identify gaps in knowledge and areas requiring further investigation. Moreover, a comprehensive synthesis of the literature enables researchers and healthcare practitioners to gain more information, design targeted studies, and develop evidence-based guidelines for the diagnosis and management of these challenging conditions. By highlighting the importance of consolidating existing knowledge, this scoping review aims to contribute to the advancement of understanding of ocular trematode infections, ultimately improving patient outcomes and guiding future research endeavors in this field.

Methodology

The proposed protocol is for a scoping review of the literature on human ocular trematode infections. The proposed scoping review will be guided by the methodological framework provided by Arksey and O'Malley and the Joanna Briggs Institute Reviewers' Manual (JBI) [8,9] and reported

using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [10]. The review method will follow the suggested structure and consist of five stages: (1) identification of the research question, (2) identification of relevant studies, (3) selection of studies, (4) charting the data (5) collating and summarizing the results.

Stage 1: Identifying the review question

The research question has been developed using the PCC (Population, Concept, Context) framework (Table 1), as per the JBI manual for evidence synthesis 2020 [9].

Table 1. Criteria for selecting the studies

Criteria	Determinants
P—population	Patients with ocular trematode infections
C—context	Prevalence Epidemiological characteristics Etiological agents Clinical characteristics Risk factors Immunological responses Histopathological characteristics Diagnosis Patient perspectives
C—concept	Global

The main research question is 'What are the clinical-epidemiological, aetio-pathogenesis, molecular, and histopathological characteristics, and patient perspectives related to ocular trematode infections in humans?'

The study's objectives were developed in response to addressing specific research questions. The specific research questions of the scoping review are;

a) What are the global and regional prevalences of ocular trematode infections in humans?
b) What are the epidemiological characteristics of ocular trematode infections in humans?
c) What are the aetiological agents of ocular trematode infections in humans and their natural animal hosts?
d) What are the risk factors for ocular trematode infections in humans?
e) What are the clinical presentations of ocular trematode infections in humans?
f) What is the immune response to ocular trematode infections in humans?
g) What are the histopathological characteristics of ocular trematode infections in humans?
h) What methods are used to diagnose ocular trematode infections in humans?
i) What are the different treatments used for ocular trematode infections and their outcomes?
j) What are the patient perspectives on ocular trematode infections?

Stage 2: Identification of relevant studies

The JBI three-stage search strategy will be used in this study to identify the relevant studies [9]. The first step will be a limited search of PUBMED using common keywords such as ((((("ocular"[All Fields]) OR ("eye"[All Fields])) OR ("ophthalmic"[All Fields])) OR (ophthalm*)) AND ((((((("trematode"[All Fields]) OR ("fluke"[All Fields])) OR ("flat worms"[All Fields])) OR (trematod*)) OR ("flukes"[All Fields])) OR ("flat worm"[All Fields])), after which the text terms found in the article's title, abstract, and index terms will be analyzed. A second search using all identified keywords and index terms will then be undertaken across all included databases such as MEDLINE/PubMed, Science Direct, CINAHL, and Google Scholar. Thirdly, a search for additional studies will be conducted through the reference list of all identified papers and articles.

Stage 3: Selection of eligible studies

The PCC framework and the following inclusion and exclusion criteria will be used to guide the selection of eligible studies. All studies that meet the inclusion criteria and are published up to August 2024 will be considered for inclusion in this review. A table will be created with the outcomes of both manual and electronic database searches. The selected articles from each

database will be uploaded into Mendeley reference management software and duplicates will be removed. Then, two reviewers will independently review each title and abstract, and those that do not meet the criteria for inclusion will be removed. Any difference of opinion will be discussed between the two reviewers to arrive at a common decision.

Inclusion criteria

All experimental or observational studies with qualitative or quantitative data on clinico-epidemiological, molecular, and histopathological characteristics, and patient perspectives related to ocular trematode infections (case reports, case series, original research articles).

Exclusion criteria

Studies that are not available in the full-text article, review articles, and studies not published in the English language will be excluded.

Stage 4: Charting the data

Essential information from relevant studies will be extracted from the table that was developed using the template data extraction instrument for scoping reviews in the Joanna Briggs Institute guidance for conducting a scoping review (2007). To reduce bias and inaccuracies, this process will be carried out independently by two reviewers in duplicate. Disagreements among the reviewers will be resolved by discussion.

The data extraction form will include the following details,

(i) Title
(ii) Author
(iii) Publication year
(iv) The country where the research was conducted
(v) Study setting/population
(vi) Study design
(vii) Sample size
(viii) Aims and objective
(ix) Criteria of participant selection
(x) Key findings

a) Prevalence
b) Epidemiological characteristics
c) Etiological agents and their natural hosts
d) Clinical characteristics
e) Risk factors
f) Histopathological characteristics
g) Immune responses
h) Diagnosis
i) Treatment and outcome
j) Patient perspectives

(xi) Conclusion/s

Stage 5: Collating, summarising, and reporting the results

The extracted data will be analyzed using descriptive and thematic analysis and summarised focusing on the aim of the review as well as the research questions. Following the PRISMA-ScR criteria, the scoping review results will be presented narratively, establishing a thorough and well-organized summary of the literature on human ocular trematode infections. The findings are anticipated to be presented in a full scoping review article.

Ethics and dissemination

Ethical approval is not essential because the scoping review technique intends to synthesize information from publicly available articles. A report summarizing the scoping review's findings will be forwarded to a scientific journal and will be presented at relevant conferences as part of dissemination strategies. We expect the scoping review's findings to contribute to the advancement of understanding of ocular trematode infections, ultimately improving patient outcomes and guiding future research endeavors in this field. Also, the review's findings could have significant policy implications and inform public health strategies related to the prevention and management of ocular trematode infections.

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Authors' contribution: PK contributed in development of search strategy, and drafting of the protocol. HW contributed in development of search strategy, drafting and editing of the protocol, AS and SW involved in editing the manuscript. KW contributed in conceptualization, development of search strategy, extensive editing of the manuscript. All authors approved the final manuscript.

Funding statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests statement: None declared

BMJ Open

A Scoping Review Protocol on the Aetiopathogenesis, Clinico-epidemiological, and Diagnostic Aspects of Human Ocular Trematode Infections

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092600.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2024
Complete List of Authors:	Kodithuwakku, Piyumi; Rajarata University of Sri Lanka Faculty of Medicine and Allied Sciences, Department of Parasitology Weerakoon, Harshi; Rajarata University of Sri Lanka Faculty of Medicine and Allied Sciences, Department of Biochemistry Silva, Anjana; Rajarata University of Sri Lanka Faculty of Medicine and Allied Sciences, Department of Parasitology Wickramasinghe, Susiji; University of Peradeniya, Department of Parasitology Weerakoon, Kosala; Rajarata University of Sri Lanka Faculty of Medicine and Allied Sciences, Parasitology
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Diagnostics, Epidemiology, Public health, Ophthalmology
Keywords:	Corneal and external diseases < OPHTHALMOLOGY, Diagnostic microbiology < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Molecular diagnostics < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES

A Scoping Review Protocol on the Aetiopathogenesis, Clinico-epidemiological, and Diagnostic Aspects of Human Ocular Trematode Infections

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Abstract

Introduction- Human ocular trematode infections, caused by parasitic flatworms, are a significant public health concern worldwide. It can lead to mild to severe consequences if untreated. This protocol outlines a scoping review methodology, which aims to explore the knowledge on the aetiopathogenesis, clinico-epidemiological and diagnostic aspects, and patient perspectives related to ocular trematode infections in humans.

Methods and analysis- The review, including development of the review protocol will be conducted over two years from January 2024. The Joanna Briggs Institute (JBI) Reviewers' Manual and the framework developed by Arksey and O'Malley will be used as the guidelines for the scoping review that is suggested in this protocol. Accordingly, the PCC (Population, Concept, Context) framework and three-stage search strategy will be used to develop the research question and to conduct the search respectively. Publications up to December 2024 will be searched across multiple databases, including MEDLINE/PubMed, Scopus, Science Direct, CINAHL, and Google Scholar.

Ethics and dissemination- Since the study will make use of secondary data, ethical approval will not be required. The scoping review's findings will be published in a scientific journal and presented at relevant conferences, aiming to improve the disease outcomes through guiding future research in ocular trematode infections and informing potential strategies to uplift the disease control and prevention measures and patient care.

Strengths and limitations of this study

- The standard protocol followed in this scoping review will ensure transparency and clarity of the synthesized evidence on ocular trematode infections in humans.
- Searching evidence in multiple electronic databases using an effective search strategy will guarantee thorough coverage of the available evidence in the literature.
- The quality assessment of the included studies will enhance the validity and reliability of the evidence discussed in this review.
- Only studies that are published in English will be included in this review.

Introduction

Eye infections include a broad spectrum of diseases caused by bacteria, viruses, fungi, and parasites, resulting from mild conjunctivitis to severe conditions that can lead to impaired vision or blindness [1]. Among parasitic eye infections, trematode eye infections represent a distinct and relatively rare subset. Trematodes, or flukes, are a diverse group of parasitic flatworms and their infection in the eye can lead to a spectrum of pathological consequences, ranging from mild irritation to severe vision impairment or even blindness if left untreated. These parasites can infiltrate various ocular tissues, causing inflammation, tissue damage, and structural alterations that compromise the visual function of the affected individual [2–4].

Trematodes have complex life cycles involving intermediate hosts, snails, and freshwater fish or crustaceans. For example, ocular trematodes, those of the genus *Philophthalmus*, are known to have complex life cycles requiring multiple hosts at different stages [5]. Accordingly, snails serve as the first intermediate hosts, releasing cercariae into the water. The definitive host, typically an aquatic bird, acquires the infection through direct eye contact with cercariae or metacercariae in the water or by consuming metacercariae [6], and the definitive host can have corneal lesions with edema and ulcers, conjunctival hyperemia, keratitis, eye discharges, and corneal abscess. Additionally, systemic signs such as dehydration and emaciation can also be seen [7,8].

Trematode cercariae can penetrate the skin or mucous membranes of mammals [9]. Though uncommon, humans can become an accidental host, and the role of humans as accidental hosts is highlighted in several studies from across the tropics [3,10–13]. The exact path of pathogen entry into the human ocular tissue still remains unknown. Cercariae or metacercariae can enter the eye directly while bathing or swimming in freshwater [14–16] or by consumption of raw or undercooked freshwater fish or crustaceans that serve as intermediate hosts for certain trematode species [12,14]. Ocular trematode infections were identified among those who have engaged in freshwater-related activities. For example, several South Indian studies highlighted the possible role of trematodes in ocular granulomas in children who used to bathe in lakes or rivers [3,10,11]. A year-long study conducted in Tamil Nadu, India, has found allergic conjunctival granulomas in 34 children from a single village who used the same freshwater pond for bathing. The clinical presentation was thus linked to potential trematode infections acquired through freshwater [10].

Another similar study revealed evidence of trematode infection in patients who presented with clinical features of allergic conjunctival granuloma and with a history of water-related activities, especially swimming in freshwater reservoirs [11].

Molecular studies conducted to identify the trematode species causing ocular infection in children and their potential vectors further indicate the high possibility of getting the infection through freshwater sources. One such study analyzed the DNA isolated from surgically removed granulomas of children and from the trematode cercariae released by the snail *Melanoides tuberculata* found in the freshwater reservoir of those children used to bathe. Real-time and conventional PCR analysis followed by bidirectional sequencing and BLAST analysis identified maximum sequence similarity between the granuloma samples and the trematode cercariae *Procerovum varium* aiding the identification of the possible trematode species and vectors for ocular trematode infection in human [3]. Moreover, digenic trematode DNA was detected in 6 out of 14 excised nodules of waterborne ophthalmic granulomas of the anterior chamber in a series of Egyptian patients [17]. Ingestion of infected intermediate hosts of certain trematode species (E.g. *Procerovum* spp)can introduce the infective larvae into the human digestive tract. These larvae can then penetrate the intestinal wall, enter the bloodstream, and migrate to various organs, including the eyes, where they can cause localized pathology [12]. However, the available information is not adequate to exclude oral inoculation in humans as not a part of the normal life cycle of those trematodes.

The clinical symptoms and signs vary, depending on the type of the infected parasite, the stage of the infection, and the ocular tissues involved. Further, the host immune responses which include local defense mechanisms play a pivotal role in determining the severity of the infection [18,19]. However, several typical features may aid in clinical suspicion and diagnosis such as eye redness, pain or discomfort, excessive tearing or watery eyes, itching or irritation, eye discharge, swollen eyelids, change in the appearance of the eye, photophobia, foreign body sensation and blurred or decreased vision [3,11]. Granuloma formation or systemic symptoms due to the infection are some occasional clinical consequences [3,20]. In the absence of timely intervention, the disease can cause serious consequences including blindness [2]. Thus, delayed diagnosis can affect the quality of life of the patient, and the overall disease burden. Further understanding the patient's perspectives of the disease is pivotal to knowing its impacts and prevention and control of these infections.

The insidious nature of these infections underscores the importance of timely detection and intervention to mitigate the risk of irreversible ocular damage. A recent study identified different trematode species causing ocular infections in Sri Lankan children denoting the need of a collective approach among clinicians and parasitologists, for improved community awareness for effective diagnosis, control, and prevention of the disease [16]. Thus, understanding the epidemiology, clinical presentation, risk factors, and patient's perception of ocular trematode infections is crucial in identifying effective disease control and prevention strategies. Summarizing the current body of evidence not only provides insights into the aetiopathogenesis, clinico-epidemiological, and diagnostic aspects, and patient perspectives related to ocular trematode infections in humans but also helps identify the areas that require further investigation. Moreover, a comprehensive synthesis of the literature enables researchers and healthcare practitioners to gain scientific information to design targeted studies and develop evidence-based guidelines for the diagnosis, management, and prevention of this challenging condition.

Methodology

The proposed protocol is for a scoping review of the literature on human ocular trematode infections. The proposed scoping review will be guided by the methodological framework provided by Arksey and O'Malley and the Joanna Briggs Institute Reviewers' Manual (JBI) [21] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [22]. The review method will follow the suggested structure and consist of five stages: (1) identification of the research question, (2) identification of relevant studies, (3) selection of studies, (4) charting the data (5) collating and summarizing the results.

The review will be conducted over a planned period from January 2024 to December 2025. This timeline includes the initial development of the protocol, database searches, study selection, data extraction, synthesis of results, and manuscript preparation. Database search will be initiated upon acceptance of the review protocol.

Stage 1: Identifying the review question

The research question has been developed using the PCC (Population, Concept, Context) framework, as per the JBI manual for evidence Synthesis [21]. The PCC framework followed in the review is given in Table 1.

Table 1. PCC framework used in developing the review question

Criteria	Determinants
P—population	Patients with ocular trematode infections
C—context	Prevalence Epidemiological characteristics Etiological agents Clinical characteristics Risk factors Immunological responses Histopathological and molecular diagnostics Patient perspectives
C—concept	Global

The main research question is 'What are the aetiopathogenic, clinico-epidemiological, and diagnostic aspects, and patient perspectives related to ocular trematode infections in humans?'

The study's objectives were developed in response to addressing specific research questions. The specific research questions of the scoping review are;

a) What are the global and regional prevalences of ocular trematode infections in humans?
b) What are the epidemiological characteristics of ocular trematode infections in humans?
c) What are the aetiological agents of ocular trematode infections in humans and their natural animal hosts?
d) What are the risk factors for ocular trematode infections in humans?
e) What are the clinical presentations of ocular trematode infections in humans?
f) What is the immune response to ocular trematode infections in humans?

g) What are the histopathological and molecular diagnostic methods of ocular trematode infections in humans?
h) What are the different treatments used for ocular trematode infections and their outcomes?
i) What are the patient perspectives on ocular trematode infections?

Stage 2: Identification of relevant studies

The JBI three-stage search strategy will be used in this review [21]. The first step will be a limited search of PUBMED using common keywords such as ((((("ocular"[All Fields]) OR ("eye"[All Fields])) OR ("ophthalmic"[All Fields])) OR (ophthalm*)) AND ((((((("trematode"[All Fields]) OR ("fluke"[All Fields])) OR ("flat worms"[All Fields])) OR (trematod*)) OR ("flukes"[All Fields])) OR ("flat worm"[All Fields])), after which the text terms found in the article's title, abstract, and index terms will be analyzed. A second search using all identified keywords and index terms will then be undertaken across all included databases such as MEDLINE/PubMed, Scopus, Science Direct, CINAHL, and Google Scholar. The search will be conducted across these databases up to December 2024. Thirdly, a search for additional studies will be conducted through the reference list of all identified papers and articles.

Stage 3: Selection of eligible studies

The PCC framework and the following inclusion and exclusion criteria will be used to guide the selection of eligible studies. All the studies that meet the inclusion criteria and are published up to December 2024 will be considered in this review. A table will be created with the outcomes of both manual and electronic database searches. The selected articles from each database will be uploaded into Mendeley reference management software. After deduplicating, two reviewers will independently review each title and abstract, considering the inclusion and exclusion criteria. The articles that do not meet the inclusion criteria will be removed. Any difference of opinion will be discussed between the two reviewers to reach a consensus.

Inclusion criteria

All original research articles, case series, and case reports reporting experimental or observational studies with quantitative or qualitative data on clinical-epidemiological aspects, aetiopathogenesis,

immunological response, risk factors, molecular and histopathological characteristics, diagnosis, treatment, and patient perspectives related to ocular trematode infections in human.

Exclusion criteria

Studies that are not available in the full-text article, review articles, studies not published in the English language and non-human studies will be excluded.

Quality assessment of the included studies

Critical appraisal tools developed by the Joanna Briggs Institute (JBI) [21] will be used to assess the quality of the included studies. Quality assessment will be used to assess the validity, reliability, and any biases of the reported evidence to enhance the transparency of this review.

Stage 4: Charting the data

Articles that are selected through the above step will be used to chart the data. Information will be extracted to a table that was developed using the template data extraction instrument for scoping reviews in the Joanna Briggs Institute guidance for conducting a scoping review [21]. To reduce bias and inaccuracies, this process will be carried out independently by two reviewers in duplicate. Disagreements among the reviewers will be resolved by discussion.

The data extraction form will include the following details,

(i) Title
(ii) Author
(iii) Publication year
(iv) The country where the research was conducted
(v) Study setting/population
(vi) Study design
(vii) Sample size
(viii) Aims and objectives
(ix) Criteria of participant selection
(x) Key findings
    a) Prevalence

b) Epidemiological characteristics
c) Etiological agents and their natural hosts
d) Clinical characteristics
e) Risk factors
f) Histopathological characteristics
g) Molecular characteristics
h) Immune responses
i) Diagnosis
j) Treatment and outcome
k) Patient perspectives

(xi) Conclusion/s

Stage 5: Collating, summarising, and reporting the results

The extracted data will be analyzed and presented focusing on the aim of the review as well as the specific research questions. This will be reviewed by two independent researchers to ensure consistency and reliability. In alignment with the objective of this study, a descriptive summary will be created to provide an overview of the study characteristics and key findings. Following the PRISMA-ScR criteria, the scoping review results will be presented narratively, establishing a thorough and well-organized summary of the literature on aetiopathogenic, clinico-epidemiological, and diagnostic aspects, and patient perspectives related to human ocular trematode infections. Visual tools such as summary tables, graphs, and conceptual frameworks will be used to present the key results. The findings are expected to be presented in a full scoping review article.

Patient and Public Involvement

None.

Ethics and dissemination

Ethical approval is not required as the scoping review technique intends to synthesize information from publicly available articles. A report summarizing the scoping review's findings will be published as a full scoping review article in a scientific journal and will be presented at relevant conferences as part of dissemination strategies. We expect the scoping review's findings to contribute to the advancement of understanding of ocular trematode infections, ultimately

improving patient outcomes and guiding future research endeavors in this field. Also, the review's findings could have significant policy implications and inform public health strategies related to the prevention and management of ocular trematode infections.

References

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Authors' contributions; PK contributed in development of search strategy, and drafting of the protocol. HW contributed in development of search strategy, drafting and editing of the protocol, AS and SW involved in editing the manuscript. KW contributed in conceptualization, development of search strategy, extensive editing of the manuscript. All authors approved the final manuscript. KW is the guarantor.

Funding statement; This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests statement; None declared.