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Research article

The use of medicinal plants in common ophthalmic disorders: A systematic review with meta-analysis

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ABSTRACT

Purpose: This study aimed to assess and compile the available research articles about medicinal plants used for ocular diseases.
Principal results: A total of 2949 articles were retrieved, 35 full-text articles were assessed for eligibility, and seven studies (4 observational and three experimental) with low to moderate quality were eligible and involved in the systematic review, with a total of 600 plants from 4 countries. Among the 600 plants, only 24 (4%) were used to assess the status. Both the fixed and random models of the studies showed that the included studies tended to predict the results for the observational studies (OR = 0.062, CI = 0.043–0.090 OR = 0.039, CI = 0.012–0.122) for different plants used for ocular diseases. High heterogeneity (estimated as $I^2 = 87.078$, $Tau^2 = 1.161$ and Q-value = 23.217 with a *p*-value of 0.000), while for experimental studies ($I^2 = 94.928$, $Tau^2 = 23.211$ and Q-value = 39.434 with a *p*-value of 0.000) and publication bias were reported.
Conclusion: Few articles representing approximately 600 plants of low to moderate quality reported using medicinal plants for ocular diseases. The meta-analysis confirmed the systematic review findings regarding the plants' traditional use with high heterogeneity and publication bias. A considerable gap was proven in the use of medicinal plants in ocular diseases requiring intensive research.

Impact statement

Recently, increasing interest has been observed focused on discovering and evaluating therapeutic potential and identifying the main bioactive compounds and possible synergisms of medicinal plants [1].

Several plants have been found to have activity against a number of ophthalmological problems [1].

Certain bioactive constituents of plant sources, including curcumin, lutein, zeaxanthin, saffron, catechin, Ginkgo biloba extract and quercetin, were reported to have substantial therapeutic effects on common ocular diseases [2]. These bioactive components are

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reported to possess a wide range of other biological activities such as antioxidant, anti-inflammatory and antimicrobial activities [3,4]. They can be used in drug formulation against several diseases, such as diabetes, cancer, and hypertension, which have significant ocular complications [4,5].

1. Introduction

1.1. Systematic reviews and meta-analysis as a recent, powerful research tool A-Systematic reviews: a qualitative part

The systematic review is a rigorous process of searching, selecting, appraising, interpreting, and summarizing results from original published studies on a specific topic. These original studies may be observational studies or randomized trials. The study summaries may be qualitative or quantitative. A systematic review involving a quantitative summary of results is called a meta-analysis [6].

Before initiating a systematic review, a protocol incorporating specific plans with sufficient clarity should be developed for each systematic review step to ensure the quality of the systematic review process and provide rigor and guidance [7].

Systematic reviews are conducted to answer specific, often narrow, clinical questions in depth. These questions can be formulated using four main components, collectively named PICO [8]. The main goals of systematic reviews are to combine results in a way that reduces the probability of chance observations that affect clinical practice, to detect defects in the literature that could not be seen by only examining individual studies [6] and to help identify other areas of research [8]. Evaluating the methodological quality of studies is an essential step in examining variation in the quality of included studies involved in systematic reviews [9]. Assessment of methodological quality involves evaluation of internal and external validity (generalizability, applicability) [11–13], as well as study design and conflict of interest in the conduct of the study [14].

The risk of bias is a systematic error or deviation from the truth. In results or inferences, five types of bias must be assessed in systematic review studies according to Cochrane collaboration groups: selection [12], performance [15], detection [14], attrition [12] and reporting bias [15,16]. Additionally, confounding bias: A confounder is an extraneous variable whose presence affects the variables being studied. The results do not reflect the actual relationship between the variables under study. Randomization, restriction, and matching can eliminate this bias within the study design. Statistical methods such as multivariate models can be used after data gathering to control for confounders [17].

1.1.1. Meta-analysis 'the analysis of analyses': A quantitative part

Meta-analysis is a statistical technique used to combine and synthesize the data from several studies into a single quantitative estimate or summary effect size to reduce bias and examine the heterogeneity of individual study results [18]. Meta-analyses play a central role in developing the impact of the results after adjustment of one or more characteristics of the studies [8]. The strength of inference is more significant if the results are unchanged under varying conditions [6]. The quality of the meta-analysis results was checked and validated using sensitivity analysis. A sensitivity analysis is used to determine whether the impact of the meta-analysis changes when different decisions related to the systematic review/meta-analysis process are made. For example, a sensitivity analysis could determine if a fixed-versus random-effects analysis reaches different conclusions [19].

1.2. Medicinal plants and ophthalmic disorders or traditional eye medicines A- ethnobotany as a significant drug source

Martin, 1995 defined ethnobotany as "all studies concerning plants, " describing local people's interaction with the natural environment [20]. As a discipline of ethnobotany, traditional herbal medicine refers to the therapeutic value of herbal medicine beyond the active ingredients of the medication. Traditional herbal medicine is the oldest known type of medical treatment and has been practiced in virtually every culture worldwide [21]. Based on ethnomedicinal and random plant collection approaches for the search for new pharmacologically bioactive agents. Folkloric information from many different cultures is essential for revealing plants with useful medicinal properties [22]. Although plants possess immense traditional applications, a few species have been screened for their biological activity; moreover, there is a lack of such information regarding ocular disorders.

1.2.1. Cross-sectional survey as a common ethnobotanical study design

Unlike a longitudinal study, a cross-sectional study is a quantitative survey that is possible at a given time. Where a four-step approach was applied, random sampling was used for more rigorous statistical analysis and to allow the generalization of conclusions about larger populations. Snowball of randomly selected informant sampling [23]. From this historical perspective, the eldest persons in the study area who might know something about the history contact all persons who have essential functions related to gardening in the study area for socioeconomic conditions in the study area [24]. During a cross-sectional observational ethnobotanical survey, informant observation is one of the best ways to study the transmission of knowledge. At the same time, quantitative data on the abundance of plant uses are critical for comparative purposes. Informal and formal techniques were used to collect qualitative and quantitative data in ethnobotany. For re-synthesis of DATA for meta-analysis purposes, quantitative ethnobotanical DATAis required where specific types of indices such as Relative frequency citation (RFC), Informant Consensus Factor (ICF), Medicinal Use Value (MUV), Use reports (UR), and others must be used [25,26]. [26–28].

1.2.2. Common ocular disorders

Commonly, several eye troubles can be categorized as follows: (i) Eye infections due to pathogenic microorganisms invading any part of the eyeball or proximate area. The infection leads to pain, redness, discharge, watering, and light sensitivity; (ii) eye disorders, including cataracts, dry eyes, and eye allergies; and (iii) vision damage, such as glaucoma and diplopia [29].

Glaucoma is a neurodegenerative condition that damages the main nerve to the eye (optic nerve) located in the back of the eye and is responsible for transmitting electrical impulses to the brain. Impairment usually occurs as a result of an elevated pressure of the aqueous humor fluid within the eye, leading to gradual visual changes and blindness. Several known risk factors for glaucoma have been reported, such as increased intraocular pressure (IOP), aging, family history, high myopia, systemic hypertension, cardiovascular disease, migraine headaches, peripheral vasospasm, and prior nerve damage [30]. In addition, other factors leading to glaucoma include glutamate-induced neurotoxicity, nitric oxide-based damage, disruption of neurotrophic factor transport, and immune-induced neuro destruction.

1.2.2.1. Cataract. Cataracts are the opacities of the crystalline lens that interfere with normal vision and are considered one of the leading causes of visual defects worldwide, especially in elderly individuals. Cataracts, as a multifactorial disease process, are caused by various toxic factors, environmental stressors, and gene mutations. Cataracts are associated with damage or death of lens epithelial cells (LECs). Cataracts are the leading cause of blindness worldwide, covering approximately 42% of all visual defects.

1.2.2.2. Conjunctivitis. Conjunctiva is a thin translucent membrane that covers the anterior part of the sclera and the interior of the eyelids, and conjunctivitis is a disease that occurs due toirritation of the mucous membranes on the inner surface of the eyelid. Conjunctivitis is the most common cause of red eye in primary care [31]. Conjunctivitis can be caused by viruses, bacteria, fungi, exposure to chemicals or irritants, or the long-term presence of a foreign body, such as hard or rigid contact lenses [32].

1.2.2.3. Dry eye disease. It is one of the conditions most commonly seen by eye care practitioners, which directly reflects the proportion of patients who suffer from dry eye symptoms [33]. Dry eye disease is a multifactorial disorder of the tears and the ocular surface that is accompanied by various ocular symptoms and signs that include discomfort, visual disturbance, tear film instability, hyperosmolarity, and inflammation of the inflammation of the ocular surface with potential impairment of the ocular surface [34].

1.2.2.4. Diabetic retinopathy (DR) and antioxidants. Diabetic retinopathy (DR) is a major complication of diabetes mellitus (DM), a leading cause of blindness in working-age populations. The diagnosis of DR is made by clinical manifestations of vascular abnormalities in the retina. Clinically, DR is divided into two stages: nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [35].

Antioxidants are compounds that retard or prevent oxidation and prolong the life of oxidizable matter. Free radicals are essential for any biochemical process and are essential to aerobic life and metabolism. The majority of diseases are mainly linked to oxidative stress due to free radicals [Velavan et al., 2007]. These species may be either oxygen-derived (ROS) or nitrogen-derived (RNS). The most common reactive oxygen species include superoxide anion (O_2), hydrogen peroxide (H_2O_2), peroxyl radicals (ROO), and reactive hydroxyl radicals (OH). Nitrogen-derived free radicals are nitric oxide (NO), peroxynitrite anion (ONOO), nitrogen dioxide (NO2), and dinitrogen trioxide (N_2O_3). Evidence suggests that oxidative stress is an essential pathogenetic factor in the development of diabetic retinopathy (DR). Experimental data showed that the use of strategies to ameliorate oxidative stress can prevent and retard the development of DR in an animal model. Clinical observations also suggest that reducing oxidative stress may help to reverse the pathological manifestations of DR [36–40].

Many studies postulated that antioxidants have preventive effects on diabetic retinopathy, and much fruit intake is associated with a low incidence of diabetic retinopathy. Diabetic adults taking fruits and vegetables enriched with flavonoids had lower degrees of inflammation [41,42], better glycemic control, and reduced diabetic retinopathy [43–48].

Eye cancer: The eye and adnexa are potential foci of neoplastic disease, either as primary sites or as sites of metastatic carcinoma. Eye cancer is rare compared to other types of cancer, and it is the only ocular disease that directly threatens life. The most common types include intraocular melanoma for adults and retinoblastoma for children, while other types are squamous cell CA and basal cell CA. The survival rate of eye cancer is almost high (80%) among people receiving early treatment, highlighting the importance of routine and early detection of such cases [49–52].

1.2.3. Traditional eye medicines for common diseases

Natural compounds constitute antioxidant or secondary anti-inflammatory metabolite anti cataract agents. The role of plant polyphenols in anticataractogenic activities has also been studied comprehensively, in vitro or in vivo [53]. A total of 41 plants were investigated for anti-cataract activity [54]. Sixty-six plants have been reported to treat conjunctivitis in folkloric medicine [55]. P.S. Sandhu and his coworkers (2011) screened 262 m plants for various ocular diseases, including different types of conjunctivitis, and revealed that 51 were found to treat conjunctivitis [56]. A Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial examining glass containing extracts of antioxidant medicinal plants against ocular surface disease using ocular surface disease index (OSDI) score found them effective in improving in DED both subjectively and objectively [57]. Medicinal plants and their bioactive compounds are used to control and normalize pathological cellular factors involved in the progression ofthe progression of diabetic retinopathy (DR) [58]. Various phytoconstituents with retinal cytoprotective effects were investigated for their beneficial experimental and clinical evidence and highlighted their use in DR management [59]. Few plants have been documented to treat eye cancer [60]. Furthermore, according to researchers at the School of Medicine of the Washington University, a natural plant compound showed a new era in treating eye cancer, such as uveal melanoma [61].

1.2.4. The theory of oxidative stress, antioxidants, and common ophthalmic disorders

In several ocular disorders, there is a high concentration of hydrogen peroxide and markers of oxidative damage to DNA, lipids, proteins observed [62], while the use of antioxidants in the treatment and prevention of such cases emphasizes the involvement of oxidative stress (OS)due to an imbalance in the redox status of prooxidant/antioxidant reactions in cells with advantage of prooxidant reactions [63]. ROS/RNS is effectively affect the eyes because their exposure to many surrounding factors can change the redox status of a tissue cell towards oxidizing conditions [64]. Chronic inflammation and tissue dysfunction occur in the eyes due to the stimulation of signal transduction pathways and activation of transcription factors [65]. OS is involved in the etiology of malignant eye diseases (lymphoma, melanoma; retinoblastoma) and nonmalignant ocular diseases (corneal and conjunctive diseases; dry eye syndrome; autoimmune and inflammatory uveitis; cataract; glaucoma; age-related macular degeneration; retinitis pigmentosa; diabetic retinopathy) [65]. Studies discuss the potential role of antioxidants in the prevention of ocular diseases and protection against ROS/RNS damage through the mediation of OS [66]. OS likely causes age-related macular degeneration (ARMD) and formation cataract because lutein is naturally found in them, the potentially protective effects of its antioxidative and photochemical properties. Trials confirm that lutein plays a prophylactic role against age-related degenerative progression and is essential for preventing ocular disease [67]. Plant-derived antioxidants are a large group of chemical compounds that include the secondary metabolites of plants (e.g., polyphenols, carotenoids, tocopherols, and coumarins) and the substances formed in food during processing [68]. ROS can cause point mutations in DNA, render enzymes nonfunctional, or react and nonspecifically modify many of the organic molecules present in a cell [69]. Plants may produce ROS as a defense mechanism against biotic stress, for example, to increase disease resistance. The accumulation of ROSpromotes uncontrolled chemical reactions if it is in the vicinity of other molecules [70,71]. ROS detoxification is mainly accomplished in two complementary ways: cells utilize enzymes such as catalases or peroxidases that react with ROS and convert them into non-aggressive forms such as molecular oxygen (O_2) or water (H_2O) and/or a range of metabolites with antioxidant capabilities are synthesized that detoxify ROS either as enzymatic cofactors or through direct interaction withROS [72]. ROS, originally considered to induce negative and injurious cellular effects, also have important positive actions such as induction of host defense genes, activation of kinases/phosphatases, regulation of transcription factors and mobilization of ion transporters. Molecular processes by which ROS influence cell function involve the activation of redox-sensitive signaling pathways [73].

1.2.4.1. The rationale for the study. Recently, there has been an outbreak of the use of different medicinal plants to treat various ophthalmic disorders; these traditional uses may potentially affect the future of ocular disorder management and the development of new, efficient, and safe drugs. Studies that addressed these problems were scattered everywhere, which weakened its benefits. Thus, combining these documents in a single manner is highly required, which can be performed using modern research techniques, such as systematic reviews with meta-analyses. The study aimed to answer the research question asked: 'What are the medicinal plants used for different common ophthalmic disorders?'by screening, retrieving, critically appraising, resynthesizing, estimating the effect size of the selected studies, and trying to combine them in one document using meta-analysis as a modern statistical tool. This will rise-up the research points in the study area.

2. Methodology

2.1. Asking a valid answerable research question

Although this review is part of a project that provides a solid background, it was intended to answer the question: 'What is the effect (s) of medicinal plants on different common ophthalmicdisorders?' or, in other words, 'What are the medicinal plants used for different common ophthalmicdisorders?'

2.2. PICOS setup, filter design, optimization, and database selection

2.2.1. Population(P)

All published data (original research articles) on medicinal plants used to treat ophthalmic disorders from January 2011 to September 2021. The study groups consisted of data in PubMed (The United States National Library of Medicine (NLM) at the National Institutes of Health), Science Direct (Elsevier's leading information solution for researchers), and the American Academy of Ophthalmology from January 2011 to May 2021. Studies included at all experimental levels (in vitro, in vivo, in situ, in silico, etc.) and all study levels (observational, case-control, clinical trial, etc.).

2.2.1.1. Inclusion criteria. All original research articles on medicinal plants used to treat different ocular disorders (January 2011 to May 2021) are in English.

2.2.1.2. Exclusion criteria. All published data outside the time frame of the study period, data published in other languages, and data challenging to be re-synthetized.

2.2.2. Intervention(I)

Use of different medicinal plants to treat patients with common ophthalmic disorders.

2.2.3. Comparison(C)

The standard drugs or agents used for common ophthalmic disorders in clinical practice.

2.2.4. Outcomes(O)

The plants' biological, therapeutic, and toxic effects on common ophthalmic disorders were determined using a hazard ratio (HR) as an outcome measure.

2.2.5. Study design(S)

All types of studies, including experimental animal studies, observational studies, case-control studies, and clinical trials, will be assessed.

2.2.6. Filter design and optimization process

Many filter design trials were performed with various outcomes; the optimum filters were selected for each database, including PubMed, Science Direct, and the American Academy of Ophthalmology.

2.2.7. Database selection and design of the search plan

PubMed was selected as the most famous database with much medical information. Then a particular filter was used by joining the predetermined PICOS using the built-in filter design feature to retrieve the articles that were able to answer our question. After many trials to find the appropriate keywords for optimal search outcomes, these keyword terms were also combined using AND and OR to retrieve any relevant studies that had used the search method and narrowed the research field. The second database selected for our study was Science Direct as the largest trusted; a special filter was designed to fit its criteria with the hope of retrieving the relevant studies that can answer our question. The third database was the American Academy of Ophthalmology (AAO.org). To design and optimize the filter, we tried different methods, such as using the four advanced features (all words, none of these, exact phrase, and custom date range), using our search terms. Then, we tried a direct search within the Journal of AAO (Ophthalmology) with Herb (112), Plants (502) or Remedy (125). Finally, we decided to use our specific phrase (Medicinal plants = 212), and 2021 was unavailable. Three different persons searched at the same time, and then their results were compared. Duplicates were removed and merged and are presented in one Prisma chart.

2.2.8. Data retrieval process using online sources

Unlike conventional studies, this investigation used online sources for data retrieval by using the selected optimal filter for each database. The search results were displayed in the form of an abstract, printed, and carefully reviewed, and the relevancy was checked.

2.2.9. Data screening process and manipulation in the Prisma flow diagram

The titles and abstracts of the articles initially identified were screened to determine their suitability for inclusion. Studies categorized into relevant (R) and non-relevant (NR) articles were automatically excluded based on the inclusion and exclusion criteria. Articles written in another language rather than English were excluded based on language restrictions for this study. Relevant studies were based on their titles or abstracts, and their full articles were retrieved using SDL facilities or by self-communications abroad. The standard Prisma flow chart diagram (The PRISMA Group) was used to conduct the main systematic review steps.

2.2.10. Data extraction and critical appraisal of the included studies

The full text of the relevant articles was reddened, and each study's characteristics were extracted from all types of studies. Data were extracted from relevant full-text articles, including the name of the first author, publication year, country, population, type of the plant, number of plants, interventions or exposures, comparison, ethnobotanical indices, and methods of estimation, outcomes, and study design. The included studies' methodological quality and risk of bias were assessed according to the Cochrane collaboration criteria [16].

2.2.11. Calculation of effect size (ES) as endpoint for SR and starting point for MA

A number of plants were used for eye purposes in correlation to the total numbers of plants studied; the pre-estimated indices were also extracted from the included articles to calculate the effect size (ES). The odds ratio (OR) was obtained as an outcome measure, and only one OR was obtained from one study. Then, Comprehensive Meta-analysis version 2 was used to join the ES of other articles in the quantitative analytical part of the study (Meta-analysis).

ES is calculated as the standardized mean difference (d) for the observational experimental studies. The standardized mean difference between two groups (mainly control and experiment), calculated by subtracting the mean of one group (Experiment) from the other (control), and dividing the result by the standard deviation (SD) of the control group, should be taken. The formula is as follows:

$$(\mathrm{ES}) = \left(\frac{\mathrm{Mean\ (E)} - \mathrm{Mean\ (C)}}{\mathrm{SD}}\right) \tag{1}$$

2.2.12. Data presentation

All data are presented as descriptive statistics using various figures, including forest plots.

2.2.13. Statistical analysis

The findings extracted from all articles were compiled into tables and analyzed using Comprehensive Meta-analysis version 2 (CMA) as statistical software. Forest plots were obtained to display the pooled effect. Its confidence interval after combining all studies, relative weight and residual were extracted from the forest plot. Clinical and methodological heterogeneity were checked qualitatively using the included studies' study and methodology characteristics. During the meta-analysis, the homogeneity and heterogeneity among studies were checked using the CMA program and standard meta-analysis models (fixed-effect, random-effect, and both) to combine the studies. The following parameters were used: Q-value, I squared (I^2) or Higgins I^2, Tau squared (Tau^2), and *p*-value (of 0.10, rather than the conventional level of 0.05) was used to determine statistical significance. Subgroup analysis was performed based on study designs and epigenetic modifications to identify the causes of heterogeneity among the studies. The publication bias among the studies was checked using the CMA program using a funnel plot to ensure any bias among the studies enrolled in this study. All the data were presented as descriptive statistics using various figures, including forest plots and funnel plots and tables. Sensitivity analysis was performed using the CMA program by changing study designs, statistical models, and one study removal analysis method. **The null hypothesis:** H_0: Are the effect sizes equal in all of the studies, Or (Are the effect measures homogeneous) was tested by assuming that all studies in the meta-analysis share a common (true) effect size. The results will be discussed based on whether there was a significant association between the different study populations that allowed their possibility to be added to the overall population.

3. Results

3.1. Qualitative synthesis (systematic review) results

3.1. 1. Search strategy outcomes

Different filters designed based on PICOS returned the following results:

3.1.1.1. Optimum filter for PubMed. **((**((((((((((((((Plant [Title/Abstract]) OR (Herb [Title/Abstract]) AND (Glaucoma [Title/Abstract]) OR (Cataract [Title/Abstract]) OR (Conjunctivitis [Title/Abstract]) OR (Dry Eye [Title/Abstract]) OR (Retinopathy [Title/Abstract]) OR (Eye tumor [Title/Abstract]) AND (Eye [Title/Abstract]) OR (Ocular [Title/Abstract]) OR (Ophthalmic [Title/Abstract]) AND (Effect [Title/Abstract]) AND (Biological [Title/Abstract]) OR (Therapeutic [Title/Abstract]) AND ("last 10 years" [Title/Abstract])))))))))))))): **904** results.

3.1.1.2. Optimum filter for science direct. (Medicinal Plant OR Herbal Remedy) and (Eye OR Ophthalmic OR Ocular) and (Disorders OR Diseases) and (Effect assessment) and (Last 10 Years): **1833** results.

3.1.1.3. Optimum filter for American Academy of Ophthalmology (Ophthalmology Journal). Medicinal plants: **212** results.

3.1.2. Qualitative results are presented as a Prisma flowchart

3.1.2.1. Interpretation of Prisma flow chart results

3.1.2.1.1. Identification. The records identified from the search were (n = 2949) as follows:

PubMed = **904** articles.

These retrieved articles were carefully screened through their titles and abstracts, and only nine were found to be relevant. Their full texts were retrieved and classified as follows: 7 were reviews, 1 was a book chapter, and 1 was in the French language. Thus, all were excluded from the resynthesis of the next step. Science direct = **1833** articles.

These retrieved articles were carefully screened through their titles and abstracts. Only 35 were found to be relevant. Their full texts were retrieved and classified as follows: 28 were reviewed and thus excluded, and the remaining seven articles were eligible for resynthesis in the next step.

American Academy of Ophthalmology (AAO) = **212** articles.

These articles were retrieved through the previous search strategies. Then only original articles that fell within the predetermined time range were screened, where two duplicate articles were excluded, and 19 papers were used in the next step. These findings are presented in Fig. 1.

3.1.3.2. Sreening. As mentioned in the methods, the screening step was followed to determine their appropriateness for inclusion. Studies are categorized into Relevant (R) and non-Relevant (NR). After applying inclusion and exclusion criteria, the NR records were equal (2146) and excluded automatically.

3.1.3.3. Eligibility. Full articles were obtained and read to ensure their relevance. Full-text articles assessed for eligibility were equal to 35 articles. Full-text articles were excluded because they were not relevant to the topic or were not the primary source (review articles or book chapter). Moreover, the non-relevancy is due to one of the following reasons: surgical manoeuvres, medical investigations, other cancer types, synthetic drugs, radiation therapy, therapeutic regimen plans and protocols, epidemiological studies, and outcome evaluation or herbal treatment for other diseases.

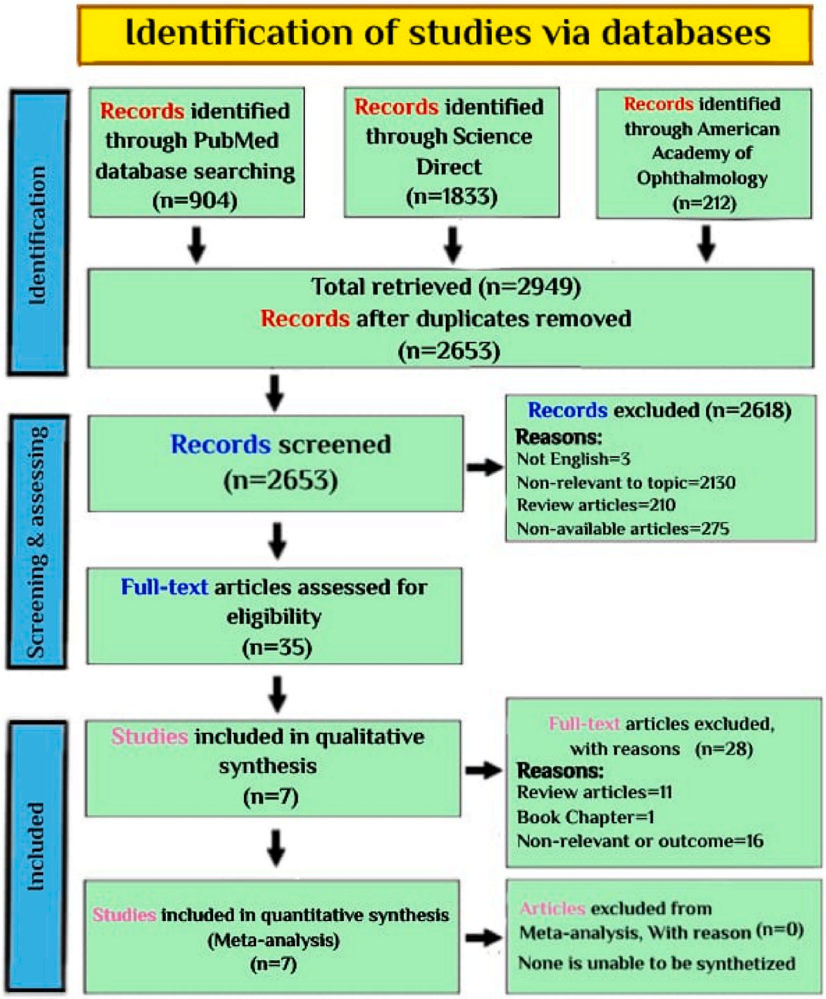

Fig. 1. Prisma Flow chart results of inclusion/exclusion of the individual studies.

3.1.4. Included studies, characteristics extracted, and critical appraisal

There were 7 articles included in the systematic review of qualitative synthesis. Data extracted from the full text of all articles included in the systematic review are shown in Tables 1–4.

3.2. Critical appraisal of the included studies

The methodological quality and the risk of bias were assessed. The assessment included adequacy and clearness of representativeness of the selected participants to the target population, measurement of exposure or intervention, measurement of results, and control of confounding, while the incomplete outcome data and follow-up were not applicable for this type of study and only suite for cohort ones, as seen in Tables 1–4 for analytical observational cross-sectional and experimental studies.

3.2.1. Detailed interpretation of Prisma flow chart results of quantitative synthesis

Studies included in the qualitative synthesis review were equal to 4 articles reporting odds ratios (ORs) in outcome measures. These articles were used in the final analysis (meta-analysis); see Table 1.

3.2.1.1. Article No. 1: [25]. They documented ethnobotanical knowledge of a neglected, restricted Pakistani area to expose them for experimental testing and scientific validation. Conducting informal conversation followed by semistructured interviews and using relative frequency citation (RFC) and medicinaluse value (MUV) to categorize the medicinal uses of these plants.

Table 1
Data extraction from full-text articles from analytical cross-sectional (Survey) studies (n = 4).

Types of Study (name of the first author and date of publication)	Country	Populations	Plant type	Number	Interventions or Exposures	Comparison	Ethnobotanical Indexes & Methods	Outcomes	Study designs
K. Rehman et al., (2015) [25]	Pakistan	Informants	Mixed	66	Eye use	tested experimentally for validation	Relative frequency citation (RFC) Medicinal Use Value (MUV) Informal conversation + semi-structured interviews	exploring the rarely or never reported plants	Documentation of Ethnobotanical Knowledge
B. Novotna et al., (2020) [26]	Angola	professional herbalists	Indigenous and Exotic	87	Eye Use	Sub-Saharan Africa	use reports (UR)	New ethnomedicinal uses absence of pharmacological studies the same use in neighboring countries	Traditional botanical knowledge
I. Sile et al., (2020) [27]	Latvia	Records	Native and imported plants	211	Eye Use	European Union herbal monographs	Card Index Use reports (UR)	Unreported plants	Ethnobotanical knowledge
Khajuria, A.K., (2020) [28]	India	Informants	Wild	236	Eye Use	Local flora	Informant Consensus Factor (ICF) Frequency of Citation (FC) Use reports (UR)	Disease treatment category	Ethnobotanical study

Table 2
Extraction data from full-text articles, the 3 observational studies.

Serial	Study	Population	Intervention	Comparison	Outcome	Design
1	N.A. Stefanova et al. , 2011 [74]	OXYS and Wistar rats	Effect of *Cistanchedeserticola* (CD) herbs	Wisterrats	Development of cataract and retinopathyin accelerated senescent OXYS rats (severity)	Observational study
2	J. Song et al., 2013	Rats & Rabbits	SIN released as a function of time from various formulations	Gel group (0.5% SIN) vs control group (0.5% SIN)	cumulative amount of SIN released from the drug	Observational study
3	T.-Y. Hong et al., 2016	streptozotocin (STZ) diabetic rats	Protective effect ofthe ethanol extract of Zingiber zerumbet on DR	EEZZR-treated diabetic rats. vs Calcium dobesilate (CD) treated diabetic rats.	DR protective effects The retinal blood vessel permeability The expression rate of vascular endothelial growth factor (VEGF) Expression rate of renal pigment epithelium-derived factor (PEDF) in diabetic rats	Observational study

Table 3
Critically appraise for the study in the case of cross-sectional studies (n = 4).

Study Name of the first author, Year of publication	representativeness of the selected participants to the target population	Measurement of Exposure or Intervention	Measurement of Results	Control of Confusion	Incomplete results and follow-up *
K. Rehman et al., (2015) [25]	Adequate More than 100 and the elderly	Inadequate (4.5%)	Clear	Adequate	NA
B. Novotna et al., (2020) [26]	Inadequate (10 informants for 2 areas)	Adequate (14.9%)	Inadequate Other relevant indices were not applied	Inadequate	NA
I. Sile et al., (2020) [27]	Adequate	Inadequate (1.9%)/plant number Adequate (56.5%) (MUR)	Inadequate Other relevant indices were not applied	Inadequate More archive details are required.	NA
Khajuria, A.K., (2020) [28]	Adequate	Adequate for other uses, but inadequate for eye use (1.7%)	Clear	Adequate	NA

* Applicable mainly to cohort studies.

Table 4
The methodological quality of the included experimental studies (n = 3).

Serial	Study	Selection of comparison	Measurement of Intervention	Measurement of results	Control of Confusion	Incomplete outcome data
1	N.A. Stefanova et al. , 2011 [74]	Adequate	Adequate	Clear	Adequate (4 weeks-aged, isolated pups, Specific OXYS generations controlled by cataract, randomized)	None.
2	J. Song et al., 2013 [75]	Adequate	Adequate	Clear	Adequate (Specific pathogen-free-grade female Lewis rats + white New Zealandrabbits without any ocular signs)	None.
3	T.-Y. Hong et al., 2016 [76]	Adequate	Adequate	Clear	Adequate (Streptozocin-induced diabetic male wistar rat)	None.

3.2.1.2. Article No.2: [26]. They interviewed a professional Angolian herbalist with knowledge and compared their findings with Sub-Saharan Africa using Use Report (UR). There are some uses in neighboring countries, new ethnomedicinal uses, and the absence of pharmacological studies.

3.2.1.3. Article No. 3: [27]. They investigated and evaluated Latvian records containing native and imported plants and compared them to the European Union herbal monographs using Card Index and Use Report techniques. Many unreported plants were found to have significant efficacy and safety.

Table 5
Effect size calculation of outcomes from the four cross-sectional eligible studies for the quantitative part.

Parameter	RFC	MUV	**UR/c atU R/Di s**	Card Index	UR/Ta xaICF	FC	Ne	NTOR/ PP	CI95%	ES
Article 1 (Rehman, Mashwani et al., 2015)								3	66	0.017
Calendula arvensis L. Flowers (Eye sight)	0.54	0.60						4.0	0.0158 ± 0.14	
*Calamintha vulgarus*L. ritating eyes)	0.41	0.44						0.0455	0.0156 ± 0.1253	
Otostegia limbate Whole (Eyes problems)	0.73	0.95								
Article 2 (Novotnaa, Polesnya et al., 2020)								13	87	0.019
Vangueriopsis lanciflora (Hyper myopia)			2	1				4.0	0.0982 ± 0.3141	
Afzelia quanzensis (Eye Complaints)								0.1494	0.0895 ± 0.2390	
Albizia adianthifolia (Eye problems)										
Aloe zebrina (Eye diseases)										
Diodella sarmentosa & Diospyros batocana (Sore eye)										
Erythrina abyssinica (Inflammation)										
Hymenocardia acida (Eye problems)										
Pterocarpus angolensis & Rumex abyssinicus (Eye disease)										
Securidaca longepedunculata (Eye problems)										
Strychnos spinosa & Syzygium guineense (Eye disease)										
Article 3 (Sile, Romane et al., 2020)								**4**	**211**	**0.134**
Matricaria chamomilla L. (eye pain)				13	23			4.0	0.0075 ± 0.0501	
Ilipendula ulmaria (L.) Maxim (Eye problems)								0.0190	0.0074 ± 0.0477	
Rosa L. & *Salix* L. (Eye pain)										
Article 4 (Khajuria, Manhas et al., 2021)								4	236	0.460
Berberis aristata DC. (Eye problems)						21		4.0	0.00067 ± 0.0447	
Berberis lycium Royle (Eye problems)						16		0.0169	0.0066 ± 0.0428	
Geranium wallichianum D.Don ex Sw. (Eye problems)						03				
Rosa brunonii Lindley (Eye problems)						14				
Conjunctivitis &Night blindness										

RFC: Relative Frequency Citation, MUV: Medicinal Use value, UR/cat: Use report/Category, UR/Dis: Use report/Disease, Card Index, UR/Taxa: Use report/plant Taxa, ICF: Informant Consensus Factor, FC: Frequency Citation, Ne: number of plants used for eye disease, NT: Total number of plants in the article, PP/OR: Estimated Population Proportion/Odds ratio, CI 95%: Confidence Interval level with its Lower & upper limits, ES: Estimated Effect size.

3.2.1.4. Article No. 4: [28]. Khajuria and his co-workers evaluated the Indian informant's response regarding 236 wild plant uses traditionally compared to the local flora. Although the plants used for eye diseases possess the application of different quantitative ethnobotanical indices, only four plants were eye-use 73.

3.3. Articles included in the meta-analysis and preparation of different article outcomes (ES calculation)

3.3.1. Article 1 [74]

Regarding DR, the severity reduction rates were 1.39 ± 0.09to 1.68 ± 0.07 for the control group, 1.00 ± 0.07 to 1.46 ± 0.10 for the treated group and 1.71 ± 0.1 to 1.42 ± 0.10 and 1.29 ± 0.11 to 1.54 ± 0.11 for **the cataract control group (see Tables 5 and 6).**

3.3.2. Article 2 [75]

The main pharmacokinetic parameters of SIN in the aqueous humor were estimated as a parameter for the cumulative amount of SIN released from the gel formula. The ES was then calculated as a standardized mean (see Tables 5 and 6).

3.3.3. Article 3 [76]

Different protective parameters were estimated and compared, such as retinal blood vessel permeability (ng/mg), the expression rate of vascular endothelial growth factor (VEGF), and the expression rate of retinal pigment epithelium-derived factor (PEDF), and further used to estimate the ES using a standardized mean (see Tables 5 and 6).

Table 6
Effect size calculated from the raw data presented in Table 4 for experimental studies (n = 3).

Parameter	Experimental (E)	Control (C)	Difference	Effect size (E-C)
Article 1 [74]:rowhead				
Cataract severity	0.25	0.29	0.04	
Retinopathy severity	0.46	0.29	0.17	
Mean	0.355	0.29	0.105	
SD	0.105	0.00	0.065	**1.62**
Article 2: [75]rowhead				
Pharmacokinetic parameters of SIN in aqueous humor				
AUC (μg ml–1h)	36.27 ± 3.54	13.46 ± 2.32	22.81	**7.78**
Cmax (μg ml–1)	0.27 ± 0.02	0.15 ± 0.024	0.120	**6.00**
Tmax (min)	40	40	0.000	**0.00**
$t_{1/2}$ (min)	81.64 ± 6.61	65.94 ± 4.32	15.70	**2.87**
MRT (0–8) (h)	124.16 ± 7.62	100.89 ± 8.33	23.27	**2.92**
Article 3: [76]rowhead				
DR protective effects: (inhibition of)rowhead				
A *The retinal blood vessel permeability (ng/mg)*				
STZ-diabetic rats	13.2 ± 1.6	2.8 ± 1.5	10.4	6.71
CD-Treatment STZ-DR	7.8 ± 1.4	2.8 ± 1.5	05.0	**3.45**
EEZZR	6.2 ± 1.2	2.8 ± 1.5	03.4	**1.35**
B *Expression rate of vascular endothelial growth factor (VEGF)*				
STZ-diabetic rats (mRNA)	30.8%↓	100%	69.2	
EEZZR (Protein)	35.7%↓	100%	64.3	
Mean	33.25	100	66.75	
SD	2.45	0.00	2.45	**27.2**
C *Expression rate of retinal pigment epithelium-derived factor (PEDF)*				
VEGF-to-PEDF ratio	61.4% ↓	100	38.6	
	3.1-fold↑	100	200.2	

3.4. Quantitative study (meta-analysis)

3.4.1. Compilation for all study outcomes: the medicinal plants used for ocular disorders

All four cross-section alanalytical observational studies and three experimental studies with calculated effect sizes were analyzed together, and the following results were obtained.

3.4.1.1. The forest plot information. The forest plot for both fixed and random models showed that most studies indicated the prediction tendency of plant use status (see Fig. 2).

3.4.1.2. Relative study weights and their residual results. The fixed model showed that the third study [27]had the highest relative weight (55.8%) with a high residual weight, while the rest of the studies possessed a relative weight of 15.7%. Moreover, the random model treated all the studies in a similar way (see Fig. 3).

3.4.1.3. Results heterogeneity parameters 1C- the clinical heterogeneity. Although all included studies were of cross-sectional and experimental types, no clinical heterogeneity could be estimated between the studies.

3.4.1.3.1. Statistical heterogeneity

Variability tests showed high heterogeneity, estimated as $I^2 = 87.078$, $Tau^2 = 1.161$ and Q-value = 23.217 with a value of 0.000 for observational studies and $I^2 = 94.928$, $Tau^2 = 23.211$ and Q-value = 39.434 with a value of 0.000, as shown in Table 7.

3.4.1.4. The funnel plot information for publication bias. Most observational ethnobotanical studies were scattered outside the funnel and segregated at the bottom, while only one study was segregated inside the funnel. Both red and blue diamonds showed identical dimensions of the estimated pooled effect and the true effect. On the other hand, the observational experimental studies were segregated inside the funnel, some at the bottom and one at the top. The red and blue diamonds showed identical dimensions of the estimated pooled and true effects, as shown in Fig. 4.

3.4.1.5. Solutions for heterogeneity problems: ($I^2 = 87.078$ and $I^2 = 94.928$) for both types of study. The standard solution is subgroup analysis based on study design types or sensitivity analysis studies for the checking of prediction tendencies by changing both statistical models and study designs or by one-study removal techniques. These solutions cannot work because the available data did not contain subgroup data or different study design types.

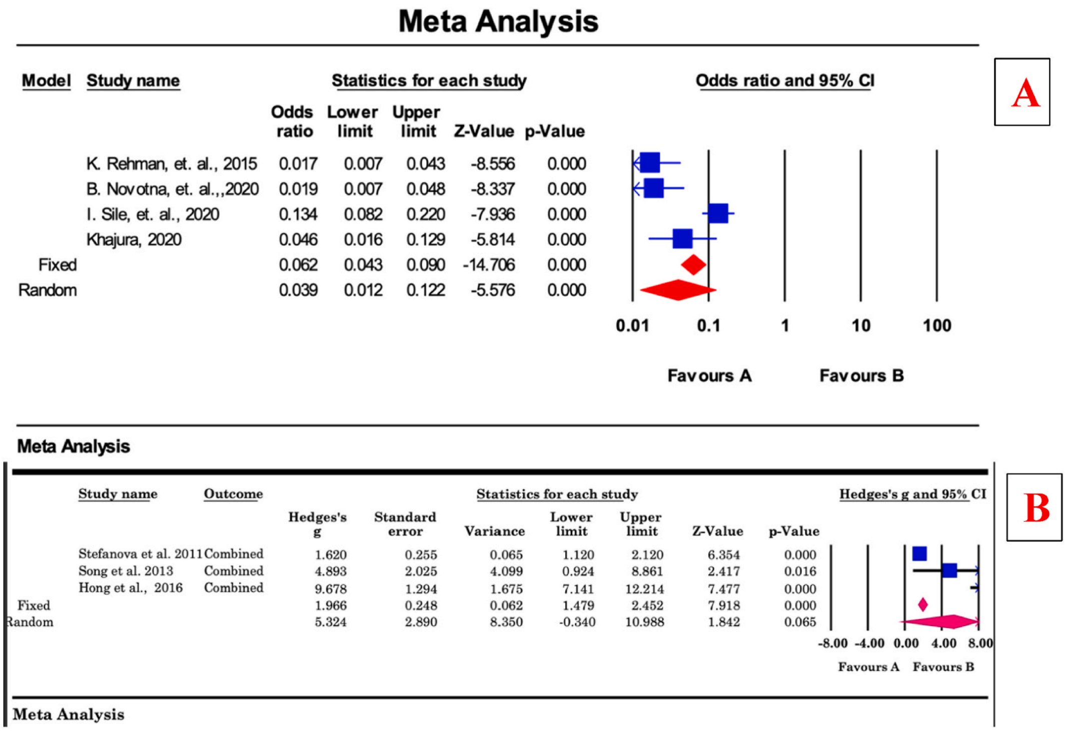

Fig. 2. The forest plot of 4 observational studies (**A**) represents their effect size on medicinal plants used for different eye disorders. For each study, the odds ratio and it's 95% CI was plotted with a blue square and horizontal line using both fixed and random-effect models, while OR = 1; no prediction, OR > or <1; prediction regardless the direction. whilst the 3 experimental studies (**B**) as plants use outcome. For each study, the standardized mean difference and its 95% CI of 4 repeated measures were plotted with circles anda horizontal line using both fixed- and random-effect models. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

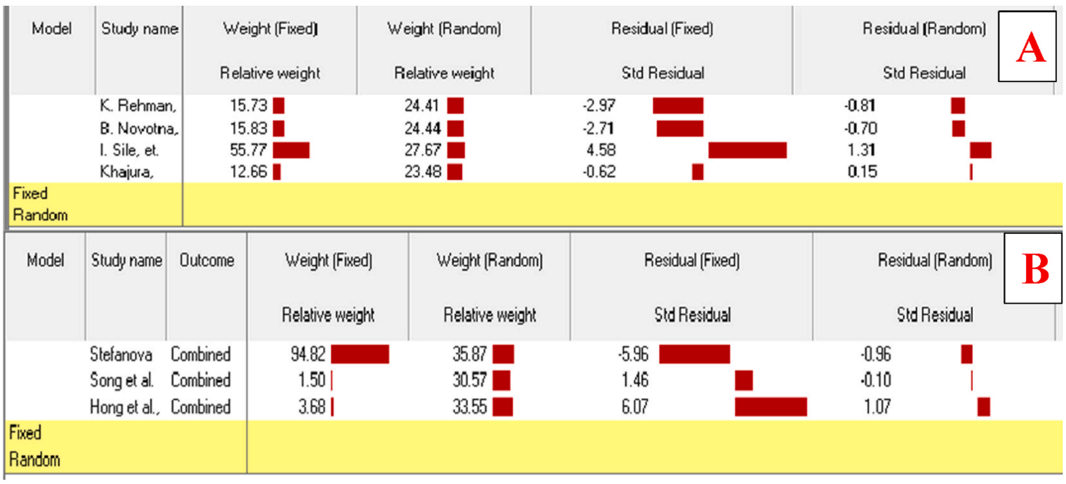

Fig. 3. The relative weights and residuals of the (**A**) Observational and (**B**) Experimental studies extracted from forest plots of the Medicinal plants used for different ocular disorders using both fixed and random-effect meta-analysis models.

Table 7
Heterogeneity parameters extracted from forest plots of the Medicinal plants used for Ocular disorders to detect heterogeneity.

Heterogeneity tests							
Q-value	df(Q)	*p*-value	I^2	Tau^2	Standard error	Variance	Tau
A- Observational:							
23.217	4	0.000	87.078	1.161	1.159	1.343	1.077
B- Experimental:							
39.434	3	0.000	94.928	23.211	28.166	793.342	4.818

Q; Cochran statistic, df; degree of freedom.

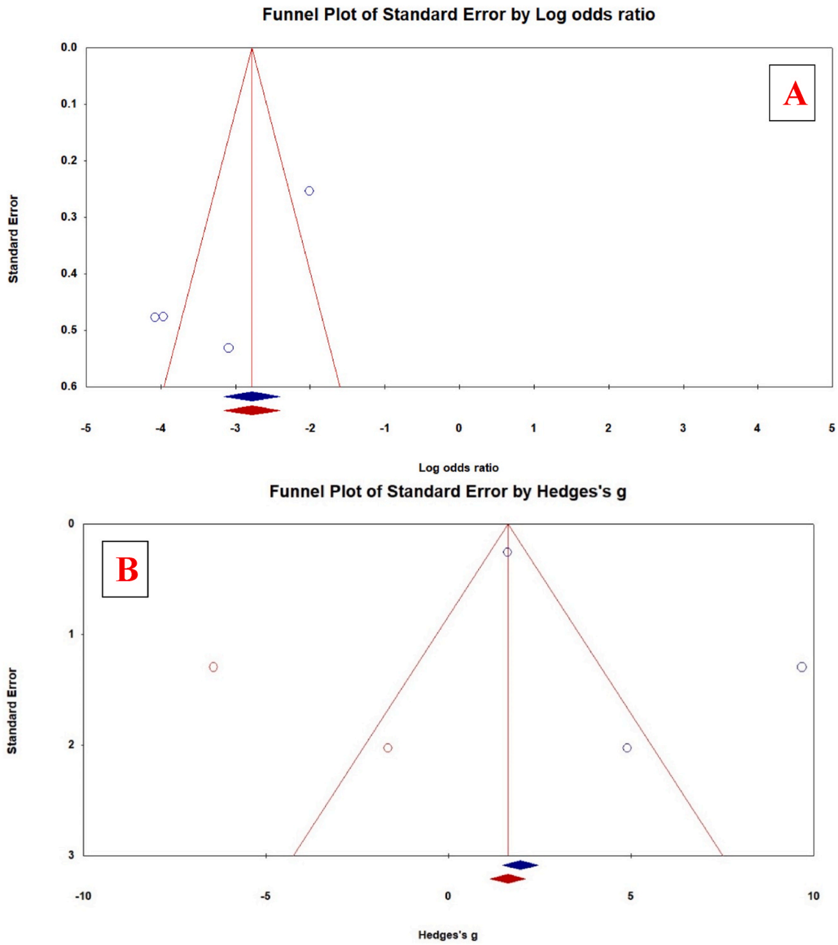

Fig. 4. The funnel plot of 4 observational studies (**A**) and 3 Experimental studies (**B**), represents the publication bias of all studies. The graph plotted the standard error versus the log of either odds ratio or the Hedge's g, the diamonds shape illustrates the summary of the observed (blue) and imputed (red) hazard ratio of all studies. Each small blue circle indicates an individual study. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

Recently, there has been a lack of studies addressing these problems, and few available studies have been scattered worldwide, which weakens their benefits. Thus, combining these documents in a single manner is highly required. Identifying natural, safe-effective medicinal plants to be participate in the treatment of ocular disorders for better cure is a tremendous challenge for the next few years.

4.1. Filter design and optimization

Our study used three different well-designed filters that enable us to search in the three selected medical databases, as no single database is comprehensive in its coverage of published research, which indicates that database diversity was precisely considered during the filter design to cover all the study inclusion criteria appropriately and to focus searches on the best quality research evidence upon which to make decisions. Moreover, our observations revealed that some databases were highly selective to keywords, and the search results retrieved were significantly related to PICOS, but others can give many unrelated studies. Only primary studies were included, which were retrieved by well-designed filters. This means that our research targeted the originality to resynthesize and compile its findings because the parameters were estimated directly. This is in line with Theresa et al. [77]. Several non-English articles were excluded due to language restriction, which was performed automatically during the search or scanning process. This can be taken as evidence for the presence of some kind of publication bias. Morrison and his co-workers reported that no significant differences were found between summary treatment effects in English restricted meta-analyses and languages other than English meta-analyses [78]. The search was performed during the last ten years in the selected databases from January 2, 0211 to May 2021, which represent the most recent articles. The old articles published before 2011 were not included due to time restrictions. In addition, unpublished studies were not included; this can lead to some bias that changes the results of this review. Our search found that most of the retrieved articles were either nonrelevant or reviewed or book chapters in nature, which were excluded by default. Although the included studies were few, they represent and cover the main three continents. Asia, Africa, and Europe. This empowers your information and can lead to reasonable conclusions that reflect the status of the word with respect to the issue addressed.

4.2. *Critical appraisal of the selected studies*

From a total of 2949 articles, only four articles (0.14%)were reached at the end of the systematic review steps. This means that most of the available literature was under the requirements of this study. Our systematic review results revealed that all studies were observational cross-sectional studies of mild to moderate quality, as seen during the critical appraisal and before it, which indicates the general rules in which these study types were ranked second or third in the scientific evidence pyramid [79]. The filtered articles were critically appraised to minimize bias as much as possible because there are many differences among studies regarding their quality. Ethnobotanical surveys can be considered a particular type of observational study and are widely used in the field of plant evaluation, and they may be of knowledge or documentation purposes using different approaches, which is in line with Bernard, 2002 [23], while quantitative surveys that apply indices that allow resynthesis are rare.

4.3. *The qualitative part: systematic review*

Our systematic literature search on the use of medicinal plants for ocular disorders revealed that few articles address this issue. This indicates the lack of these data types among the retrieved articles.

Although a few studies were conducted in this area, since the retrieved studies were detected in their current status and only four ethnobotanical studies were resynthesized [25–28], the weakness of these studies can be overcome by using a diachronic approach, which suggests limiting the sample size but repeating the studies every few years, as suggested by Vogl and Vogl-LUKASSER, 2004 [24]. While 3 experimental studies were resynthesized using a powerfull ES estimated from the standardized mean of the control and treated groups, this was confirmed by Dunlap et al., 1996 [80], who reported that the best was to directly use the standardized mean difference when the correlation between measures was not provided, as we did in this study, following the equation (d =(ME - MC)/SD).

4.4. *The quantitative part: Meta-analysis*

5.4.1. *Compilation of studies using forest plot tool*

Our meta-analysis of fixed and random models summarized in the forest plot provides that all 4 studies contain few plants with eye use; therefore, it can be used to reflect this global area.

The pooled effect odds ratio obtained by the forest plot was less than 1, meaning that medicinal plants' ocular use has potential importance among other uses. These results agree with most studies in this area.

4.4.2. *The determination of among studies heterogeneity*

Although all included studies were cross-sectional and experimental types, clinical heterogeneity between the studies could not be estimated. This is because it is only related to the types of clinical trial studies. Clinical heterogeneity is tested qualitatively, does not involve any calculations, and can be discussed by talking about the similarities or differences between the trials. A high level of significant heterogeneity among our pooled studies was reported (I^2 = 87.078). The heterogeneity test indicates that the null hypothesis must be rejected, which indicates the homogeneity among the studies and to accepted the alternative hypothesis. This heterogeneity may be attributable to our inclusion criteria, which allow for a wide methodological diversity among the studies to be involved. This includes variability in our search strategies term (PICOS). This high heterogeneity observed (I^2 = 87.07 and 94.92) means there is no variability due to sampling error within the studies, but these studies cannot be combined using fixed effects model. Furthermore, we rely mainly on the I^2 value, because it does not depend on the number of studies that suit well in our condition. Regarding the high heterogeneity, our observations revealed a significant heterogeneity between the compiled studies (*p*-value = 0.000), which required further addition of articles that could be done by channeling the time framework and search term to determine the origin of this heterogeneity.

4.4.3. The publication bias using the funnel plot tool

The funnel plot of our results showed that some sort of publication bias appeared as scattered and asymmetrically distributed studies. This indicates that publication bias was found either due to selective outcome reporting or unpublished research excluded from this review. The asymmetry of the funnel plot may be due to reasons other than publication bias, such as the poor methodological quality of smaller studies and true heterogeneity, as mentioned by the Cochrane Collaboration [16].

5. Conclusions and future perspectives

The current study revealed that only 7 out of 2656 unduplicated published articles fit the eligibility criteria and were included in the meta-analysis part. The 4 observational studies reported the use of medicinal plants for general ocular diseases (Eye diseases, eye problems, eye complains) or specific eye conditions such as (Eyesight = eye vision, visual defects), (Irritating eye = allergy), (Hyper myopia = myopia), (Sore eye = burning sensation as a pain type), (Inflammation = infectious or non-infectious), (Eye pain = symptom of eye complains), (Conjunctivitis = allergic on nonallergic) and nightblindness. The three experimental studies used medicinal plants for cataract severity (maturity) or diabetic retinopathy (severity class) or protective effects (Blood vessels permeability, VEGF and PEDF expression rate). High heterogeneity was observed, which in turn banned the possibility of study compilation. Due to lack of sub-groups within the analyzed data and limited study design types, neither sub-group analysis nor study removal procedure can be used to solve the resulted heterogeneity. Treating all studies in a similar manner, a random model revealed that I. Sile 2020 [27] study exhibited high relative weight and residual. Publication bias assessment using funnel plot showed that only one study out of four cross-sectional studies was segregated inside the funnel, whilst all experimental studies were segregated inside the funnel. More data searches are needed for studies that address this problem to elucidate the natural and safe-effective ocular therapeutic agent(s) for the upcoming cascade. Functional studies will need to be extended to in vivo testing in animal models. Finally, large-scale studies of human tissues with good clinical records and large-scale studies of human tissues with good clinical records will need to be performed to put the in vitro and animal studies into a firm clinical context. We can conclude that search strategies should include several databases and that a unique filter should be used for every database, in addition to changing the search terms for commonly used databases. This topic is an exciting research area with a high level of novelty and a lack of data. Therefore, new studies should focus on this topic.

6. Limitations and Recommendations

We strongly recommend that this review be repeated to include old published articles that were not included in our review. Unpublished, non-English studies and data from other databases should also be involved to cover all studies conducted in the area of this review to cover all these scarce information areas.

Other terms, such as alternative and complementary medicine, must be used to boarden the scope and find more relevant studies.

The following are some of the limitations of this review, which can serve as future interesting research points. The articles are limited to certain countries. Meta-analysis was only performed for the original research of observational studies, and the number of review articles available was high among different databases.

Comparative quantitative ethnobotanical studies must be encouraged to resynthesize their results and be more applicable and beneficial.

Clinical trials for different medicinal plants should be started immediately to treat different diseases, particularly ocular diseases.

Author contribution statement

Ali Hendi Alghamdi, Asaad Khalid, Sheraz Gul: Conceived and designed the experiments.

Mahadi Bashir, Haidar Abdalgadir: Performed the experiments; Contributed materials and analysis data; Conceived and designed the experiments.

Aimun A. E. Ahmed: Analyzed and interpreted the data; Performed the experiments; Contributed materials and analysis data; Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Ethics approval and consent to participate

As per Al Baha University standards, all the funded project proposals must have undergone critical review followed by approval by the Scientific Research Affairs relevant committees before acceptance.

Consent for publication

Not Applicable.

Availability of data and materials

All data generated or analyzed during this study are available with Dr. Ali as the correspondence author and can be provided upon request.

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A preprint has previously been published [81].

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