Thymoquinone as a Natural Anti-Angiogenic Agent: Experimental Pharmacology insights into Schematic and Meta-Analysis of Ocular Neovascularization and Retinal Pathology

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ABSTRACT

Background: Thymoquinone is seen to combat angiogenesis, reduce inflammation, and act as an antioxidant. This systematic review and meta-analysis aimed to assess the role of thymoquinone in angiogenesis, damage involving reactive oxygen species, and preservation of the retina in different preclinical models.

Methods: This study followed the PRISMA approach, and PubMed, Scopus, Web of Science, and Cochrane Library were searched to identify studies published by 2025. This study included in vivo and in vitro studies examining how thymoquinone influences the growth of new blood vessels in different cell lines and animal models. Excluded studies were reviews, case studies, reports, and studies in a non-English language. For quality assessment, the OHAT risk of bias assessment tool was used, and effect sizes were measured to determine the therapeutic role of thymoquinone on eye diseases. GRADE framework was employed to assess the certainty of evidence.

Results: Ten preclinical articles were reviewed to assess the impacts of thymoquinone on ocular angiogenesis. Meta-analysis demonstrated an in vivo and in vitro pooled effective concentration of 32.31 and 7.37 μM, respectively. Effect sizes were in constant support of the antioxidant and anti-inflammatory properties of thymoquinone. Bias across studies was low, and on GRADE assessment, it had moderate certainty, having therapeutic potential in neovascular retinal disorders.

Discussion: Overall, thymoquinone appears useful in reducing the formation of new blood vessels and reducing oxidative damage in diseases affecting the eyes. Because it seems promising in the role of a treatment supplement, more research through clinical studies should be carried out.

Keywords: Thymoquinone, Retinal Neovascularization, Corneal Neovascularization, Neovascularization, Pathologic, Vascular Endothelial Growth Factors, Diabetic Retinopathy, Oxidative Stress, Angiogenesis, Anti-Angiogenic Agents, Meta-Analysis.

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INTRODUCTION

Most blinding diseases, such as DR (Diabetic Retinopathy), AMD (Age-related Macular Degeneration), and ROP (Retinopathy of Prematurity), develop due to the extra blood vessels found in the retina or choroid of the eye (ocular neovascularization) [1]. These anti-angiogenic agents, bevacizumab and ranibizumab, are costly, typically given by injection, and sometimes work better on some people than others [2]. For this reason, scientists are now exploring natural products that have anti-angiogenic ability and offer several beneficial effects with a good safety record [3]. This has drawn increased awareness on the use of thymoquinone, a plant product, with the potential of safe blocking the aberrant blood vessel growth in eye diseases [4].

Thymoquinone (TQ), which is the main element in Nigella sativa, has been shown to significantly reduce inflammation, fight free radicals, and prevent angiogenesis in various types of disease[5]. Evidence from laboratory studies reveals that TQ may influence vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 alpha (HIF-1α), and nuclear factor-kappa B (NF-κB), all of which are essential for the development of abnormal blood vessels in the eye[6,7].

Various studies are now investigating how thymoquinone can help curb abnormal blood vessel formation in ocular diseases [8]. Experiments on cells and animals have found that TQ reduces the levels of inflammation and oxidative stress in the body, both of which may lead to pathological angiogenesis [9]. It has also been proven that thymoquinone interacts with main proteins in eyes experiencing abnormal blood vessel formation, particularly VEGF, HIF-1α, and NF-κB [10]. This shows that it is useful in medicine, safe, and can be used along with conventional anti-angiogenic treatments [11]. While several studies assessed how TQ affects tumors and the heart, its use in ocular angiogenesis was explored less and had not yet been evaluated by an updated systematic review and meta-analysis [12]. This unmet need identified that it should be necessary to extrapolate current experimental evidence in the direction of comprehending the potential of thymoquinone as a therapeutic agent in retinal neovascular diseases [13].

This systematic review and meta-analysis reviewed and summarized the available preclinical experiments to examine the effects of thymoquinone on angiogenesis in eyes affected by neovascularization and retinal diseases. The review highlighted the similar findings and tested the strength of scientific methods to deliver key pharmacological advice and proposals for further research into TQ and ocular neovascularization, and retinal pathology.

METHODS

PRISMA Guidelines

Following the PRISMA 2020 guidelines, this study was done to assess the effect of thymoquinone on diabetic retinopathy (DR), retinopathy of prematurity (ROP), and age-related macular degeneration (AMD) [14]. There was no need for registration on PROSPERO since the majority of the experiments used for this review were preclinical (in vivo and in vitro).

Data Search

A search was done on the literature in four recognized databases: PubMed, Scopus, Web of Science, and the Cochrane Library. Until 2025, literature was retrieved by searching using related keywords “thymoquinone”, “Nigella sativa”, “VEGF”, “eye diseases”, and “anti-angiogenesis”, using Boolean operators (OR, AND) to improve the search accuracy. This study checked each reference list from the relevant articles manually to see if they had other appropriate studies.

Studies chosen for this review included original research reviewed by experts, in vivo, in vitro, or ex vivo studies with thymoquinone on neovascularization models, and investigated the levels of VEGF, decreased the area of neovascularization, evaluated oxidative stress, or looked at inflammatory factors, and were available in English. This study did not include review articles, editorials, case reports, conference abstracts, or studies that had nothing to do with eye disorders or those without quantifiable results.

Study Features and Funneling

The primary outcome was to establish the effective concentration of thymoquinone (TQ) in the treatment of ocular diseases in both the in vitro and in vivo experiments. Reduction of oxidative stress, inflammation, amelioration of tissue histology, and healing response were listed as secondary outcomes. Two reviewers reviewed all of the study's titles, abstracts, and full texts to check for relevance to the study. If there were any disagreements, they were addressed with the help of a third party. A specific form was used to capture information about the study, such as its author and year, the model, the types of animals or cells used, dosage, and administration route of thymoquinone, length of treatment, and outcome measures. Missing data was taken by contacting the authors or estimated.

Study Tools

To evaluate the quality of the studies, the OHAT (Office of Health Assessment and Translation) Risk of Bias Rating Tool (Version January 2015) was used. Furthermore, this study assessed how different the study methods were and how strong the evidence was using the GRADE method.

Meta-Analysis

Using an inverse-variance weighted random effects model, meta-analytical procedures were performed to find pooled ORs and their 95% CIs. It was considered that there was substantial heterogeneity when the I^2 statistic showed more than 50% variability. RevMan 5.4.1 software was used for this purpose. A total of 10 studies, of which 7 were in vivo and 3 were in vitro were included in meta-analyses[15,16,17,18,19,20,21,22,23,24]. All concentrations of thymoquinone across different studies were converted to a common unit, i.e., micromolar, and forest plots were generated using Raw Means and their ranges. By excluding some of the studies one at a time, this study evaluated the impact of each study on the results by sensitivity analysis. Subgroup analyses were performed across in vitro and in vivo studies.

A PRISMA flow diagram was developed to show how the selection process took place. The data were organized and presented in the form of tables and forest plots. This study was self-funded, and as only public information was studied, ethical review was not necessary.

RESULTS

A total of 114 studies were collected to study the effect of thymoquinone in ocular disease models. After removing duplicates 92 studies were further taken for abstract and full text screening, out of which 30 could not be matched and were therefore omitted. 41 studies were then taken for full text screening, but due to the presence of secondary data, lack of primary data, and lack of thymoquinone examination, only 10 studies were taken. The steps involved in selecting studies are illustrated in **Figure 1**.

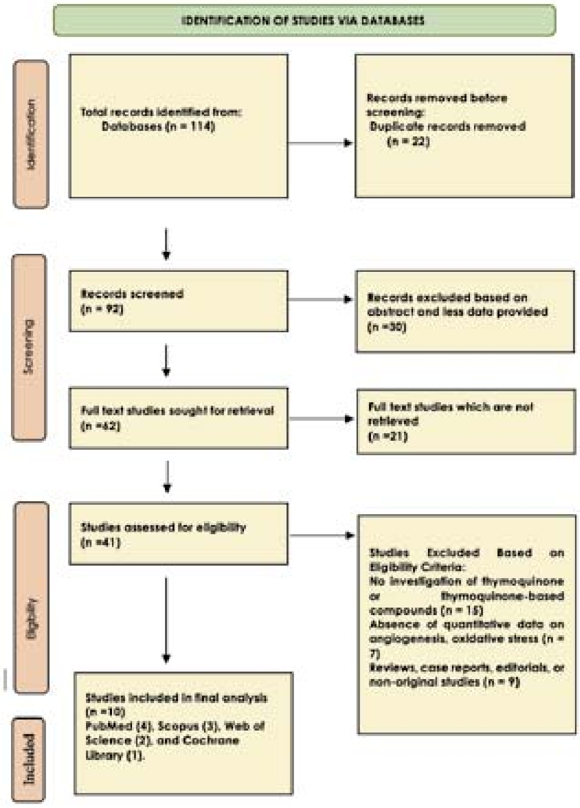


Figure 1: PRISMA flow diagram

The body of research included more than 330 animals in the in vivo model, with a variety of in vitro studies compensated by a considerable number of experimental runs and subruns that were performed under triplicate or quadruplicate settings with three to six independent repetitions. Depending on the experimental model and route of administration, effective concentrations of thymoquinone (TQ) ranged between 2 uM and 87.06 uM in vitro, 0.05-0.5% of topical formulations, while in vivo studies, demonstrated systemic doses of 10 and 80 mg/kg/day through intraperitoneal (IP) or oral administration.

TQ showed strong antioxidant and anti-inflammatory effects across a wide range of ocular disease models. In radiation-caused cataracts, it was found to decrease incidence by 50 % (compared to 80 %) and decrease the levels of malondialdehyde (MDA), a marker of oxidative stress. In the allergy conjunctivitis model, topical TQ (0.5 %) showed similar effects to dexamethasone by effectively suppressing clinical symptoms and inflammatory mediators. Its anti-inflammatory potential was further highlighted in in vitro studies where TQ was found to decrease the expression of proinflammatory genes and proteins in hyperosmolarity-induced dry eye models.

Notably, TQ was also seen to trigger the repair of tissues and structure preservation. At 21.76 µM concentration, it accelerated retinal pigment epithelial (RPE) cell wound healing up to 94.77%, and in retinal degeneration models, it maintained the retinal ultrastructure and expanded the outer nuclear layer (ONL) thickness. TQ therapy in glaucomatous rabbits led to histologically normal ocular structure, such as iris, trabecular meshwork, and corneal stroma, which emphasizes its broad range of application in ocular diseases.

Studies show that thymoquinone (TQ) inhibits tumor growth and angiogenesis by targeting Wnt/PI3K and miRNA pathways. It also reduces proliferation, induces apoptosis, and lowers VEGF-A in cancer cells. Animal studies demonstrate TQ's anti-inflammatory and tissue-protective effects. **Table 1** highlights the characteristics of in vivo studies evaluating thymoquinone in ocular health.

Table 1: In Vivo Studies on Thymoquinone in Ocular Health

Authors (Year)	Study Design	Experimental Model	Ocular Condition Studied	TQ Dose and Route	Sample Size	Duration	Key Findings
Pelin Erguven et al. (2024)	In vivo, experimental	Adult Wistar albino rats	Retinal degeneration (SI-induced)	10 mg/kg IP ×2 before or daily ×14 after SI = 1,522.6µM per dose	25 rats (5 groups of 5)	14 days	SI+TQ ↑ONL thickness, RPE65, HO-1; ↓caspase-3; preserved retinal ultrastructure.
Elif Demir et al. (2016)	In vivo, radiation study	Sprague–Dawley rats	Radiation-induced cataracts	50 mg/kg/day IP, DMSO = 7,614µM	74 rats (10 in TQ group)	10 days	Cataract incidence ↓ to 50%; ↓MDA, XO. Less effective than NSO/propolis.
Tolga Kocatürk et al. (2018)	In vivo, topical eye drop	BALB/c mice	Dry Eye Disease (BAC-induced)	2µL twice daily= 4,870 µM	36 mice (6 groups of 6)	7 days	TQ ↓inflammatory cell density, ↑goblet cells; IL-1a/IL-2 unexpectedly ↑.
Heba Fahmy et al. (2018)	In vivo, glaucoma model	NZ albino male rabbits	Glaucoma (betamethasone-induced)	0.7 mg TQ in liposomes, subconjunctival injection every 36–84 h = 85,400µM	70 rabbits (7 groups of 10)	6 weeks	TQ ↓IOP, improved tissue histology, ↑GSH, partial oxidative rescue.

Amr Fouad & Fahad Alwadani (2015)	In vivo, diabetic cataract model	Sprague-Dawley rats	Diabetic cataract (STZ-induced)	Max 80 mg/kg/day oral TQ = 12,180 µM	55 rats (5 groups)	12 weeks	Dose-dependent ↓MDA, NO, TNF-α, aldose reductase; ↑SOD, CAT, GPx. Protected lens proteins.
Khizar Hayat et al. (2011)	In vivo, allergic conjunctivitis	BALB/c mice	OVA-induced allergic conjunctivitis	Max 0.5% TQ in Tween 80, eye drops QD= 30,450 µM	70 mice (7 groups of 10)	7 days	TQ ↓ocular symptoms, eosinophils, IgE, histamine, IL-4/5/13, TGF-β.
Arumugam Paramasivam et al. (2012)	In vivo, angiogenesis model	Zebrafish embryos	Retinopathy-linked angiogenesis	Max 5 µM TQ in embryo medium	≥3 reps	48 h	2–4 µM TQ ↓ISV formation, ↓VEGF-A mRNA; >5 µM toxic.

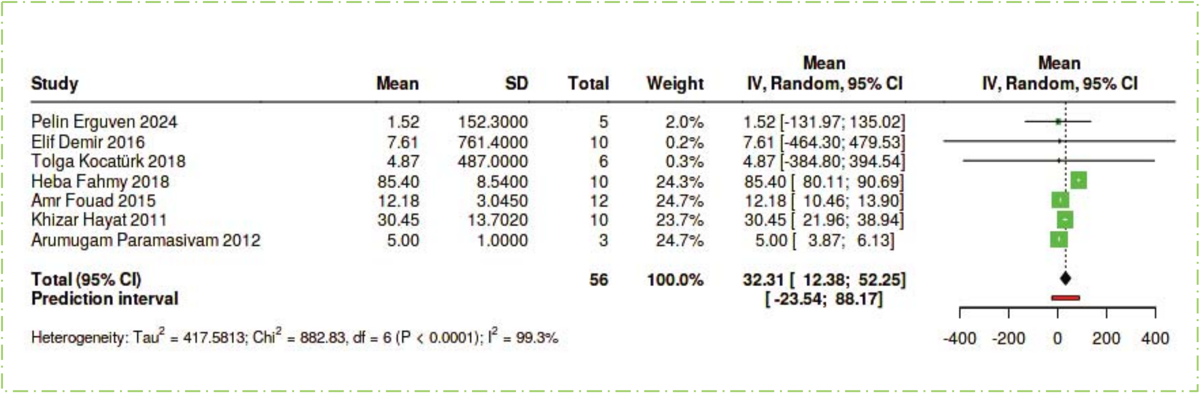
Table 2 demonstrates the characteristics of in vitro studies that studied thymoquinone with respect to ocular health.

Table 2: In Vitro Studies on Thymoquinone in Ocular Health

Authors (Year)	Study Design	Experimental Model	Ocular Condition Studied	TQ Dose and Route	Sample Size	Duration	Key Findings
Serkan Sen & Murat Kasikci (2023)	In vitro, wound healing assay	ARPE-19 (Human RPE cells)	RPE wound healing	21.76, 43.53, 87.06 µM TQ in DMSO	Triplicates (MTT)	24 h	Low-dose TQ (IC50/4) accelerated healing (94.77% closure), ↑TGF-β1/MMP-9, ↓TLR3/IFN-γ; high-dose cytotoxic.
Xin Hu et al. (2018)	In vitro, oxidative stress model	ARPE-19 (Human RPE cells)	H_2O_2-induced oxidative damage	5, 10, 20 µM TQ pre-treatment	≥3 replicates	12 h pre-treatment, 24 h H_2O_2	TQ ↓ROS & apoptosis, ↑GSH, SOD via Nrf2/HO-1; effect lost on Nrf2 knockdown.
Elisa Landucci et al. (2023)	In vitro, dry eye model	HCE-2 (Human corneal epithelial cells)	Hyperosmolarity-induced dry eye	5 µM TQ (free, LP-TQ, LP-TQ-HA)	≥4 replicates (mRNA/protein); 6 for mtROS	5 h	TQ (esp. liposomal) ↓IL-1β, IL-6, COX-2, p-p65 & mtROS. HA coating enhanced effect.

This meta-analysis synthesized the preclinical evidence of the effectiveness of thymoquinone (TQ) in various models of ocular diseases. Both in vitro cell-based tests and in vivo animal models involving TQ antioxidative, anti-inflammatory, and tissue-restorative capabilities, were studied. Ten studies were analyzed that included more than 330 animals and several repeated in vitro experiments up to 6 times. This was done to estimate the mean effective concentrations of TQ and to determine consistency between experimental systems.

The seven in vivo studies were utilized to generate the forest plot, and the conditions studied were as follows: radiation-induced cataracts, glaucoma, dry eye, diabetic cataracts, and retinal degeneration. All doses were adjusted to µM equivalents. The pooled effect was 32.31 uM (95% CI: 12.38-52.25) using a random-effects model. Nevertheless, a large heterogeneity was noted (I2 = 99%; p < 0.01), probably due to differences in administering routes (IP, oral, topical, subconjunctival), timing, and types of animal models. However, regardless of its heterogeneity, all studies affirmed the protective effectiveness of TQ and designated its in vivo systemic and local pharmacotherapeutic potential.

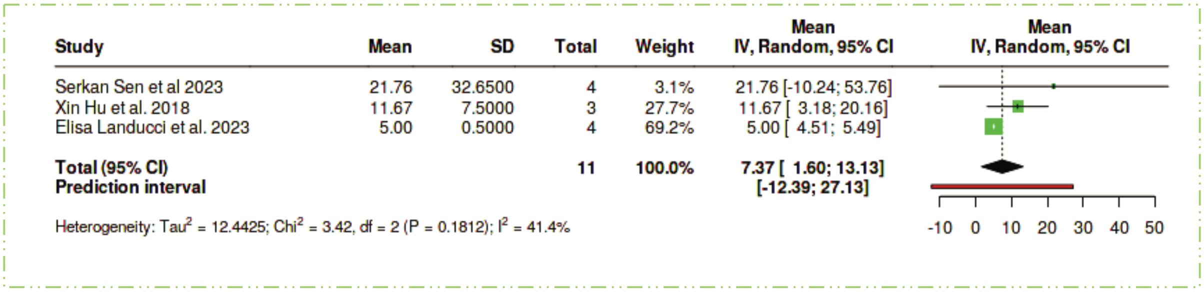


Study	Mean	SD	Total	Weight	Mean IV, Random, 95% CI
Pelin Erguven 2024	1.52	152.3000	5	2.0%	1.52 [-131.97; 135.02]
Elif Demir 2016	7.61	761.4000	10	0.2%	7.61 [-464.30; 479.53]
Tolga Kocatürk 2018	4.87	487.0000	6	0.3%	4.87 [-384.80; 394.54]
Heba Fahmy 2018	85.40	8.5400	10	24.3%	85.40 [80.11; 90.69]
Amr Fouad 2015	12.18	3.0450	12	24.7%	12.18 [10.46; 13.90]
Khizar Hayat 2011	30.45	13.7020	10	23.7%	30.45 [21.96; 38.94]
Arumugam Paramasivam 2012	5.00	1.0000	3	24.7%	5.00 [3.87; 6.13]
Total (95% CI)			**56**	**100.0%**	**32.31 [12.38; 52.25]**
Prediction interval					**[-23.54; 88.17]**

Heterogeneity: $Tau^2 = 417.5813$; $Chi^2 = 882.83$, df = 6 ($P < 0.0001$); $I^2 = 99.3\%$

Figure 2: Dose Summary of Thymoquinone (µM) in In-vivo Models of Eye Disease

Three studies with the ocular epithelial cell lines (e.g., ARPE-19, HCE-2) were used in the in vitro forest plot to evaluate the role of TQ in wound healing, oxidative stress, and the antioxidant response. The overall efficacious concentration was 7.37 µM (95% CI: 1.6-13.13), and there was no significant heterogeneity, meaning that the overall effect was approximately equivalent in experimental designs. These findings demonstrated that the effective concentrations of TQ in cellular models were reproducible, which were consistent with its direct protection and anti-inflammatory effects. The small variance in the confidence intervals indicated the consistent dose response, particularly in the formulation containing liposomes or Hydroxyapatite (HA)-coating, which supports the efficacy of TQ as an effective choice in the pharmacological field of the ocular surface.



Study	Mean	SD	Total	Weight	Mean IV, Random, 95% CI
Serkan Sen et al 2023	21.76	32.6500	4	3.1%	21.76 [-10.24; 53.76]
Xin Hu et al. 2018	11.67	7.5000	3	27.7%	11.67 [3.18; 20.16]
Elisa Landucci et al. 2023	5.00	0.5000	4	69.2%	5.00 [4.51; 5.49]
Total (95% CI)			**11**	**100.0%**	**7.37 [1.60; 13.13]**
Prediction interval					**[-12.39; 27.13]**

Heterogeneity: $Tau^2 = 12.4425$; $Chi^2 = 3.42$, df = 2 ($P = 0.1812$); $I^2 = 41.4\%$

Figure 3: Effective In Vitro Concentrations of Thymoquinone (TQ) in Ocular Cell Models

Subgroup analysis was done to compare the in vitro and in vivo use of thymoquinone (TQ) in ocular models. The pooled mean effective concentration of the 7 in vivo studies was 32.31 µM (95% CI: 12.38-52.25), which had a high heterogeneity (I2 = 99%). These differences were probably due to variations in the disease models (e.g., glaucoma, cataract, retinal degeneration), route of administration (IP, oral, topical), as well as formulation (free TQ vs. liposomal). Contrastingly, the three in vitro studies recorded a pooled mean of 7.37 µM (95% CI: 1.6-13.13) with no significant heterogeneity, thus demonstrating consistent results across cellular systems such as ARPE-19 and HCE-2. The in vitro concentrations were lower and more uniform, indicating better control of exposure and response, whereas the in vivo results indicated greater biological variation. This subgroup designation brought out the relevance of customized dosing in context; cellular vs. whole-organism, as well as supported the effects of TQ under both regulated vs. physiological circumstances.

The leave-one-out sensitivity analysis showed great stability in the in vivo and the in vitro datasets. In in vivo experiments (n = 7), pooled mean concentrations varied between 29.84 and 35.11 µM but consistently within the original 95% CI (12.38 to 52.25 µM), with ongoing heterogeneity (I2 = 98.8 to 99.3%). In in vitro experiments (n =3), the adjusted pooled mean concentration slightly differed between 6.89 and 8.01 µM, all within the original CI (1.6-13.13 µM) with insignificant heterogeneity throughout. Results validated that there were no individual studies that distorted outcomes and that the effective concentrations of TQ were scalable across models, indicating that it could have a strong therapeutic value in ocular-based studies.

The overall risk of bias in the included studies was low, and all studies were otherwise well-controlled and designed, interventions were standardized, and outcome reporting was performed consistently. Selection, performance, and detection domains were sufficiently tackled in most studies, which made their results very reliable. **Table 3** demonstrates low-risk-of-bias studies that did well in selection, outcome, and several other important areas. The GRADE method indicated that the studies were moderately certain due to the small number of subjects, the quick follow-ups, and the many ways the studies were conducted.

Table 3: Risk of Bias Assessment of In Vitro and In Vivo Studies

Author & Year	Detection Bias – Exposure	Selection Bias	Other Bias	Detection Bias – Outcome	Selective Reporting Bias	Confounding Bias	Attrition/Exclusion Bias
Pelin Erguven et al. (2024)	++	+	+	++	+	+	++
Elif Demir et al. (2016)	++	+	+	++	+	+	++
Tolga Kocatürk et al. (2018)	++	+	+	++	+	+	++
Heba Fahmy et al. (2018)	++	+	+	++	+	+	++
Amr Fouad & Fahad Alwadani (2015)	++	+	+	++	+	+	++
Khizar Hayat et al. (2011)	++	+	+	++	+	+	++
Arumugam Paramasivam et al. (2012)	++	+	+	++	+	+	++
Serkan Sen & Murat Kasikci (2023)	++	+	+	++	+	+	++
Xin Hu et al. (2018)	++	+	+	++	+	+	++
Elisa Landucci et al. (2023)	++	+	+	++	+	+	++

++ Definitely low risk, + Probably low risk, - Probably high risk, -- Definitely high risk

DISCUSSION

Several experiments have demonstrated that thymoquinone (TQ) shows promise as a natural substance that protects the eye from angiogenesis and prevents retinal illnesses [25]. In a variety of experimental models, TQ was found to decrease several important steps of angiogenesis, including the growth, movement, and formation of blood vessels by endothelial cells, groups that are responsible for abnormal vascular development in diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion[26,27].

The effect of TQ happens by directing the control of certain pathways that manage the expression of VEGF and the series of angiogenesis signals it causes. When VEGF and related angiogenesis factors decrease, and the body's defense against inflammation is enhanced, it provides multiple obstacles to the growth of blood vessels[28]. Because TQ is an antioxidant, it helps to protect the brain in the eye by reducing cell death and maintaining eye architecture [29]. It also scavenges the reactive oxygen species (ROS) and inhibits the pro-apoptotic signaling pathways, thus maintaining the integrity of the retinal neurons [30]. Moreover, TQ promotes mitochondrial activity and prevents oxidative impairment of the retinal pigment epithelial cells, which are vital in visual functioning and avoiding neurodegenerative alteration of ocular tissues [31].

The anti-angiogenic effects of TQ increased with a higher dose and longer treatment in laboratory studies. Still, using various kinds of regimens, methods, and models in the study made some results differ, which means future research should aim for standardization so that differences are reduced [32,33]. Importantly, the use of TQ delivery both by systemic and direct methods to the eyes showed that it could be used in different ways and applied in medicine [34].

TQ was found to reduce inflammation, which is vital because inflammation and the increased growth of blood vessels are strongly linked in retinal diseases. By checking the oxidative damage and decreasing the number of inflammatory mediators, including TNF-a, IL-1b, and COX-2 (inflammatory pathways), TQ can decelerate the evaluation of the retinal functionality and sight [35]. It also suppresses angiogenic signaling, such as VEGF, and the unnecessary development of blood vessels in retinal diseases [36]. TQ also maintains the structure of the retina, as well as reduces stressful cellular responses, and has a therapeutic potential for diseases like diabetic retinopathy and age-related macular degeneration [37].

Overall, thymoquinone could potentially be used as an additional or alternative therapy for treating retinal neovascular diseases. Since it powerfully acts against angiogenesis, inflammation, and harmful compounds, its use could be useful as further research looks into improving care for retinal disorders with abnormal blood vessel growth [38,39]. Investigating new methods for administering drugs such as nanoparticles and sustained-release preparations could increase the effectiveness and bioavailability of TQ in treating eye diseases [40].

Although this review supports the potential of thymoquinone as an anti-angiogenic and anti-inflammatory agent, the findings are limited by the lack of randomized controlled trials and the exclusion of non-English publications. Most of the available evidence comes from in vitro and animal studies, which may not fully reflect clinical outcomes in humans. Additionally, it is difficult to generalize findings and reach conclusions because various study designs, animals, and outcomes were used.

Therefore, larger, well-designed clinical trials are essential in the future to determine effective dosing strategies, assess long-term safety, and establish clear dose–response relationships in relevant patient populations.

CONCLUSION

Research has shown that thymoquinone may be a useful agent for treating retinal problems caused by disorders that cause uncontrolled growth of blood vessels in the eye. The results from earlier studies show that it stops angiogenesis, reduces the presence of free radicals, and lessens inflammation factors involved in worsening retinal diseases. Thanks to its diverse qualities, thymoquinone could serve as a supplement or alternative to traditional treatments, which sometimes have drawbacks related to how effective they are, their price, and the side effects they cause.

Still, although scientists have made good progress in labs and with animals, patients have not reaped many benefits yet. Proper clinical trials should be carried out to understand the effective dosages, the proper ways to deliver thymoquinone, long-term safety issues, and the drug's effectiveness in patients.

LIST OF ABBREVIATIONS

TQ Thymoquinone
PI3K Phosphoinositide 3-Kinase
Wnt 3aWingless-related Integration Site 3a
IL Interleukin
IFN-γInterferon-gamma
VEGF-A Vascular Endothelial Growth Factor A
ROS Reactive Oxygen Species

ACKNOWLEDGMENTS

None

CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All contributed equally as per ICMJE.

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