Review Article

Effect of Coenzyme Q10 in Inhibiting Retinal Ganglion Cell Apoptosis on Glaucomatous Neuro Degeneration Model

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ABSTRACT

This study aimed to explore CoQ10 properties in inhibiting retinal ganglion cell (RGC) apoptosis in the glaucomatous animal model.A comprehensive literature search was performed in Medline/ PubMed, Science Direct, ProQuest, and Web of Science till August 8th, 2023. The authors conducted study selection, data extraction, and risk of bias assessment independently. This study was registered at PROSPERO (registration number CRD42023454777).A total of 5 studies which vary in glaucomatous animal models were selected. All the studies showed a decreased mean of apoptotic RGCs in the glaucomatous CoQ10-supplemented model compared to control. Studies suggest CoQ10 may modify Bax/Bad/BcL-xL-mediated apoptotic pathway.Oxidative stress was also shown to be decreased in several studies which was marked by reducing protective oxidative stress markers (SOD2; HO1).Further research on human subjects was needed to explore CoQ10 potentials.

Key Words: Ubiquinol, Coenzyme Q10, Retinal Ganglion Cell, Apoptosis, Oxidative Stress, Glaucoma.

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INTRODUCTION

Elevated intraocular pressure is known as the main risk factor of glaucoma and is still the only target therapy. However, glaucoma is a neurodegenerative disease which involves multiple pathogenesis, such as altered neurotrophins signalling, excitotoxicity, mitochondrial dysfunction, protein misfolding, and oxidative stress, which results in retinal ganglion cell (RGC) death.[1] Oxidative stress plays a significant role in the development of glaucoma. This condition arises from an imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidants and repair systems to counteract them. As a result, apoptosis and autophagy occur, antigen-presenting cells (APCs) are stimulated, and inflammatory responses are activated in the affected cells.[2] Specifically in glaucoma, oxidative stress may affect trabecular meshwork, optic nerve head and lamina cribosa, and retinal ganglion cells (RGC).[3]

Given the potential pathophysiology of glaucoma, antioxidant supplements may have the potential to inhibit RGC death. Coenzyme Q10 (CoQ10) is a very effective antioxidant that has become increasingly popular recently. Ubiquinone, also referred as coenzyme Q10, is a vitamin-like benzoquinone compound produced naturally in the human body from tyrosine. CoQ10 has demonstrated neuroprotective properties in neurodegenerative disorders such as Alzheimer's disease (AD), stroke, and epilepsy.[4] Similar neuroprotective properties were also shown in the ischemic retina. Several mechanisms such as inhibiting oxidative stress, blocking the apoptotic

pathway, preserving mitochondrial function, and inhibiting microglial activation were known to inhibit RGC death.[5] In this study, we aim to evaluate the efficacy of CoQ10 supplementation in several animal experimental studies and the possible mechanism of CoQ10 in inhibiting RGC death.

METHODS

This study was conducted according to The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[6] The review process was pre-registered on the PROSPERO register with the registration number CRD42019149253.

A comprehensive search was performed in Medline/PubMed, Web of Science, ProQuest, and Science Direct to identify all in vivo experimental studies investigating the impact of coenzyme Q10 on the glaucomatous model (up until August 8th, 2023). Date restriction was not applied in the search. The review focused on three primary components: coenzyme Q10, glaucoma, and retinal ganglion cells. These phrases were utilized as keywords and medical topic headings (MeSH) where applicable. The PRISMA flow diagram (Figure 1) displayed the studies that were identified, removed, screened, included, and excluded.

The titles and abstracts of studies acquired from online databases were imported to Rayyan (Rayyan.ai). In resolving duplicates, a manual review was performed for the potential pairs in which Rayyan's duplicate automation previously detected article duplicates. The titles and abstracts screening were done by the authors independently (HHPI, NHM, VFF, and JR) according to established inclusion criteria such as (1) all in vivo animal models of human glaucoma, whether transient ocular ischemia induced by acute high IOP elevation or inherited animal model of human glaucoma, (2) coenzyme Q10 (CoQ10) is given through oral supplementation, (3) age-matched non-glaucomatous control that received placebo. All original research articles in English and published at any time were included in the study. All numerically comparable outcomes, especially retinal ganglion cell count as the primary outcome, were included as the main outcome. During the screening process, we excluded the following studies: cross-over studies, studies involving combined treatments or any alternative modalities for glaucoma or neuroprotective agents, and studies where methods other than oral administration were employed.Review studies, posters, and conference abstracts were also excluded.

Potential full-text studies were assessed after the screening process was done by the authors independently (HHPI, NHM, VFF, and JR). Any disagreements and uncertainties among the authors in both abstract and title screening or full-text review were resolved by discussion with the expert (AAMPT).

Data Extraction and Risk of Bias Assessment (ROB)

Study characteristics (study designs, animal model, treatment dose and intervention duration) and outcomes were recorded. Retinal ganglion cells in the mid retina area, were extracted in cells per millimetre square in the glaucomatous animal model who received CoQ10 supplementation and placebo. All other comparable outcomes, which were expressed as means and standard deviation (SD) of each numerical parameter such as Bax protein expression, pBad protein expression, and GFAP protein intensity were also extracted as the secondary outcome. Numerical outcomes presented in charts and graphs were extracted using Web Plot Digitizer, Version 4.2).[7] All Numerical data required from charts and graphs were also recorded in means and SD. Inconsistencies and discrepancies were discussed among the authors.

The risk of bias (ROB) in all experimental animal trials included in the analysis was assessed using SYRCLE's risk of bias tool.[8] The tools, derived from the Cochrane RoB, included 10 entries/domains that pertain to 6 different types of bias. Signalling questions were employed to assist in addressing each domain.

RESULTS

Characteristics of Included Studies

A total of 5 studies were included. The publication year ranged from 2008 to 2020. All the studies were in-vivo models with adult mice, male and female, with weight varying among each study. Each study used a different kind of glaucomatous animal model. The inherited glaucoma animal model was used in one study,[9] the glaucoma-induced animal model was used in three studies,[10–12] and both inherited and induced glaucoma animal model was used in one study.[13] Glaucoma was induced by injecting saline into the anterior chamber, NMDA into the vitreous body, and

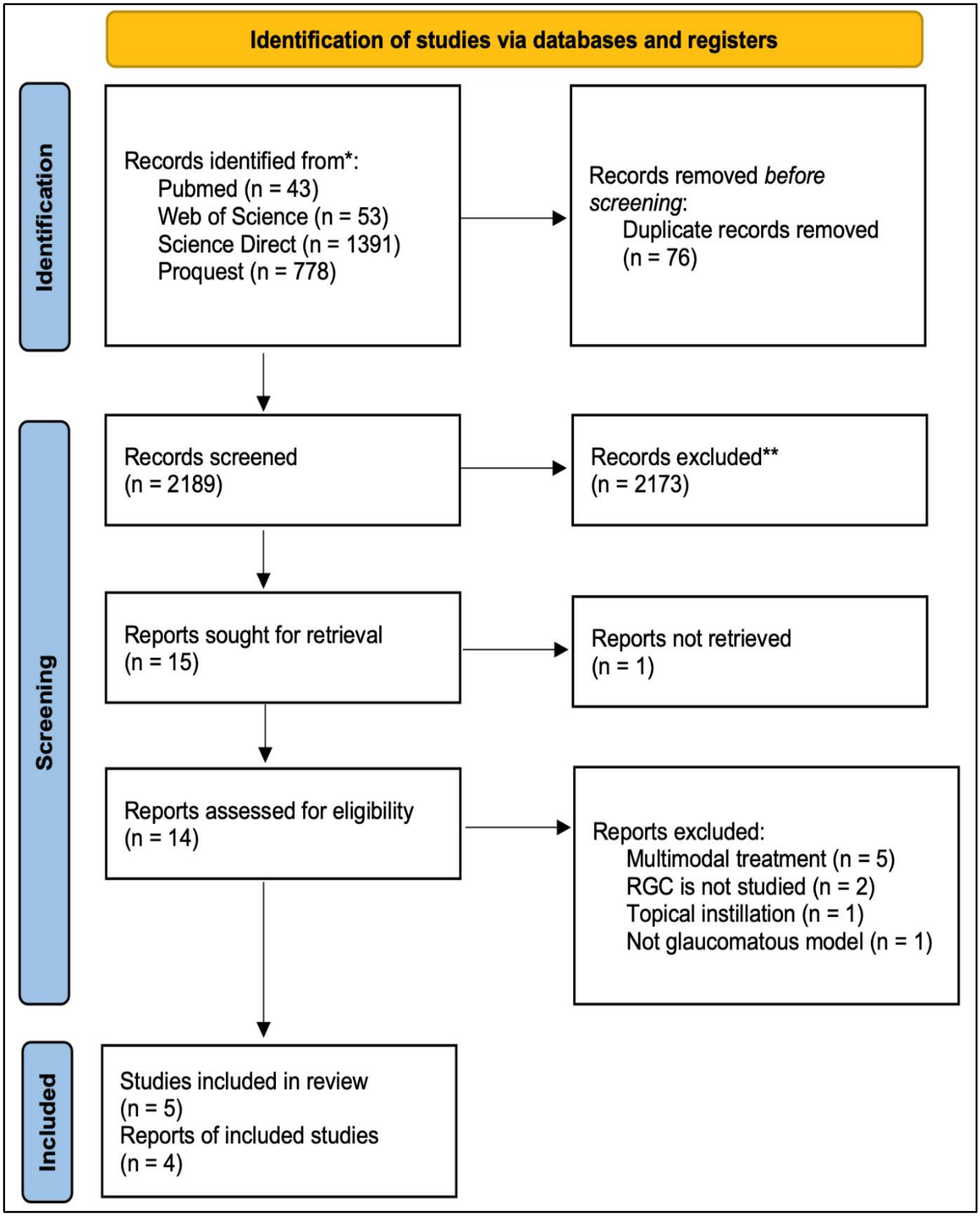

Figure 1: Flow diagram of the study selection process.

Table 1: Characteristics of the included studies.

Author, year	Glaucomatous Animal Model	Control Model	Weight	Coenzyme Q10 administration (dose, route, frequency)	Interval Period
Lee et al, 2014 (B)	Adult, female, 4-month-old DBA/2J mice.	Adult, female, 4-month-old DBA/2J-Gpnmbþ (D2-Gpnmbþ) mice.	25–30 g	An exact 1% CoQ10 diet (vol/vol) (which equals a daily dose of 1600–2000 mg/kg body weight in mice.	Diet was given daily for 6 months.
Lee et al, 2014 (A)	Adult, female, 4-month-old C57BL/6 mice were injected by using 30-gauge needle with saline into the anterior chamber of right eye until IOP 70–80 mmHg reached for 50 min.	Adult, female, 4-month-old C57BL/6 mice.	20–25 g	An exact 1 % CoQ10 diet (vol/vol), which equals a daily dose of 1600–2000 mg/kg body weight in mice.	Diet was given daily for 1 week before the induction of transient retinal ischemia and then continued diet treatment for 2 weeks.
Ju et al, 2018	Adult, female, 4-month-old C57BL/6J mice were injected with saline into the anterior chamber until IOP 70-80 mmHg reached for 50 minutes.	Adult, female, 4-month-old C57BL/6J mice.	25–30 g	An exact 1% CoQ10 diet (vol/vol) (which equals a daily dose of 1600–2000 mg/kg body weight in mice.	Diet was given 1 month before glaucoma induction, then continued 12 h until 2 weeks after induction.
Nakajima et al, 2008	Adult male ddY mice was induced by the injection (2 µl/eye) of N-methyl-D-aspartate (NMDA) into the vitreous body of the left eye	Adult male ddY mice, right eye	36–43 g	Coenzyme Q10 at 10 mg/kg (0.1 ml/10g) with or without α-tocopherol at 10 mg/kg, or vehicle (olive oil) was administered orally (p.o) each day.	Diet was given each day for 14 days, with NMDA being intravitreally injected at 7 days after the start the treatment.
Edwards et al, 2020	Adult male and female DBA/2J	Adult age-matched control DBA/2J-Gpnmb^{+} (D2-Gpnmb^{+})	25–30 g	An exact 1% Ubiquinol diet [(v/v), which equals a daily dose of 1600-2000 mg/kg body weight.	Diet was given for 5 months.
	Adult, male and female, 4-month-old C57BL/6J mice were injected with 5 mM paraquat into the vitreous humour using a Hamilton syringe with 34-gauge needle.	Adult age-matched control C57BL/6J			Diet was given for 1 months and a week after induction

paraquat into the vitreous humour.[10-13]. Detailed characteristics of the included studies are shown in Table 1.

Risk of Bias in the Included Studies

SYRCLE's risk of bias tool determined that all the studies included in the analysis exhibited a low risk of bias across four specific domains: blinding (detection bias), incomplete outcome data, selective outcome reporting, and other potential sources of bias. There were no studies that provided data on random sequence generation, allocation concealment, random housing, blinding of the investigator, or random outcome evaluation. A study by Nakajima et al,[10] did not mention the baseline characteristics (selection bias).[10]Figure 1 provides a concise summary of the evaluation of potential bias.

Primary Outcome: Effect of CoQ10 supplementation in inhibiting RGC apoptosis

There have been more animal studies that revealed the

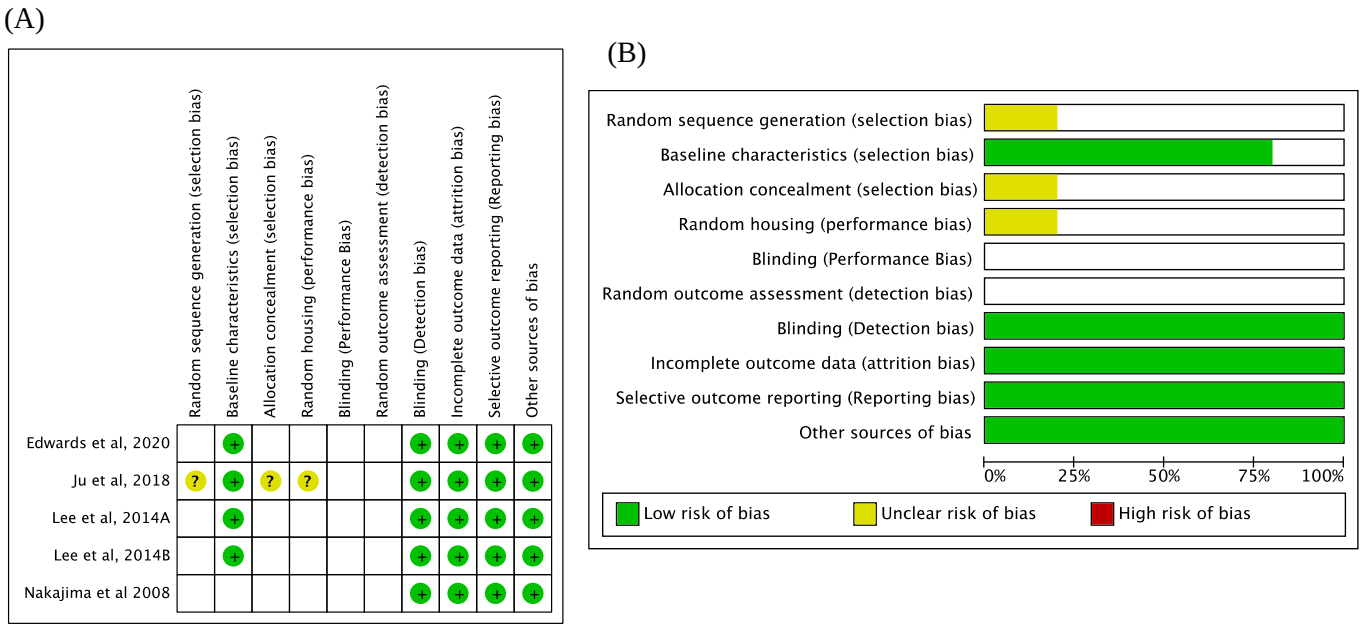

Figure 1 (a-b): Summary of the risk of bias assessment of the included studies.

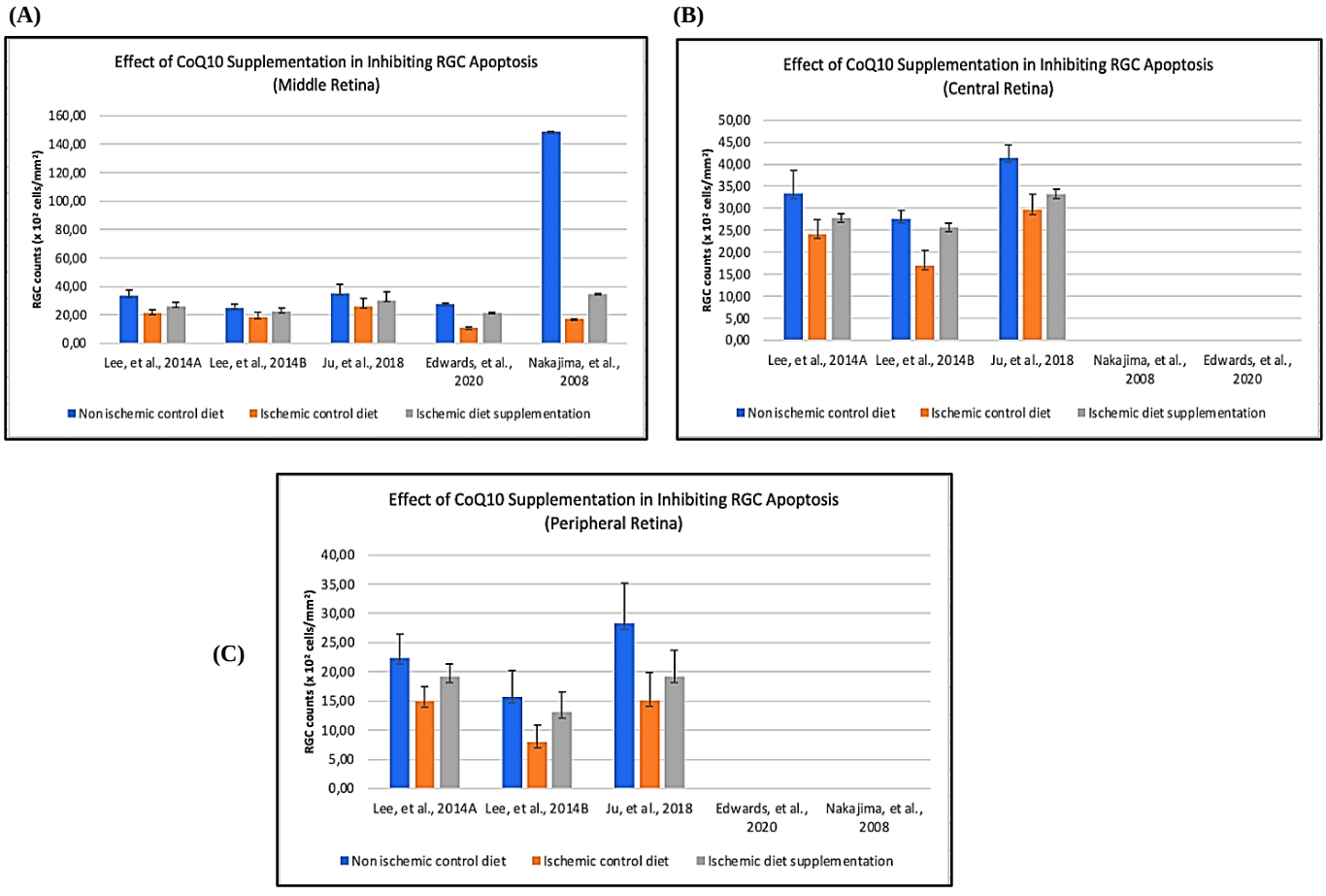

Figure 3: The RGC survival in glaucomatous model mice treated with Coenzyme Q10 supplementation. (A) Shows the RGC survival in the middle areas of the retina from the included studies. (B) Shows the RGC survival in the central areas of the retina from the included studies. (C) Shows the RGC survival in the peripheral areas of the retina from the included studies.

Table 2: *Coenzyme Q10 effect towards proapoptotic markers and antiapoptotic markers.*

Author	Proapoptotic Markers		Antiapoptotic Markers
	Bax	pBad	BcL-xL
Lee, et al., 2014A	↓	↑	NM
Lee, et al., 2014B	↓	↑	NM
Ju, et al., 2018	↓	NM	↑
Edwards, et al., 2020	↓	NM	NM
Nakajima, et al., 2008	NM	NM	NM

Table 3: *Coenzyme Q10 effect toward oxidative stress markers and astroglial activation markers.*

Author	Protective Stress Markers, Antioxidants		Astroglial and/or microglial activation markers	
	SOD2	HO1	GFAP	Iba-1
Lee, et al., 2014A	↓	↓	↓	NM
Lee, et al., 2014B	↓	↓	↓	NM
Ju, et al., 2018	NM	NM	↓	NM
Edwards, et al., 2020	NM	NM	NM	NM
Nakajima, et al., 2008	NM	NM	NM	NM

effectiveness of Coenzyme Q10 supplementation in inhibiting retinal ganglion cell death in glaucoma. Edwards et al, used Brn3a immunohistochemistry to determine whether Coenzyme Q10 supplementation inhibited RGC apoptosis in glaucomatous DBA/2J retinas.[13] Other studies used the same method to analyse the RGC counting and one study conducted by Nakajima, et al, used the cell culture to assess the cell viability.[10] The result of the RGC survival from each study is shown in Figure 3.

Figure 3 shows the effect of CoQ10 supplementation in inhibiting RGC apoptosis in three zones of the retina, which are middle, central, and peripheral. Both Nakajima, et al and Edwards et al., did not assess the RGC survival in the central and peripheral retina.[10,13] The non-ischemic control retina showed a higher average RGC count in the middle, central, and peripheral retina than both the ischemic control diet and CoQ10 diet supplementation. In contrast, the CoQ10 diet supplementation showed more RGC count than the control diet. The CoQ10 diet supplementation promoted RGC survival.

Secondary outcome: Effect of CoQ10 supplementation protects against oxidative stress

Coenzyme Q10 diet supplementation is considered to have an important contribution in protecting the retina against oxidative stress which may initiate neurodegeneration. All the included studies assessed its effect on the oxidative stress-mediated mitochondrial alteration in the glaucomatous mouse.

Based on Table 2 and Table 3, CoQ10 supplementation showed a decrease in the active Bax protein expression in Lee et al., studies.[12] The decrease in active Bax protein expression was also shown in other studies conducted by Ju, et al., and Edwards,

et al.[11,13] Other results show that CoQ10 diet supplementation promotes the cells' survival against the mitochondria-related apoptotic pathway in glaucomatous model. This effect is demonstrated not only by reducing the levels of Bax protein but also by raising the expression of pBad protein. These findings suggest that increased pBad expression may illustrate an endogenous repair mechanism against the apoptotic process that CoQ10 may assist in preventing Bax-mediated rise in the glaucomatous model. The expression of SOD2 and HO1 proteins increases in the ischemic retina due to oxidative stress. Several studies have demonstrated that adding CoQ10 to the diet can effectively prevent oxidative stress which is indicated by reduced expression of SOD2 and HO1 proteins.[9,12]

DISCUSSION

Oxidative stress is a significant factor in the loss of retinal ganglion cells in glaucomatous environment. It is marked by the increasing total oxidative stress level and decreasing total antioxidant status in serum and aqueous humour.[14] Interaction of Bcl-2 family proteins, which regulate and mediate mitochondria, in contributing to apoptosis and cell survival was affected by oxidative stress conditions.[15] Pro-apoptotic Bcl proteins, such as Bax and Bak, translocate to and oligomerize in the mitochondrial membrane, thus causing the release of cytochrome c and apoptotic cascade resulting in retinal ganglion cell death.[16] In contrast anti-apoptotic Bcl proteins, Bcl-xl, bind to pro-apoptotic Bcl2 proteins to block its apoptotic signalling.[17] The increased activity of pro-apoptotic Bcl protein in the glaucomatous model was documented by several studies.[16,18] In comparison, Bcl-xl activity was decreased due to proteolytic, cleavage altered formation of Bcl-xL-mediated multiprotein complexes and altered accessibility of microRNA to mRNA.[19]

The elderly, as one of risk factors of glaucoma, were observed to have a lower level of coenzyme Q10 (CoQ10) in the retina than in the younger (< 30 years old).[20] Therefore, CoQ10 supplementation may have the potential to inhibit RGC death under oxidative stress condition in glaucomatous eyes.[21] Our study included 5 studies on this subject that evaluated the mean number of retinal cells following CoQ10 administration.[9–13] Regardless of difference in the glaucoma-induced animal models, acute IOP elevation-induced ischemic retinal degeneration or aged inherited glaucomatous model, the mean difference in retina ganglion cell count was significantly larger in the CoQ10 group than in control studies ($p<0,001$).[9,11-13] There were no differences in mean retinal ganglion cell count between subgroups of aged glaucoma animal model and acute IOP induced glaucoma.

Evidence suggests that CoQ10 supplementation may protect RGCs by modifying the apoptotic pathway regulated by Bax/Bad/BcL-xL. Bax, a pro-apoptotic member of the Bcl-2 family, plays a critical role in various apoptotic pathways by directly interacting with a component of the mitochondrial permeability transition pore (MPTP) that allows proteins to be released from the mitochondria into the cytosol, initiating apoptosis. Dephosphorylation of Bad leads to the formation of heterodimers with Bcl-xL, resulting in the inactivation of Bcl-xL. When the process of dimerization is prevented by p-Bad, Bax becomes activated. CoQ10 in ischemic retina may enhance the p-Bad-mediated endogenous repair process, which protects against the apoptotic pathway. It also prevents the Bax-mediated increase of MPT and helps preserve mitochondrial homeostasis.[16]

In this review, we found that animal model studies show significant RGC survival after CoQ10 supplementation presented with lower Bax expression. Edwards, et al, showed 50% lower Bax expression after CoQ10 supplementation.[13] Similar results were presented by Ju, et al.[11] Bax expression is lower in CoQ10 groups showing a possible mechanism in inhibiting RGC cell death in glaucomatous rodents ($p<0,001$).

In response to oxidative stress, damaged ischemic retinal ganglion cells produce several physiological antioxidants. Superoxide dismutase (SOD), as a ROS-scavenging antioxidant enzyme, showed a protective role against oxidative stress that induced retinal ganglion cell death. SOD is composed of cytosolic SOD1 and mitochondrial SOD2, both of which are expressed in the ganglion cell layer (GCL) and inner plexiform layer.[22] Studies found a significant increase inSOD2 protein expression in the aged glaucomatous model and IOP-induced glaucoma model. However, CoQ10 supplementation decreases SOD2 expression in both glaucomatous models.[9,12] SOD2, which is localized in the mitochondrial matrix, catalyses the dismutation of superoxide radicals through transition metal ions present at the active site.[23] By reducing oxidative stress and nitrosative stress, SOD expressions may prevent retinal ganglion cell

apoptosis in glaucomatous models. CoQ10 supplementation could also reduce superoxide anion transformation and prevent oxidative stress in the glaucomatous model.[9,12]

Another enzyme known for anti-apoptotic and anti-inflammatory properties was hydrogen oxygenase (HO)-1. It was expressed under oxidative stress conditions and significantly reduced apoptosis and injury of RGC in glaucomatous eyes.[24] HO enzymes' main function was to catalyse heme degradation to Fe^{2+}, biliverdin and carbon monoxide (CO). As the last product of heme degradation, CO has anti-apoptotic, anti-proliferative and anti-inflammatory effects.

CoQ10 supplementation has also shown neuroprotective properties in retinal glial cells against oxidative stress.[9,11,12] Astrocytes in resting states, form the retinal-blood barrier, regulate neuronal activity, and maintain homeostasis. In glaucomatous eyes, reactive astrocytes form astrocytic scars and prevent degenerative effects followed by GFAP upregulation.[25] CoQ10 supplementation prevented activation of astroglial cells in the glaucomatous eye by blocking oxidative stress. Studies showed a significant decrease in GFAP expression, an intermediate filament of the glial cell cytoskeleton, in the CoQ10-supplemented glaucomatous model compared to the placebo glaucomatous model.[9,11,12]

This review has several limitations. Heterogeneity, which includes variations in participant characteristics, interventions, and outcome measures, may make it more difficult to perform a pooled analysis and derive conclusive findings from all the included research. To minimize the possibility of overlooking pertinent studies and guarantee the selection of high-quality research, we addressed these restrictions by executing a thorough search strategy across several databases and enforcing stringent inclusion criteria. In addition, our study contained a meta-analysis, which increased the statistical power of our investigation and enabled a quantitative synthesis of the data.

In conclusion, the results of this systematic review showed the protective properties of CoQ10 supplementation by reducing the number of RGC apoptosis in the glaucomatous model. CoQ10 promotes RGC survival by inhibiting oxidative stress, blocking the Bax/Bad-mediated mitochondrial apoptotic pathway, and preserving the reaction of glial. Our systematic review and meta-analysis may contemplate further extensive research on human subjects.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

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Authors Designation and Contribution

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