Research Article

Effect of red ginseng on visual function and vision-related quality of life in patients with glaucoma

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ABSTRACT

Background: Red ginseng has been found to improve ocular perfusion and dry eye syndrome in glaucomatous eyes; however, its effects on visual function and vision-related quality of life have not been investigated. This study sought to evaluate the effects of red ginseng on visual function and vision-related quality of life in glaucoma patients using contrast sensitivity and a questionnaire.

Methods: Participants were randomly assigned to two groups in this prospective, randomized, double-blind study: in one group, red ginseng was taken first, followed by a placebo, and in the other, placebo was taken first, followed by red ginseng. We measured and compared changes in contrast sensitivity and vision-related quality of life between the two groups. Contrast sensitivity was measured using OPTEC® 6500P, and vision-related quality of life was evaluated using the 25-item National Eye Institute Visual Function Questionnaire. One-way and two-way repeated measure analyses of variance were used for the comparison. Relationships between respective changes in dry eye syndrome and contrast sensitivity were also analyzed.

Results: Daytime contrast sensitivity and ocular pain improved after the administration of red ginseng. Nighttime contrast sensitivity was improved in early or moderate glaucoma. Improved contrast sensitivity was not associated with improvement in dry eye syndrome.

Conclusion: Red ginseng could improve contrast sensitivity and ocular pain in patients with glaucoma. The mechanism underlying improvement in contrast sensitivity appears to be associated with enhanced retinal perfusion or retinal ganglion cell function, but not dry eye syndrome.

1. Introduction

Glaucoma, one of the leading causes of blindness worldwide, is characterized by progressive optic neuropathy with specific changes in the optic disc and visual field (VF) loss. Although the first line of treatment for glaucoma is intraocular pressure reduction with anti-glaucoma eye drops, oral supplements have also gathered interest for the management of glaucoma. For example, Gingko biloba has been reported to improve VF in patients with normal-tension glaucoma [1], while Forskolin and Rutin have been found to help control intraocular pressure [2,3].

Ginseng (Panax ginseng Meyer, Araliaceae) is a folk remedy that is widely used in East Asian countries. Ginseng is processed into red ginseng after steaming and drying or white ginseng after simple drying, since fresh ginseng degrades easily at room temperature. Red ginseng is known to elicit greater biological effects, because the steaming process results in the formation of active constituents, such as Rh4 and Rf2, which have higher pharmacological activity [4,5]. Red ginseng has been reported to be effective in cardiovascular disease, cerebrovascular disease, and Alzheimer's disease [6–9]. Moreover, research has indicated that red ginseng also improves ocular perfusion and dry eye in patients with glaucoma [10,11]. However, these studies involved a few limitations: one study focused on dry eye syndrome and its symptoms, while the

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effects of ginseng on visual function in glaucoma eyes were not evaluated [11]. Another study reported improvement in peripapillary blood flow, but failed to show improvement in VF after ginseng administration [10]. Since VF in glaucomatous eyes changes very slowly, VF may not be a good parameter with which to assess visual function after short-term drug administration. Thus, studies using other methods to evaluate visual function are needed. Also, no research has investigated vision-related changes in quality of life.

This study aimed to evaluate the effects of red ginseng on visual function and vision-related quality of life in patients with glaucoma. Visual function was evaluated using contrast sensitivity and the mean deviation (MD) of VF exams. Questionnaire was used to assess vision-related quality of life. We also analyzed correlations between changes in visual function and in dry eye to determine whether observed changes in visual function are induced by improvement in dry eye syndrome.

2. Materials and methods

2.1. Ethical statement

This prospective, randomized, double-blind, placebo-controlled, crossover study was performed at the glaucoma clinic of Severance Hospital, Seoul, Korea. The study was conducted in accordance with the Declaration of Helsinki, and informed written consent was obtained from each participant. The institutional review board of the Yonsei University Health System approved the study protocol (IRB 4-2019-0090).

2.2. Participants

This study enrolled patients with glaucoma who agreed to participate in the study between June 2019 and February 2020. Assessed by a glaucoma specialist (H.W.B.), glaucomatous eyes were defined by the presence of a glaucomatous VF defect confirmed by two reliable VF tests and the typical appearance of a glaucomatous optic nerve head, including cup-to-disc ratio > 0.7; inter-eye cup asymmetry > 0.2; neuroretinal rim notching, focal thinning, and disc hemorrhage; or vertical elongation of the optic cup. Patients with an occludable angle, history of ocular surgery within 3 months of enrollment in the study, or other diseases affecting VF were excluded. Women of childbearing age were also excluded. Ophthalmic surgery was prohibited during the study period.

2.3. Study design

Patients were randomized to the following two groups: the first group took 3.0 g of Korean Red Ginseng (KRG) (KRG group) orally every day for 4 weeks, followed by an 8-week washout period, and subsequent placebo intake for 4 weeks. The second group (placebo group) took the placebo first, followed by KRG, and the duration of drug use and washout period were the same as those in the first group. The medication and washout periods were determined by referring to a previous study performed by our group [10]. The KRG and placebo regimens were as follows: KRG 1 g (two 500 g powder capsules) was taken thrice daily; two identically shaped capsules of the placebo were also taken three times daily. KRG powder was manufactured by the Korea Ginseng Corporation (Seoul). The roots of a 6-year-old Panax ginseng were harvested in Korea, followed by steaming at 90−100°C for 3 h, subsequent drying at 50−80°C, and grinding. The KRG extract contained major ginsenosides Rb1, 5.61 mg/g; Rb2, 2.03 mg/g; Rc, 2.20 mg/g; Rd, 0.39 mg/g; Re, 1.88 mg/g; Rf, 0.89 mg/g; Rg1, 3.06 mg/g; Rg2s, 0.15 mg/g; Rg3s, 0.17 mg/g; Rg3r, 0.08 mg/g; and other minor ginsenosides. The placebo

capsules, also provided by the same organization, were identical in size, weight, color, and taste. They were filled with corn starch 95.25%, red ginseng fragrance 4.0%, natural food color 0.15%, and caramel food color 0.6%. Participants were instructed to avoid taking other forms of KRG or another type of ginseng until the end of the study.

Participants and researchers were both masked to the treatment allocation. The medication was masked and coded by the manufacturer. An independent researcher distributed the patients into groups according to computer-generated randomized numbers. The boxes were labeled with the study numbers and recorded in a separate database that identified which box contained the KRG and placebo. These data were concealed until the study was completed. Right before scheduled visits, an independent researcher called the participants to ensure that they had taken the planned medications. Participants were re-checked to make sure they were taking planned medicines by bringing any leftover medicine or empty boxes at each visit.

2.4. Visual acuity, intraocular pressure, blood pressure, and VF examinations

Visual acuity was measured with the Snellen chart and converted to logMAR values. Intraocular pressure was determined using a Goldmann applanation tonometer. Arterial blood pressure was measured at the right upper arm using an automated oscillometric device. Three consecutive readings were obtained 5 min apart, and the last two were averaged for use in the analysis. All examinations were performed while the patients were seated. Visual acuity, intraocular pressure, and blood pressure were measured at each visit. VF examinations were also performed at the same time. All VF tests were performed using standard automated perimetry (Humphrey Field Analyzer II with the Swedish interactive thresholding algorithm standard 24-2; Carl Zeiss Meditec, Dublin, CA, USA). The VF test was repeated if it was not reliable. A reliable test was defined as one with false-positive errors < 15%, false-negative errors < 15%, and fixation loss < 20%. All VF tests were performed with the best correction for near vision for each patient.

2.5. Dry eye evaluation

Tear break-up time (TBUT) was measured using the following procedure: A fluorescein strip (Haag-Streit AG, Köniz, Switzerland) was applied with a drop of saline solution and placed on the inferior palpebral conjunctiva. Patients were asked to blink several times to mix the fluorescein with the tear film and were then instructed to open their eyes and not blink. The time between eye opening and the appearance of the first dry spot was measured in seconds. This procedure was repeated three times, and the average of the three measurements was recorded. Corneal fluorescein staining was performed by applying 5% fluorescein to the inferior conjunctival sac of both eyes. The cornea was subsequently examined with slit-lamp biomicroscopy using cobalt blue light 3 min after fluorescein instillation. Punctate staining was performed in a masked fashion, using a standardized (National Eye Institute) grading system (0 to 3) for each of the five subdivisions of the corneal surface [12]. The Schirmer I test was performed under anesthesia. All ocular structures were anesthetized by applying more than three drops of topical anesthetic (0.5% proparacaine hydrochloride ophthalmic solution 0.5%) to the conjunctiva and margins of the upper and lower lids. A Schirmer strip was subsequently placed over the lower lid 2 mm lateral to the lateral canthus. Patients were asked to close their eyes for 5 min, after

which the strip was removed and the length of the wet area of the strip was measured in millimeters.

2.6. Contrast sensitivity

Contrast sensitivity refers to the ability to distinguish differences in luminance, which reportedly decreases in several ophthalmic conditions [13,14]. We measured contrast sensitivity using slides of the Functional Acuity Contrast Test chart in OPTEC® 6500P (Stereo Optical Co., Inc., Chicago, IL). The stimuli included linear sine-wave grating charts of 1.5, 3, 6, 12 and 18 cycles per degree [13] in nine circular grating charts (diameter: 1.7°) arranged in two rows (five patches above, four patches below) (Supplemental Fig. 1). The back transitioned into a gray field to maintain retinal illumination and prevent ghost image formation. The participants were asked to report the direction of the stripe pattern to either the left, upside, or right, and the last response for each spatial frequency was recorded. The three-alternative forced-choice method was abandoned after the first wrong reply. Testing was performed under two different conditions: day (photopic: 85 cd/m^2) and night (mesopic: 3.0 cd/m^2) without any additional light glare. The tests were always started at the lowest spatial frequency.

2.7. Vision-related quality of life

Vision-related quality of life was assessed using the validated Korean version of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) [15]. The NEI VFQ-25 consists of 25 items that measure vision-related quality of life and are grouped into 12 subgroups: general health (one item), general vision (one item), ocular pain (two items), difficulty with near-vision activities (three items), difficulty with distance-vision activities (three items), limitation of social functioning because of vision (two items), mental health problems because of vision (four items), role limitations because of vision (two items), dependency on others because of vision (three items), driving difficulties (two items), difficulty with color vision (one item), and difficulty with peripheral vision (one item). Each sub scale score was converted to a score ranging between 0 and 100. Higher scores indicated better vision-related quality of life. The composite NEI VFQ-25 score was the mean score of all items, except for the general health item.

2.8. Statistical analysis

The carryover effect, which could be induced by the crossover study design, was analyzed using a linear mixed model. Variables identified as having a significant carryover effect were excluded from further analysis. Differences in variance between and after medication were analyzed by one-way repeated measure analysis of variance in the placebo and KRG groups, respectively. To compare the effects of KRG in relation to placebo, two-way repeated measure analysis of variance was used. Contrast sensitivity was evaluated by calculating and comparing area under contrast sensitivity curves [16–18]. We performed subgroup analysis by dividing the participants according to the components of the eyedrops (benzalkonium chloride [BAK] versus non-BAK and prostaglandin analog [PG] versus non-PG) if the variables for dry eye exhibited significant changes after KRG administration. The purpose of this subgroup analysis was to identify possible mechanisms for the improvement of dry eye syndrome and to determine if they could be applied to improvement of visual function and vision-related quality of life. We assessed differences before and after treatment between dry eye symptoms and contrast sensitivity, respectively, and then compared them using a linear mixed model. Statistical analysis was performed using R software v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). *P* values < 0.05 were considered significant.

3. Results

A total of 40 patients participated in this study. Two participants were excluded because they stopped taking the medication, and 76 eyes of 38 participants were included in the final analysis (Fig. 1). The participants' mean age was 58.8 ± 13.5 years, and another baseline characteristic is described on Table 1.

No significant carryover effect was observed in the outcome measurements except for the Schirmer test (supplemental table). Therefore, the results of the Schirmer test were not further analyzed in this study. The clinical variables before drug administration did not differ significantly between the placebo and KRG groups (all P > 0.05).

Intraocular pressure, systolic and diastolic blood pressure, corneal erosion, and MD of the VF did not differ significantly between the placebo and KRG groups. In the placebo group, the pre-treatment and post-treatment systolic blood pressure values were 121.6 ± 13.2 mmHg and 121.4 ± 16.3 mmHg, respectively, while the pre-treatment and post-treatment diastolic blood pressure values were 70.8 ± 11.1 mmHg and 71.3 ± 12.2 mmHg, respectively. In the KRG group, the pre-treatment and post-treatment systolic blood pressure values were 121.1 ± 14.5 mmHg and 122.8 ± 14.1 mmHg, respectively, while the pre-treatment and post-treatment diastolic blood pressure values were 71.5 ± 11.8 mmHg and 72.1 ± 10.6 mmHg, respectively. Changes in systolic and diastolic blood pressure did not differ significantly between the KRG group and placebo group (P = 0.514 and P = 0.936, respectively). TBUT improved in the KRG group, and the improvement was more significant than that of the placebo group (Table 1, Fig. 2). The improvement in TBUT was greater in the non-PG and non-BAK groups than in the PG group and BAK group, respectively (P = 0.011 and P < 0.001 respectively, Fig. 2).

The MD of the VF test improved in the placebo group. Although the MD of the VF test also improved in the KRG group, it was not as prominent as that in the placebo group (Table 2). There was no significant difference between the improvement of MD in the placebo and KRG groups (Table 2).

Daytime contrast sensitivity improved in the KRG group, and the improvement differed significantly from than that in the placebo group (Table 2, Fig. 3). Nighttime contrast sensitivity showed greater improvement in the KRG group, compared to the placebo group, although the difference was not statistically significant (Table 2, Fig. 3). However, analysis of early or moderately glaucomatous eyes (MD ≥ −12.0 dB) revealed that both daytime and nighttime contrast sensitivity improved in the KRG group (P = 0.002 and P = 0.004, respectively), and the improvement differed significantly from that in the placebo group (P = 0.038 and P = 0.026, respectively) (Fig. 3). The increases in daytime and nighttime contrast sensitivity induced by KRG were not associated with an increase in TBUT (P = 0.678 and P = 0.964, respectively) (Fig. 4).

The NEI VFQ 25 scores are presented in Table 3. The ocular pain score improved in the KRG group, and its effect differed significantly from that in the placebo group (Table 3). Distance activities score decreased in the placebo group, but not in the KRG group, and the difference was statistically significant (Table 3). Differences in other scores were not significant.

4. Discussion

This study investigated the effect of KRG on dry visual function and vision-related quality of life in patients with glaucoma. KRG
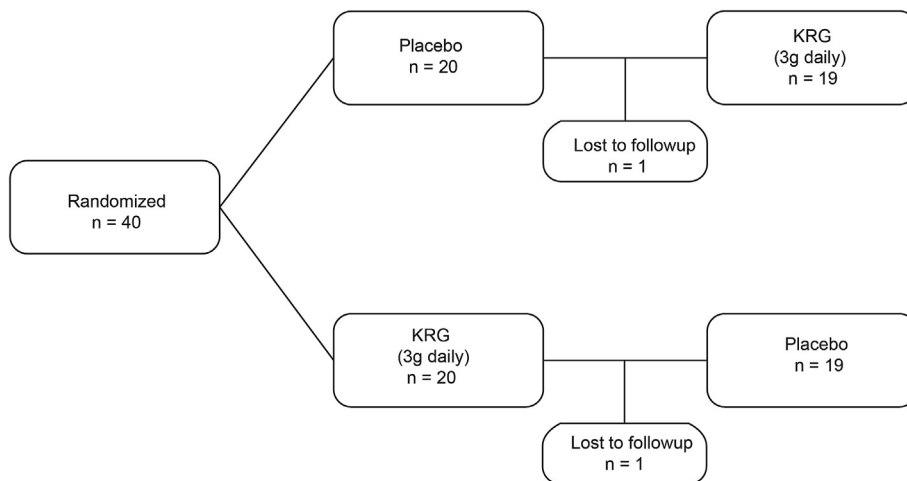
Fig. 1. Participant enrollment flowchart.

Table 1
Baseline characteristics of the study patients

Variables	
Number of patients	38
Age (Yrs)	58.8 ± 13.5
Female (n, %)	18 (47.4%)
Number of eyes	76
Baseline visual acuity (logMAR)	0.3 ± 0.4
Baseline visual field mean decibel (dB)	−5.4 ± 5.7
Type of glaucoma medication, prostaglandin analogue (n, %)	42 (55.3%)
Medication containing benzalkonium chloride (n, %)	58 (76.3%)

Data are expressed as means ± standard deviations.

improved day contrast sensitivity and patient-reported ocular pain. Nighttime contrast sensitivity also improved in eyes with early or moderate glaucoma. TBUT was improved by KRG, although the relationship between respective improvements in TBUT and contrast sensitivity were not significant.

Oral administration of KRG improved TBUT, and the effect was more significant in the non-BAK and non-PG groups, although significant improvements were also observed in the BAK and PG groups. It has been reported that KRG improves TBUT and subjective dry eye symptoms in glaucomatous eyes [11], which is consistent with the findings of the present study. However, the
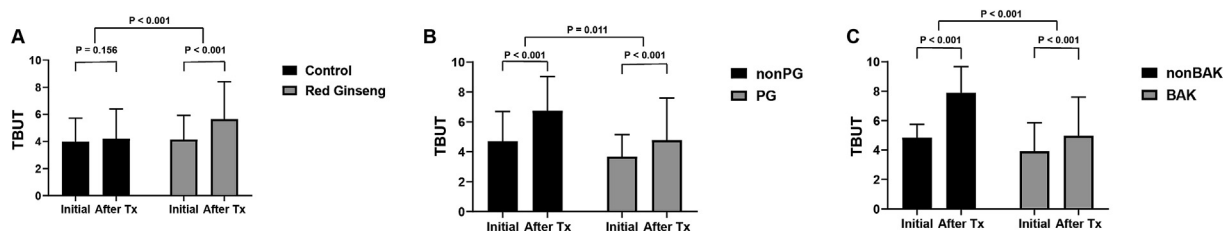

Fig. 2. (A) Changes in tear break-up time (TBUT) before and after treatment. (B) Changes in TBUT before and after Korean Red Ginseng administration. Group using eye drops with prostaglandin analog (PG) and group using eye drops without prostaglandin analog (non-PG). (C) Changes in TBUT before and after Korean Red Ginseng administration. Group using eye drops containing benzalkonium chloride (BAK) and group using eye drops without BAK (non-BAK).

Table 2
Comparison of variables before and after treatment: Placebo group and Korean Red Ginseng group

Medication	Placebo			KRG			
Month	0	1	P^a	0	1	P^a	P^b
	(N = 76)	(N = 76)		(N = 76)	(N = 76)		
Visual acuity (logMAR)	0.3 ± 0.5	0.3 ± 0.5	>0.999	0.3 ± 0.5	0.3 ± 0.5	0.375	0.568
IOP	13.3 ± 1.8	13.5 ± 1.9	0.462	13.5 ± 2.1	13.4 ± 2.1	0.658	0.476
TBUT	4.0 ± 1.8	4.2 ± 2.2	0.156	4.1 ± 1.8	5.7 ± 2.8	**<0.001**	**<0.001**
Cornea staining	6.4 ± 5.2	6.0 ± 5.7	0.366	6.2 ± 6.2	5.5. ± 5.8	0.160	0.699
MD	−5.4 ± 5.7	−4.8 ± 5.7	**0.006**	−5.5 ± 5.3	−5.1 ± 5.5	0.092	0.543
Daytime contrast sensitivity	414.3 ± 243.1	422.7 ± 239.2	0.445	419.4 ± 238.9	466.5 ± 259.4	**0.004**	**0.033**
Nighttime contrast sensitivity	247.6 ± 206.7	254.4 ± 166.9	0.682	264.0 ± 214.2	303.7 ± 222.6	**0.016**	0.098

Data are expressed as means ± standard deviations. P values were calculated using t-tests. P < .05 indicates statistical significance (presented in bold type).
KRG, Korean Red Ginseng; IOP, intraocular pressure; TBUT, tear break-up time; MD, mean deviation of the visual field test.
[a] P values were derived from one-way repeated measure analysis of variance for baseline and 1-month visits in each group.
[b] P values were derived from two-way repeated measure analysis of variance for changes in the KRG and placebo groups.
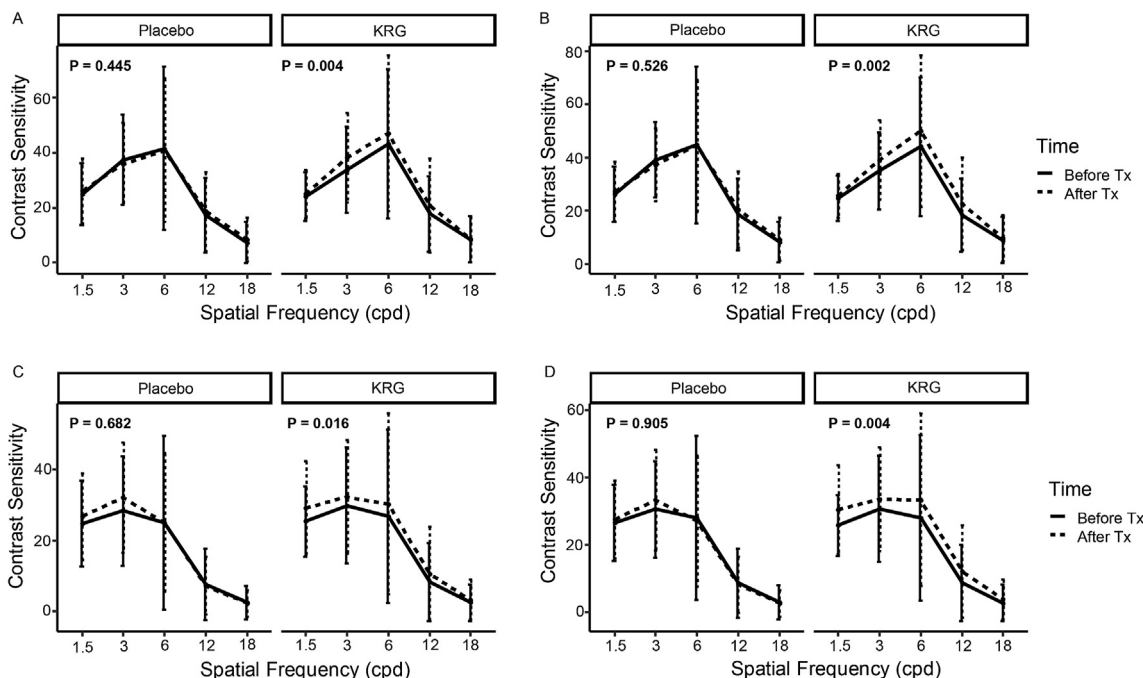
Fig. 3. Contrast sensitivity before and after treatment (placebo and Korean Red Ginseng [KRG]). (A) Daytime contrast sensitivity for all eyes (B) Daytime contrast sensitivity for eyes with early or moderate glaucoma (mean deviation ≥ −12.0 dB). (C) Nighttime contrast sensitivity for all eyes. (D) Nighttime contrast sensitivity for eyes with early or moderate glaucoma (mean deviation ≥ −12.0 dB).
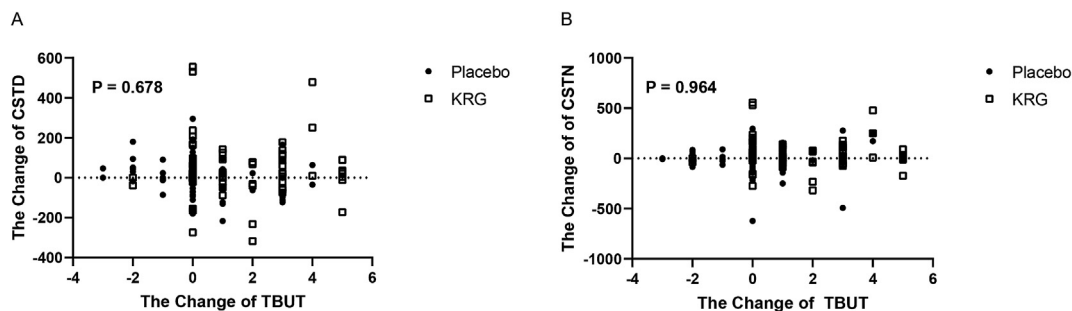

Fig. 4. (A) Scatter plot showing the relationship between changes in daytime contrast sensitivity (CSTD) and tear break-up time (TBUT). (B) Scatter plot showing the relationship between changes in nighttime contrast sensitivity (CSTN) and TBUT. The change in contrast sensitivity was not correlated with that in TBUT (P = 0.678 and P = 0.964, respectively).

greater significance of the effect of KRG in the non-BAK and non-PG groups is a novel finding of this study. Ginsenosides, which are unique saponins found in the Panax species, are believed to be responsible for most of the pharmacological actions of ginseng, which include anti-inflammatory activity [19–21]. Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and Rg2 have been reported to possess anti-inflammatory properties [22]. Although dry eye is a multifactorial disease, recent studies have shown that inflammation plays a pivotal role in its pathogenesis [23]. The anti-inflammatory effect of KRG is thought to have improved tear film instability, consequently increasing the TBUT. However, these anti-inflammatory effects appear to be inhibited by ocular inflammation caused by BAK or PG [24,25]. Nevertheless, our results showed that KRG can be used as an effective treatment modality for treating dry eye in patients with glaucoma.

VF MD increased in the placebo and KRG groups, without any significant difference between them. However, one should consider that KRG was administered only for 4 weeks, when interpreting these results. Glaucoma is a slow progressive disease, which

advances over a long period of time; therefore, a period of 4 weeks is probably insufficient to evaluate disease progression. A previous study that administered KRG for 12 weeks also showed no significant effect on VF [10]. Therefore, research of longer than 12 weeks is needed to investigate whether KRG intake can improve VF MD. Similarly, one study reported that Gingko biloba improved MD in VF after oral administration for an average of 24 months [26], although another study reported conflicting results: Gingko biloba administration for 4 weeks did not have any significant effect on VF [27]. Otherwise, the functional improvement induced by KRG may not be large enough to be detected by VFtest, which supports a previous study that administered KRG for 12 weeks and reported no significant changes in VFindices [10]. Therefore, further studies are recommended to determine whether improvement in VFresults could be induced by a longer period of KRG administration. On the other hand, the improvement in VF MD identified in this study could be explained by the learning effect. The learning effect is a phenomenon in which a result is improved as an inexperienced participant repeats the test. Previous studies have shown that MD

Table 3
Comparison of NEI-VFQ 25 scores before and after treatment: Placebo and Korean Red Ginseng groups

Medication	Placebo			KRG			
Month	0	1	P^a	0	1	P^a	P^b
	(N = 38)	(N = 38)		(N = 38)	(N = 38)		
General health	50.7 ± 15.9	52.0 ± 17.8	0.624	52.6 ± 18.2	52.0 ± 18.7	0.845	0.649
General vision	57.4 ± 16.9	56.8 ± 17.1	0.850	58.9 ± 14.7	54.2 ± 19.1	**0.048**	0.263
Ocular pain	81.6 ± 19.9	81.9 ± 18.3	0.868	76.3 ± 21.3	85.9 ± 17.0	**<0.001**	**0.002**
Near activities	78.7 ± 18.0	75.4 ± 19.5	0.129	78.3 ± 17.8	79.4 ± 17.6	0.515	0.154
Distance activities	83.1 ± 16.8	78.5 ± 15.3	**0.022**	82.5 ± 14.5	83.6 ± 17.4	0.529	**0.027**
Social functioning	87.5 ± 18.6	88.8 ± 16.4	0.487	88.2 ± 18.1	88.2 ± 17.4	0.999	0.566
Mental health	74.5 ± 20.5	75.8 ± 19.9	0.551	73.9 ± 22.4	77.5 ± 19.3	0.108	0.458
Role difficulties	77.6 ± 25.0	76.3 ± 22.7	0.593	80.9 ± 22.8	77.6 ± 24.0	0.077	0.547
Dependency	88.7 ± 16.6	87.1 ± 18.1	0.337	89.0 ± 18.7	89.9 ± 16.0	0.606	0.276
Driving	84.1 ± 13.4	82.9 ± 15.2	0.545	82.9 ± 13.6	85.7 ± 12.4	0.149	0.178
Color vision	92.1 ± 16.5	92.8 ± 11.5	0.786	92.8 ± 12.9	91.4 ± 14.6	0.487	0.543
Peripheral vision	86.2 ± 17.1	84.9 ± 16.0	0.644	83.6 ± 17.7	84.2 ± 19.6	0.831	0.635
Composite	80.8 ± 14.9	79.9 ± 13.1	0.447	80.4 ± 14.4	81.3 ± 14.0	0.404	0.254

Data are expressed as mean ± standard deviation. p-values were calculated with t-tests. p < .05 indicates statistical significance (presented in bold type).
KRG, Korean Red Ginseng; TBUT, tear break-up time; NEI-VFQ 25, National Eye Institute Visual Function Questionnaire (25 items).
[a] P values were derived from one-way repeated measure analysis of variance for baseline and 1-month visits in each group.
[b] P values were derived from two-way repeated measure analysis of variance for changes in the KRG and placebo groups.

improved in subsequent tests, compared to the initial test, due to the learning effect [28], which is consistent with the results of our study.

Contrast sensitivity, which is a parameter of visual function, improved. Decreased contrast sensitivity has been reported in glaucomatous eyes [29–32] and may be an important cause of deteriorating vision. Therefore, the results of our study indicating that KRG improves contrast sensitivity is notable in that KRG could contribute to the treatment of glaucoma. However, the mechanism underlying this improvement is unclear. Based on our analysis, the improvement in contrast sensitivity was not related with that in dry eye syndrome. Increased retinal perfusion could be the reason of this improvement since retinal circulation has been reported to have an important role in influencing contrast sensitivity [33]. Meanwhile, KRG has been reported to increase ocular blood flow [10], and ginseng extract has been found to protect against diabetes-induced retinal microvascular damage [34]. It is also known that as glaucoma progresses, microvascular damage occurs, resulting in reduced perfusion [35]. KRG may be able to prevent such glaucoma-related damage and improve contrast sensitivity. Another possible explanation for the improved contrast sensitivity is that ginseng could improve the function of retinal ganglion cells. Red ginseng has been reported to increase of the amplitude of electroretinography b wave peak, suggesting that red ginseng extract may modulate the retinal neural network, including Muller cells and bipolar cells [34]. Likewise, KRG may enhance the function of the inner retina, including retinal ganglion cells, and elicit improvement in contrast sensitivity. Further investigations are needed to analyze the relationship between retinal perfusion, light responses of the retina, and contrast sensitivity.

In this study, we found that KRG had effects on vision-related quality of life (measured by a questionnaire). Ocular pain improved in the KRG group, compared to the placebo group. Improvement in dry eye could have resulted in the amelioration of this pain, since it is one of the principal causes of ocular pain [36]. This finding is consistent with previous studies, which reported that TBUT is related to dry eye symptoms [37,38]. Meanwhile, distance activities scores worsened in the placebo group, but did not change significantly in the KRG group. Short-term follow-up may be responsible for the apparent impairment in the perception of distance activities. Improved contrast sensitivity could have prevented the reduction in the distance activities score in the KRG group. However, other scores for vision-related quality of life did not change significantly. KRG treatment for 4 weeks may not be sufficient to significantly alter vision-related quality of life.

This study has several limitations. First, the administration period in this study was 4 weeks, based on a previous study that analyzed the effects of other oral supplements on glaucoma [27]. However, this period may not be sufficient to demonstrate the efficacy of KRG on glaucoma. Nevertheless, dry eye may be improved by even short-term administration. The insignificant relationship between the improvement in contrast sensitivity and that of TBUT could be attributed to the fact that administration of KRG for 4 weeks could induce a greater improvement in dry eye than that in ocular function. Second, we did not measure ocular perfusion or electrical responses of retinal ganglion cells. Recently, several methods, such as optical coherence tomography angiography and pattern electroretinography, have been introduced to measure ocular perfusion and electrical responses of retinal ganglion cells, respectively. Measuring these variables can identify the mechanism of improvements in visual function induced by KRG administration. Third, the sample size of the study was relatively small. We enrolled 40 participants, and 38 completed the entire study until follow-up. This sample size was calculated based on a previous study, which investigated the effect of KRG on dry eye [11]. It is recommended to determine the sample size based on past research on KRG and visual function to obtain more accurate results. However, this was difficult because of the scarcity of previous studies on these relationships.

In conclusion, KRG administration improved contrast sensitivity and patient-reported ocular pain, as well as TBUT. The anti-inflammatory effect of KRG may have improved tear film stability and patient-reported ocular pain. KRG also improved visual function in patients with glaucoma, the underlying mechanism of which is thought to differ from that of dry eye and may be attributed to increased retinal perfusion or improved retinal ganglion cell function. Our results suggest that KRG could be a useful adjunct treatment for improving visual function and reducing ocular discomfort in patients with glaucoma.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2021.03.004.

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