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ORIGINAL PAPER

Ginkgo Biloba affects microvascular morphology: a prospective optical coherence tomography angiography pilot study

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Abstract

Purpose To analyze the vascular morphology changes after consumption of *Ginkgo biloba* in healthy volunteers by optical coherence tomography angiography (OCTA).

Methods Sixty healthy volunteers without systemic and ocular disease were included in this prospective pilot study. After receiving the informed consent of the volunteers, *Ginkgo biloba* extract (120 mg oral capsule) was administered to sixty volunteers for 4 weeks, once a day in the morning. The main outcome measures were the difference between before and after four-week of consumption in best-corrected visual acuity (BCVA), retinal nerve fiber layer (RNFL) and subfoveal choroidal thickness (sfCT) with optical coherence tomography; whole, foveal, parafoveal and perifoveal regions' superior and deep macular vascular plexus vessel density, foveal avascular zone area (FAZ), FAZ perimeter (PERIM), vessel density in a 300 μm wide region around FAZ (FD-300), choroidal and outer retinal flow area, radial peripapillary capillary (RPC) vascular density of whole, inside the disc, peripapillary and four quadrants with OCTA.

Results The study group consisted of sixty eyes of 32 women and 28 men with a mean age of 20.57 ± 1.16 years. In post-consumption measurements, peripapillary and superior, inferior, temporal quadrant RPC vascular density (%) was statistically significantly higher than pre-consumption measurements (p 0.020, p 0.021, p 0.008 and p 0.014, respectively). No significant difference was observed for BCVA, sfCT, other macular or RPC vascular

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density and flow area OCTA parameters between measurements.

Conclusion Four-week consumption of *Ginkgo biloba* leads to vascular morphological changes in RPC. Further clinical studies are needed to demonstrate its use and effects/benefits in glaucoma, optic neuropathy and other diseases affecting the optic nerve.

Keywords Ginkgo biloba · Optic nerve head · OCTA · RPC · Microvascular morphology

Abbreviations

GBE	Ginkgo biloba extract
FAZ	Foveal avascular zone area
OCTA	Optical coherence tomography angiography
IOP	Intraocular pressure
OPP	Ocular perfusion pressure
AL	Axial length
BCVA	Best-corrected visual acuity
RNFL	Retinal nerve fiber layer
sfCT	Subfoveal choroidal thickness
SD-OCT	Spectral-domain optical coherence tomography
PERIM	Foveal avascular zone area perimeter
FD-300	Vessel density in a 300 μm wide region around the foveal avascular zone
RPC	Radial peripapillary capillary

Introduction

The maidenhair tree, known as *Ginkgo biloba*, has grown in popularity by spreading to Europe and other parts of the world after it was discovered in the Far East. In this section, there is a single class (Ginkgoopsida), a single order within the class (Ginkgoales), a single family within the order (Ginkgoaceae), a single genus within the family (*Ginkgo*), a single species within the genus (*Ginkgo biloba)* [1]. The extract of ginkgo leaves is increasingly used in the pharmaceutical field. *Ginkgo biloba* extract (GBE) consists of flavonoids, terpene lactones and other organic acids [2]. Flavonoids have anti-oxidative, anti-inflammatory, anti-carcinogenic and anti-mutagenic properties coupled with their capability to modulate key cellular enzyme function [3].

GBE is used in the treatment of vascular diseases such as peripheral vascular disease and cerebrovascular insufficiency due to its positive effect on blood circulation [4–6]. Despite many clinical controversies, many pieces of evidence have been shown to support its use as adjuvant therapy in patients with dementia, vascular cognitive impairment and schizophrenia [1, 5, 6]. There is a limited number of publications in the literature regarding its usefulness for ocular and especially peripapillary blood flow, but there is no complete consensus [7–9].

With optical coherence tomography angiography (OCTA) technology, quantitative morphological imaging of the vascular system at the retinal and choroid levels is possible at high speed and quality without using any invasive procedure [10–13]. With this technology, macular superficial and deep plexus microvascular density, foveal avascular zone (FAZ) features, choriocapillaris flow areas and optic nerve head vascular morphology can be measured quantitatively [14–16]. Therefore, the possible morphological effects of GBE consumption on the retina and optic nerve head vascular morphology have become evaluable.

In this study, we aimed to investigate the retinal and optic nerve head vascular morphological effects of GBE in healthy volunteers using optical coherence tomography angiography (OCTA).

Material and methods

Sixty-four healthy volunteers without systemic and ocular disease were included in this prospective pilot study. All procedures were performed by following the tenets of the declaration of Helsinki. Institutional review board approval was obtained from the local ethics committee (2011-KAEK-2) (Approval Code: 2020/3-120).

The following inclusion criteria were applied: (1) healthy volunteers between the ages of 18–30 years, (2) spherical refraction between -2.0 and $+2.0$ diopters and (3) $20 <$ axial length (AL) < 24 mm. The following exclusion criteria were applied: (1) the history of using any kind of nutritional supplements, including GBE, in the past month, (2) the history of using any kind of drug in the past month, (3) smoking

or alcohol use history in the past month, (4) failure to intake GBE capsules orally every morning for four weeks, (5) opacity on the cornea or lens in the anterior segment that prevents imaging, (6) having any systemic or ocular disease and (7) having a history of undergone any ocular surgery.

Whole volunteers underwent complete ophthalmological examination including a review of medical history, detection of the best-corrected visual acuities (BCVA), ocular movement and pupillary reflex examination, anterior segment examination using slit-lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometry and dilated fundus examination using slit-lamp biomicroscopy.

After receiving the informed consent of the volunteers, GBE (120 mg, oral capsule) was administered to sixty volunteers for four weeks, once a day in the morning. The 120 mg GBE commercial capsule contained 27% ginkgo flavone glycosides and 6.8% terpene lactones. The main outcome measures were the difference between before and after four-week of consumption in BCVA, retinal nerve fiber layer (RNFL) and subfoveal choroidal thickness (sfCT) using spectral-domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany); whole, foveal, parafoveal and perifoveal regions' superior and deep macular vascular plexus vessel density, foveal avascular zone area (FAZ), FAZ perimeter (PERIM), vessel density in a 300 μm wide region around FAZ (FD-300), choroidal and outer retinal flow area, radial peripapillary capillary (RPC) vascular density of whole, inside the disc, peripapillary and four quadrants using OCTA.

OCTA scans were taken with RTVue XR Avanti AngioVue OCTA (Optovue, Fremont, CA). OCTA scans were achieved by using a spectral-domain system with software AngioVue OCTA, version 2018.0.0.18. Central macular 6 × 6 mm scans were achieved using the AngioVue Imaging System Optovue RTVue XR 100 Avanti with software (Fig. 1). OCTA measurements were made accordingly

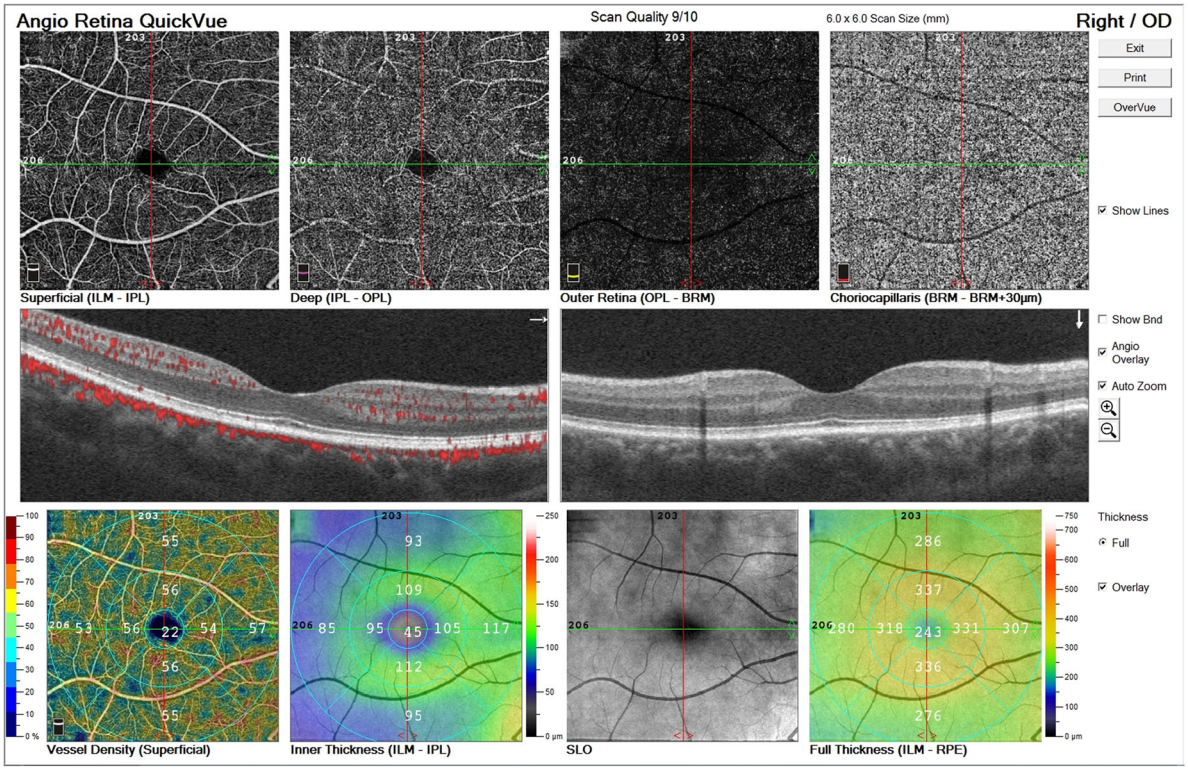

Fig. 1 En-face and cross-sectional images of superficial and deep vascular plexus, outer retina and choriocapillaris by optical coherence tomography angiography display (RTVue XR Avanti with the AngioVue, Optovue, Fremont, CA)

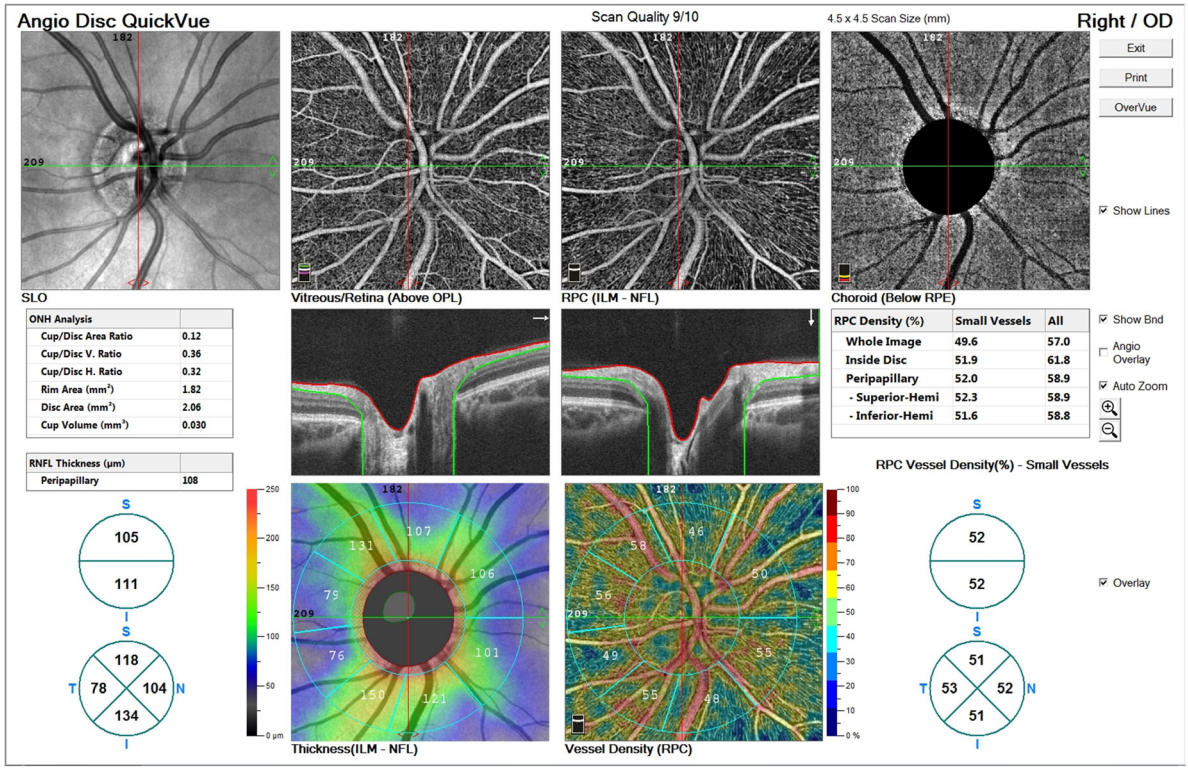

Fig. 2 En-face and cross-sectional images of the optic nerve head; visualization of RPC and RNFL by optical coherence tomography angiography (RTVue XR Avanti with the AngioVue, Optovue, Fremont, CA) (*RPC* Radial peripapillary capillary network, *RNFL* Retinal nerve fiber layer)

to the Early Treatment Diabetic Retinopathy Study grid, containing 3 concentric rings with diameters of 1, 3 and 6 mm to split the macula into foveal, parafoveal and perifoveal regions. The outer retinal and choroidal flow area of the 2.97 mm central macular circle diameter was determined with flow area circle mode in the software. The FAZ, PERIM and FD-300 were also obtained in the FAZ mode of the software by the OCTA. OCTA optical disc imaging was performed in Angio Disc OCTA mode with 4.5 × 4.5 mm, and RNFL and RPC values were obtained (Fig. 2). All scans were performed with the quality index of ≥ 7/10 to ensure accurate segmentation and adequate image quality. Poor-quality scans were excluded from this study. AL measurement was performed with AL-Scan (Nidek CO., Gamagori, Japan). The sfCT was defined as the distance from the hyperreflective line of the outermost retinal pigment epithelium to the innermost hyperreflective line of the choroidoscleral junction. The sfCT was performed semi-automatically measurement with an enhanced depth image mode of SD-OCT. Only the right eyes were included in the study. Blood pressure was noted on the participant file before and after four-week of GBE consumption. Ocular perfusion pressure (OPP) was calculated according to the formula: OPP = 2/3 [diastolic blood pressure + 1/3 (systolic blood pressure—diastolic blood pressure)–IOP [17]]. Axial length measurement was performed with AL-Scan (Nidek CO., Gamagori, Japan). OCTA and OCT analyses were performed in follow-up mode to aimed to minimize the errors between consecutive analyses. All measurements were made before and after four-week of consumption and then compared statistically with each other. All scans and measurements were performed by the same researcher at the same time of the day (between 9:00 A.M. and 10:00 A.M.) after at least 8 h starvation period to avoid diurnal fluctuations.

Statistical analysis

Statistical analysis was performed using SPSS software, version 22.0 (IBM SPSS, Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the data. The categorical variables were analyzed using the Chi-square test. All parameters were analyzed for distribution by the Shapiro–Wilk test for normality analysis. The variations in parameters were tested for significance using the Wilcoxon signed ranks test in the abnormal distribution and paired sample t test in the normal distribution for consecutive measurements. The evaluations were made at the 95% confidence interval, and the *p*-values of less than 0.05 were a statistically significant difference.

Results

After the inclusion and exclusion criteria were taken into account, the 2 participants were excluded from the study because they could not take the GBE capsule regularly in the morning every day, one participant left this study with own demand, and one participant excluded for the consumption of energy drinks in the study period. Consequently, the study group consisted of 60 eyes consisting of 32 women and 28 men with an average age of 20.57 ± 1.16 years. The demographic data of the study group are shown in Table 1. Only the right eyes of patients were included in the study. No complications or side effects were observed/reported in the four-week of consumption.

Table 1 Demographics of the study group

	Study group (*n*:60)
Age (year (mean ± SD)	20.57 ± 1.16
Male/female ratio	28:32
BMI (kg/m^2) (mean ± SD)	21.83 ± 1.41
Axial length (mm) (mean ± SD)	22.09 ± 1.73

BMI Body mass index

Results from the study group are summarized in Table 2. In post-consumption measurements, peripapillary and superior, inferior, temporal quadrant RPC vascular density (%) was statistically significantly higher than pre-consumption measurements (*p*:0.020, *p*:0.021, *p*:0.008 and *p*:0.014, respectively) (Fig. 3). No significant difference was observed for BCVA, systolic and diastolic blood pressure, sfCT, other macular or RPC vascular density and flow area OCTA parameters between measurements.

Discussion

In this study, using the OCTA in healthy volunteers, four-week consumption of GBE was observed to increase the RPC vascular density in peripapillary and superior, inferior, temporal quadrant regions. There was no significant change in other retinal or optic nerve head vascular density or flow parameters.

GBE contains more than sixty bioactive compositions, approximately thirty of which are found nowhere else in world nature [18, 19]. These include flavone glycosides, ginkgolides and bilobalide, proanthocyanidins and numerous other compounds [19]. Flavonoids can dilate blood vessels by increasing the release of endothelium-derived relaxing factor and prostacyclin, especially prostaglandin I2, from vascular endothelial cells, and decrease blood viscosity by antagonizing the platelet-activating factor [20]. Also, flavonoid glycosides and terpene lactones act as antioxidants by scavenging free radicals [21, 22]. In many animal studies, ginkgo's neuroprotective and antioxidant effects have been shown in the brain and eye [9, 23, 24]. Lu et al. [24] showed in their animal study that GBE has protective effects on several pharmacological targets in the progress of diabetic cataracts and is a remedy for the prevention of diabetic cataracts. There are a limited number of clinical studies on the effects of GBE on the optic nerve head and retina. Park et al. [7] showed that GBE administration appears to have a desirable effect on ocular blood flow in normal-tension glaucoma (NTG) patients and suggested that it is a beneficial systemic treatment for NTG patients. Quaranta et al. [18] showed that GBE administration appears to improve preexisting visual field damage in some patients with NTG. Similar results were reported by Ha et al. [25]. Lee et al. [26] showed that GBE slowed the

Table 2 Comparisons and results of pre-consumption and after four-week of GBE consumption measurements (*GBE* Ginkgo biloba extract)

Parameters	Pre-consumption of GBE	After four-week of GBE consumption	*p* value
BCVA (LogMAR)	0.000 ± 0.00 (0.000, 0.000–0.000)	0.000 ± 0.00 (0.000, 0.000–0.000)	1.000[a]
IOP (mm-Hg)	12.96 ± 2.36 (12, 11–15)	12.76 ± 2.01 (12, 11–14)	0.133[a]
Systolic blood pressure (mm-Hg)	113.28 ± 6.99 (111, 110–120)	113.33 ± 6.69 (110, 110–120)	0.729[a]
Diastolic blood pressure (mm-Hg)	72.67 ± 5.40 (70, 70–80)	71.83 ± 5.96 (70, 70–78.75)	0.250[a]
Calculated ocular perfusion pressure (mm-Hg)	44.27 ± 3.64	44.21 ± 3.51	0.899[b]
Quality index of OCTA images (x/10)	8.75 ± 0.51 (9.00, 9.00–9.00)	8.73 ± 0.52 (9.00, 9.00–9.00)	0.833[a]
Superior whole vascular density (%)	52.06 ± 2.10 (52.00, 51.10–53.20)	51.92 ± 2.65 (51.80, 50.30–53.20)	0.238[a]
Superior foveal vascular density (%)	22.67 ± 7.23 (22.30, 15.80- 28.80)	22.83 ± 8.99 (21.60, 16.70–28.90)	0.624[a]
Superior parafoveal vascular density (%)	54.47 ± 2.70	53.69 ± 3.24	0.056[b]
Superior perifoveal vascular density (%)	52.58 ± 2.23 (52.40, 51.50–54.40)	57.17 ± 6.43 (58.60, 54.60–61.80)	0.321[a]
Deep whole vascular density (%)	55.84 ± 5.91 (57.00, 54.00–60.30)	55.89 ± 5.58 (56.30, 53.00–60.40)	0.734[a]
Deep foveal vascular density (%)	41.16 ± 7.56 (42.30, 34.30–47.70)	40.68 ± 7.68 (40.70, 35.00–45.30)	0.383[a]
Deep parafoveal vascular density (%)	56.98 ± 8.11 (58.90, 55.30–61.20)	58.26 ± 4.71 (59.30, 54.80–62.00)	0.589[a]
Deep perifoveal vascular density (%)	57.17 ± 6.43 (58.60, 54.60–61.80)	57.30 ± 6.09 (58.20, 54.20- 62.00)	0.821[a]
FAZ (mm^2)	0.256 ± 0.100	0.257 ± 0.098	0.949[b]
PERIM (mm)	1.92 ± 0.39	1.93 ± 0.41	0.451[b]
FD-300 (%)	56.90 ± 2.84 (56.96, 54.81–58.18)	56.16 ± 3.66 (56.34, 53.60–59.20)	0.157[a]
Outer retinal flow area (%)	8.29 ± 1.87	8.75 ± 1.91	0.106[b]
Choriocapillaris flow area (%)	20.88 ± 2.27 (20.32, 19.98–20.56)	20.19 ± 1.79 (20.26, 19.86–20.69)	0.868[a]
sfCT (μm)	310.40 ± 41.24	312.33 ± 37.08	0.501[b]
RPC density whole image (%)	48.40 ± 2.25	48.81 ± 2.24	0.127[b]
RPC density inside disc (%)	53.41 ± 4.09	53.58 ± 3.99	0.676[b]
RPC density peripapillary (%)	49.92 ± 2.65	50.75 ± 2.59	0.020[b]
RPC density superior quadrant (%)	50.60 ± 3.28	51.67 ± 3.97	0.021[b]
RPC density inferior quadrant (%)	49.78 ± 3.70	51.09 ± 3.75	0.008[b]
RPC density temporal quadrant (%)	52.87 ± 3.13	53.74 ± 2.89	0.014[b]
RPC density nasal quadrant (%)	47.48 ± 3.66	48.10 ± 3.01	0.085[b]
Global RNFL (μm)	112.67 ± 8.44	112.64 ± 8.23	0.875[b]
RNFL superior quadrant (μm)	133.95 ± 11.76	134.09 ± 11.74	0.646[b]
RNFL inferior quadrant (μm)	141.38 ± 14.03	141.58 ± 13.47	0.572[b]
RNFL temporal quadrant (μm)	77.63 ± 9.93	78.17 ± 9.94	0.060[b]
RNFL nasal quadrant (μm)	98.95 ± 13.31	98.38 ± 13.11	0.090[b]

Mean ± standard deviation results were given in table (additionally, median, 25th and 75th percentiles were given in parenthesis for nonparametric test results). $p < 0.05$ was considered statistically different in 95% confidence interval

[a]Wilcoxon signed ranks test

[b]Paired sample t test results

BCVA Best-corrected visual acuity, *IOP* Intraocular pressure, *OCTA* Optical coherence tomography angiography, *FAZ* Foveal avascular zone, *PERIM* foveal avascular zone perimeter in mm, FD-300: vessel density 300 μm from the fovea, *sfCT* Subfoveal choroidal thickness, *RPC* Radial peripapillary capillary network and *RNFL* Retinal nerve fiber layer

progression of visual field damage in patients with NTG. Although controversial, ginkgo is recommended as an additional neuroprotective supportive therapy in glaucoma patients [27, 28]. In the study of Park et al. [7], they found increased blood velocity associated with GBE in the peripapillary area. Similarly, in this study, although we could not measure flow in the optic nerve head region due to the lack of OCTA device feature, the increase in retinal vascular density indirectly can be attributed to the increase in blood flow. The absence of macular vascular change, only a peripapillary change, may strengthen the relationship with blood flow. Furthermore, the optic nerve head may be the target of the antioxidant effect.

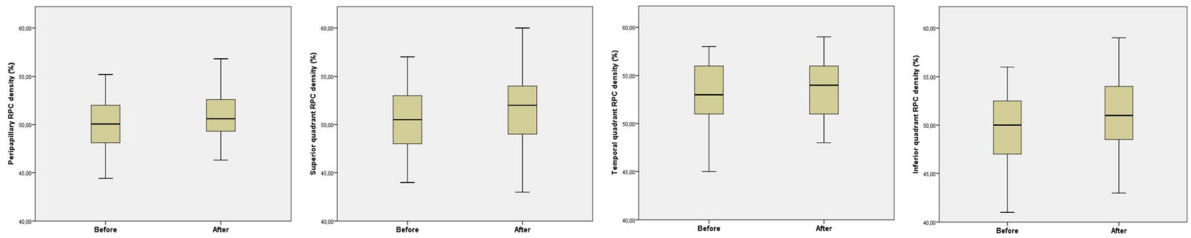

Fig. 3 Distribution of peripapillary RPC, superior, temporal and inferior quadrant RPC vascular density, with before and after four-week GBE consumption (*RPC* Radial peripapillary capillary network, *GBE Ginkgo biloba* extract)

The exact explanation for these effects is unclear, but it may be related to endothelial-associated cytokine release and antioxidant effects.

The blood supply and circulation of the head and surroundings of the optic nerve are quite complicated. This circulation is roughly as follows: Firstly, radial peripapillary capillaries are located in the anterior (with centrifugal perfusion from the central retinal artery); in the continuation of this, secondly, by the prelaminar network (composed of peripapillary choroid vessels arising from the short posterior ciliary arteries); thirdly, behind this network lies the laminar vascularization composed of short posterior ciliary arteries; lastly, the retrolaminar vascularization layer (composed of anastomoses of the short posterior ciliary arteries and vessels of the pia mater) is located in the most posterior position [29]. Although there are a limited number of studies on the effects of GBE in long-term use, 80 mg, orally, twice a day for four weeks GBE treatment affects the peripapillary blood flow, volume, and velocity in normal-tension glaucoma patients [7]. They found an increase in both flow, volume and velocity was detected in the peripapillary region. In our study, we found an increase in RPC vascular density in the peripapillary region. Wimpissinger et al. [8] reported a single dose of 240 mg GBE affects the optic nerve head blood flow significantly increased in response to *Ginkgo biloba* but does not influence the ocular blood flow to a relevant degree in healthy volunteers. Conversely, long term use of GBE has been reported to increase ocular blood flow and velocity in primary open-angle glaucoma patients [30]. In our study, no significant change in calculated OPP and IOP was detected in four-week GBE use. This situation may indicate that the short-time changes [8] in systemic blood pressure and intraocular pressure of GBE return to normal limits with long-term use. Although blood pressure, volume and velocity are related, long-term use of GBE may affect only ocular blood flow velocity. The fact that the movement of red blood cells is measured with the OCTA device may support this situation. However, it should be kept in mind that these effects can be explained by the fact that GBE has potent antioxidant effects [21, 22].

Within the participants in this study, no one has ocular or systemic adverse events related to the use of GBE for four weeks.

The main strengths of this study are that it included a cohort of healthy participants who received regularly four-week consumption and apart from OCTA measurements, the fact that sfCT and RNFL were also measured. This article is the first prospective OCTA study on the effect of GBE on retinal and optic nerve head vascular morphology in healthy volunteers. To the best of our knowledge, there have not been any previously reported studies on this method and subject.

The limitations of the study are that the study was conducted only on healthy volunteers, the absence of a placebo control group, and demonstrated the relatively short-term effects of four-week of GBE consumption. Results may vary in longer consumption duration, follow-up periods and patients with diseases associated with optic disc involvement. Thus, appropriate further studies are needed to confirm (or not) these results.

In conclusion, this study showed that the four-week consumption of GBE leads to an increase in peripapillary and superior, inferior, temporal quadrant RPC vascular density in healthy volunteers. The concept to be investigated carefully is the possible neuroprotective action of GBE in optic neuropathies associated with peripapillary atrophy. It is necessary to investigate possible beneficial use in diseases with

peripapillary loss or atrophy, also unexpected effects that may occur in neovascular conditions such as peripapillary choroidal neovascular. Further studies are needed.

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Author contributions All authors attest that they meet the current ICMJE criteria for authorship. All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data availability Dataset not available due to ethical restrictions: Due to the nature of this research, participants of this study did not agree for their personal data to be shared publicly, so dataset is not available.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest for this research. The authors alone are responsible for the content and writing of this article.

Ethical approval Institutional review board approval was obtained from the local ethics committee (2011-KAEK-2) (Approval Code: 2020/3-120, including publishing and participating).

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